The Evelyn F. McKnight Brain Research Foundation

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Capital Room ABC

Washington DC Convention Center

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Dedicated to the Understanding and Alleviation of Age-Related Memory Loss

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Poster #1

Adiponectin and components of Metabolic Syndrome are associated with cortical thickness: the Northern Manhattan Study

M.R. CAUNCA, M. SIMONETTO, H. GARDENER, M. NG-REYES, D. GUERRERO, N. ALPERIN, S.H. LEE, A.M. BAGCI, M.S.V. ELKIND, R.L. SACCO, C.B. WRIGHT, T. RUNDEK

University of Miami, Miami, FL

Objective: Examine the association of adiponectin and metabolic syndrome components with measures of global and lobar cortical thickness.

Background: Metabolic syndrome has been associated with structural brain changes, but the relationship of adiponectin and cortical thickness is understudied.

Methods: The Northern Manhattan Study MRI Sub-Study is a mostly Hispanic, stroke-free, prospective cohort study of older adults. Cortical thickness (mm) was obtained from T1-weighted brain MRIs using the publically-available Freesurfer software. Regional cortical thickness metrics were averaged to obtain mean lobar cortical thickness. Adiponectin (μg/mL) was measured at baseline (1993-2001). Metabolic syndrome components were measured at MRI Sub-Study baseline (2003-2008). We estimated the cross-sectional associations of adiponectin (per 1 SD) and metabolic syndrome components with global and lobar cortical thickness (per 1 SD) using multivariable linear regression models adjusted for sociodemographic factors, APOE ε4 allele presence, and health-related behaviors. All hypothesis testing was two-sided with an alpha level of 5%.

Results: Freesurfer data were available in 947 participants (mean±SD age=70±9 years, 63% women, 66% Hispanics, 16% black, and 15% white). Global cortical thickness was normally distributed (mean±SD = 2.3±0.1mm). In fully adjusted models, 1 SD (4.9μg/mL) increase in adiponectin was associated with smaller overall (β [95%CI] = -0.07 [-0.14, -0.0002]) and parietal cortical thickness (β [95%CI] = -0.08 [-0.03, -0.0002]). Greater blood glucose levels significantly associated with smaller occipital cortical thickness (β [95%CI] = -0.003 [-0.006, -0.0007]). Greater waist circumference was significantly associated with smaller frontal cortical thickness (β [95%CI] = -0.02 [-0.04, -0.0007]). Neither blood pressure (systolic and diastolic) nor cholesterol (total, HDL-C, and LDL-C) were associated with global or regional cortical thickness.

Conclusions: There was heterogeneity in the cross-sectional associations between adiponectin, metabolic syndrome components, and regional cortical thickness. Further studies are needed to explore the temporal relationship between risk factors and cortical thinning.

Poster #2

The effects of a 12-week exercise and cognitive intervention on gait, posture and Transcranial Magnetic Stimulation plasticity measures individuals post stroke - an ongoing study

D. CABRAL; KAYLEE CAI, N. CASSIDY, S. ALDRAIWIESH, J. RICE, J. GOMES-OSMAN
University of Miami, Miami, FL

Background: Cognitive impairments greatly contribute to decreased function and disability in individuals post-stroke. Improvements due to both, cognitive training and physical training interventions, are attributed to neuroplasticity. Single-pulse transcranial magnetic stimulation (TMS) interleaved with intermittent theta-burst stimulation (iTBS) allows for a non-invasive assessment of neuroplasticity. Our objective was to compare the effects of a 12-week exercise program to a combined program of exercise and cognitive training on measures of brain plasticity, gait and postural control in individuals post-stroke.

Methods: All 8 participants fulfilled the following criteria: diagnosis of ischemic or hemorrhagic stroke, Modified Rankin Score of <4, sedentary prior to stroke, ability to walk ≥10 meters with or without assistance, and no absolute contraindications to receiving TMS. Subjects were randomized to receive either combined aerobic and resistance training (CARET, 45-60 minutes at 60-70% of HR max initially), (n=2); or CARET and a computer-based cognitive training (CTI, 30 minutes),(n=5). Both interventions were performed 3x/week for 12 weeks. Brain plasticity and gait function were assessed at baseline and post intervention.

Outcomes: Brain plasticity was assessed by comparing the amplitude of motor evoked potentials (MEPs) from single TMS pulses prior to (T0) and following iTBS (T10). For the gait and postural control assessment, individuals were fitted with a sensor-based gait analysis system (Mobility Lab; APDM, Inc), and performed the following tests: the Timed-Up and Go (TUG), TUG with dual-task (TUG-DT), and static standing balance (eyes open, eyes closed, and dual-task).

Results: At a group level, all participants demonstrated improved dual-task time (mean=-4.1s, p=0.02) and peak velocity (mean=28.5m/s, p=0.054). In addition, there were within-group differences. The CARET+CTI group demonstrated an improvement in peak velocity (mean=41.5m/s, p=0.02) and the CARET only group demonstrated improved dual-task time (mean=-3.3s, p=0.03) and decreased double-support time (mean=-2.1s, p=0.005). Brain plasticity with TMS remained stable between assessments, and no differences were found.

Conclusion: The results of this preliminary trial suggest that exercise delivered in isolation and combined with cognitive training may be useful in improving gait and postural control in persons post-stroke. The potential of TMS plasticity warrants further investigation.

Poster #3

Sexual dimorphism in inflammasome activation: Possible cause of exacerbated ischemic brain damage in reproductively senescent female rats

A.P. RAVAL, J. DE RIVERO VACCARI

University of Miami, Miami, FL

A woman's risk of a stroke increases exponentially following the onset of menopause, and underlying mechanisms remains unknown. The current study tests the hypotheses that: (1) inflammasome activation is significantly higher in the brain of RS females as compared to their young counterparts and senescent male rats, (2) RS triggers an innate immune inflammatory response in the ovaries that spreads to the brain, making the brain more susceptible to ischemic damage. We tested our hypotheses using Sprague-Dawley rats of both sexes (6-7 and 9-12 months). The estrous cycles of female rats were monitored for 14-20 days prior to experimentation by daily examination of vaginal smears. Rats that remain in constant diestrus were considered RS. Rats (n = 4-7) of both sexes and ages were sacrificed and hippocampus, gonads, serum and cerebrospinal fluid (CSF) were collected. Additionally, cerebrospinal fluid (CSF) of women (<40 and >50 age) was obtained. Extracellular vesicles (EV) were isolated from serum and CSF using an Invitrogen kit. Inflammasome proteins caspase-1, apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and IL-1β significantly increased in the hippocampus, serum, and ovaries of RSF as compared to YF ($p<0.05$). This was not observed in the hippocampus or gonads of age-matched males. Importantly, EV obtained from RSF contains significantly higher levels of the inflammasome proteins as compared to YF ($p<0.05$). EV containing inflammasome proteins originates in the ovaries of RSF and then are carried to the brain via blood. The observed increase in ovary-derived EV containing inflammasome proteins in the brain contributes to the inflammation present in the brain of RSF, and it might exacerbate ischemic brain damage. Future studies investigating the role of ovarian EV in post-ischemic inflammation are underway to understand how modulating EV trafficking can reduce the incidence and impact of cerebral ischemia in post-menopausal women.

Poster #4

Potential role of endoplasmic reticulum stress in recurrent hypoglycemia-induced increase in ischemic brain damage

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University of Miami, Miami, FL

Diabetes is a serious metabolic disease and stroke among diabetics is noted to be associated with wide spread brain damage. Anti-diabetic drug therapy related episodes of hypoglycemia cause hypoglycemia associated autonomic failure and eventually lead to development of recurrent hypoglycemia (RH). Our laboratory have previously reported that prior exposure of RH exacerbates ischemic brain injury in insulin-treated diabetic (ITD) rats. However, mechanisms known to cause this injury are least understood. Acute hypoglycemia activates unfolded protein response in liver. Glucose starvation also activates endoplasmic reticulum (ER) stress. Cerebral ischemia activates one of three ER stress pathways namely protein kinase RNA-like endoplasmic reticulum kinase (PERK) -eukaryotic initiation factor 2α (eIF2α) pathway. However, the role of ER stress in RH-induced aggravation of ischemic brain damage among treated diabetics is not known. Therefore, aim of the study was to evaluate post-cerebral ischemic ER stress in ITD rats exposed to RH. We determined levels of total and phospho-PERK, and C/EBP homologous protein (CHOP) (using western blot analysis) as markers of ER stress in Naïve (n=6), ITD (n=5), and ITD + RH (representing RH exposed treated diabetic) (n=8) groups. Rats were rendered diabetic by administration of streptozotocin and 2-3 weeks later, insulin pellet implantation was done to treat diabetic hyperglycemia. After 2-3 weeks, sub-cutaneous injection of insulin was given to induce hypoglycemia for 3 hours per day for 5 consecutive days. Overnight after last hypoglycemia exposure, global cerebral ischemia was induced by bilateral carotid artery occlusion with hypotension for eight minutes. We observed that pPERK to total PERK ratio in the ITD + RH group was higher by 57% ($P<0.05$), and 36% ($P<0.05$) as compared with naïve and ITD groups, respectively. We found that the level of CHOP in the ITD + RH group was higher by 30% ($P<0.05$), and 59% ($P<0.05$) as compared with naïve and ITD groups, respectively. Thus, we conclude that cerebral ischemia increases ER stress in RH-exposed ITD rats and may play a role in increased cerebral ischemic damage observed in RH exposed ITD rats. Confirming the role of ER stress in RH-induced aggravation of ischemic brain damage may help in developing new therapeutic options for diabetic stroke patients.

Poster #5

Transcranial direct current stimulation augmented individualized gait training targeted at freezing of gait in Parkinson's Disease: a case description

J. RICE, A. SWAROWSKY, K. CAI, S. ALDRAIWEISH, J. GOMES-OSMAN
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Background: Fifty to 70% of people with Parkinson's Disease (PD) experience freezing of gait (FOG). Freezing episodes are significantly correlated with the risk of falling, which can lead to injury, fear of falling, decreased activity levels and increased functional impairments. Current treatments for PD, such as pharmacologic agents and deep brain stimulation have a variable effect on FOG, making treatment options limited. Recent evidence demonstrates disrupted cortical networks in individuals who exhibit FOG, with alterations in the supplementary motor area (SMA) and executive function disorder. Transcranial direct current stimulation (tDCS) can modulate cortical excitability non-invasively, and may be a useful adjuvant to gait training in individuals who freeze. Our objective is to report on a case study assessing feasibility and preliminary efficacy of an individualized gait training targeting FOG and augmented with tDCS.

Methods: The participant was a female with Hoehn and Yahr stage II PD with FOG, and initial unified Parkinson's disease rating scale (UPDRS) motor sub score of 29. An assessment battery was performed in the "on" phase at baseline and following the 3-week CMCLT protocol. Feasibility was assessed by measuring the percentage of adherence and occurrence of adverse events. Preliminary efficacy was assessed with the outcome measures: the freezing of gait questionnaire (FOG-Q) to assess freezing, Timed up-and-go (TUG) and TUG with dual-task (TUG-DT) to assess walking function and cognitive reserve, and the Montreal Cognitive Assessment (MOCA) for used for global cognition. The intervention was comprised of 45-minute training sessions, 3x per week for 3 weeks, where the individual performed tasks specifically designed to provoke and train freezing, increasing in complexity throughout the training and incorporating motor and cognitive dual-tasks. TDCS (1mA) was applied to the SMA concomitantly with training.

Results: Adherence to the protocol was 100% without any adverse events reported. The participant demonstrated: a decrease in severity and frequency of freezing episodes (FOG-Q baseline=15, posttest= 8); improved walking function (TUG baseline=19.69s, posttest= 17.14s); cognitive reserve (mean TUG-DT baseline=25.52s, posttest=23.07s); and improved global cognition MOCA (baseline=16, posttest=26).

Conclusions: The results of the present study demonstrate safety and preliminary efficacy of an individualized gait training protocol augmented by tDCS in an individual in Stage II Hoehn and Yahr who experiences FOG. Our results suggest further examination of this protocol in a larger sample.

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Poster #6

Influence of systemic inflammation on cognition and the hippocampal transcriptional profile

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Chronic systemic inflammation increases with age and is associated with cognitive impairment. To examine the role of systemic inflammation on cognition and brain function, young (5-7 months; n = 22) and middle-age (14-16 months; n=22) Fischer 344 Brown Norway hybrid rats were behaviorally characterized using water maze. Animals were matched for performance and assigned vehicle or lipopolysaccharide (LPS, 1 mg/kg, i.p.) treatment (once per week for 6 weeks) to mimic chronic systemic inflammation. Seventy-two hours following the seven treatment, animals were re-tested for spatial memory performance and animals were sacrificed forty-eight hours after the final treatment. Pro-inflammatory cytokines were analyzed in the blood plasma and hippocampus. In the plasma, Eotaxin, IL-1β, MCP-1, and IP-10 significantly increased across age groups with LPS treatment, and IL-1β and IL-6 negatively correlated with memory across all age groups. LPS treatment significantly impaired memory performance in young ($p = 0.005$) animals. Next generation RNA sequencing was performed to determine treatment effects on transcription for the CA1 and dentate gyrus (DG) regions of the hippocampus from young animals. Across both regions, LPS treatment increased expression of inflammatory gene, C3. Statistical filtering and functional annotation clustering (DAVID) within each region indicated that LPS treatment decreased expression of ribosomal subunits in region CA1 and increased expression of neuron projection genes, including C4a, Nlgn2, and Mtor. LPS treatment increased expression of mRNA processing genes in the DG. These results indicate that chronic systemic inflammation influences cognition and brain gene transcription. Currently, we are processing hippocampal tissue from middle-age animals for RNA sequencing in order to address how chronic inflammation interacts with aging.

Poster #7

Age-related changes in the perirhinal-hippocampal-prefrontal cortical circuit: evidence for neural compensation in aged rats

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The increase in the average lifespan has not been met with a commensurate improvement in cognitive healthspan. In fact, loss of cognitive function and declining neuronal metabolism are hallmarks of advanced age, and little is understood regarding how changes in neuronal signaling affect behavioral output. Moreover, there is considerable variability in the behavioral phenotypes of old humans and animals. Critically, it is not known whether neural systems in the aged brain reorganize in cognitively intact older animals, showing evidence of compensation, or conversely if these systems maintain function into advanced age. The aim of the present study was to determine the extent to which brain activation patterns during a bi-conditional association task (BAT), which is sensitive to detecting age-related impairments and requires interactions between the prefrontal cortex (PFC), perirhinal cortex (PER), and hippocampus (HPC), differ between young and aged rats. Importantly, all rats were trained to perform similarly in order to examine the extent to which activation patterns across the PFC, PER and HPC reorganize in old age when behavioral output is comparable. Cellular activity during BAT and a control task was measured by quantifying the number of cells expressing the immediate early gene, *Arc*. *Arc* transcription is initiated by patterned neuron spiking associated with behavior. Because *Arc* is an effector protein that is translocated to the cytoplasm ~20 min after cell activity, we can determine the neural ensembles activated at two distinct time points based on the cellular location of *Arc* mRNA. The results indicated that there was a significant main effect of task ($p < 0.02$) for all regions examined, as well as an age by region interaction ($p < 0.05$), suggesting that age did not impact all regions similarly. In fact, aged rats showed elevated activity, compared to young animals, in the PFC during both tasks. In contrast, all rats had elevated activity in CA1 (HPC) during the BAT as compared to the control walking task. In the PER there was decreased activity in aged rats compared to young rats across both tasks. Together, these data suggest that anterior regions may be compensating for a decrease in function in the PER. The observation that neural activity patterns differ between young and old animals, even when their behavioral performance is comparable, supports the idea that neural networks in the aged brain may reorganize to optimize behavioral output as one region becomes dysfunctional. Future studies will incorporate retrograde tracing with *Arc* imaging to investigate signaling across these regions with anatomical specificity.

Poster #8

Optogenetic inactivation of basolateral amygdala in young rats recapitulates aged rats' ability to delay gratification in an intertemporal choice task

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Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. Such decisions require integration of existing reward representations (based on prior experience) with valuation of the organism's current wants and needs (incentive motivation). Prior studies in both humans and rodents show that relative to young adults, aged subjects are better able to delay gratification, and generally prefer large, delayed over small, immediate rewards. While the neural circuit and molecular changes that mediate these age differences in intertemporal choice are unknown, lesion studies consistently implicate the basolateral amygdala (BLA) in motivation and affective decision making. The current experiments first used optogenetic approaches to determine the effects on choice behavior of temporally discrete BLA inactivation during an intertemporal choice task. Young adult (6 mo., n=8) Fischer 344 x Brown Norway F1 hybrid (FBN) rats were surgically implanted with cannulae targeting BLA, into which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered, and optic fibers were cemented. Rats were subsequently trained on an adjustable delay, intertemporal choice task in which preference for small vs. large rewards was evaluated in presence of increasing delays to large rewards. Upon reaching stable baseline performance, light-induced BLA inactivation was performed during the trial epoch in which rats deliberate between large, delayed and small, immediate reward options. To control for effects of repeated laser stimulation on choice behavior, in other sessions, rats received discrete light-induced inactivation only during intertrial intervals (ITIs). In comparison to both baseline and ITI inactivation, discrete BLA inactivation during deliberation significantly biased rats towards choice of the large, delayed reward, and produced a pattern of choice performance that mimics that of aged rats. In a second cohort of behaviorally naïve young and aged FBN rats, total RNA was extracted from the BLA and low-density RT-qPCR plates were used to assess basal expression of genes involved in excitatory glutamatergic and inhibitory GABAergic signaling. Broadly, transcripts associated with glutamatergic signaling were reduced in the aged BLA, suggesting this brain region undergoes molecular changes in aging that render it hypoactive. Together, these findings suggest that age-associated shifts in BLA excitatory/inhibitory signaling dynamics attenuate the influence of incentive motivation on cost-benefit decision making, and contribute to the enhanced ability of older subjects to delay gratification.

Poster #9

Role of CA3 and dentate gyrus in the discrimination of perceptually similar objects depends on novelty of stimuli

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Memory requires that similar episodes with overlapping features be represented distinctly. Notably, many symptoms of age-related memory loss appear to derive from the decreased ability to distinguish between similar events. In human neuroimaging experiments, discrimination of similar objects has been linked to activity in CA3 and dentate gyrus (CA3/DG; Doxey and Kirwan 2015, Yassa and Stark 2011), and discrimination impairments in the elderly correlate with altered CA3/DG activity (Yassa et al. 2011). Yet, work in animal models points to a critical role of the perirhinal cortex in distinguishing between similar visual stimuli (Bussey et al. 2005), and the requirement of CA3/DG in these tasks remains unexplored. We therefore asked whether neural activity in CA3/DG is required for accurate discrimination of a known target from lure objects. Adult male F344 x Brown Norway hybrid rats were shaped and trained to identify a target object (S+) in a forced-choice discrimination task, then surgically implanted with bilateral guide cannulae targeting dorsal CA3/DG. Rats were next tested on a target-lure LEGO object discrimination task in which feature overlap of a well-learned target object (S+) to lures (S-) was systematically varied (Johnson et al. 2017). The effect of reversibly inactivating CA3/DG on target-lure discrimination was first assessed within subjects in randomized blocks. Infusion of the $GABA_A$ agonist muscimol initially impaired discrimination of the target from distinct and similar lures (drug: $P<0.004$). On subsequent test blocks, however, performance improved across all overlap conditions irrespective of CA3/DG inactivation (drug: $P=0.37$). To clarify these results, a second experiment examined whether prior experience with stimuli influenced the effect of CA3/DG inactivation on object discrimination performance. Rats that received vehicle control infusions in a first test block, followed by muscimol, did not show discrimination impairments for target-lure pairs of any similarity (drug: $P=0.15$, similarity x drug: $P=0.42$). In contrast, rats that received muscimol infusions in the first test block were impaired across all target-lure pairs (drug: $P<0.0001$). Sustained efficacy of muscimol in silencing neural activity after repeated infusions was verified behaviorally and by absence of *Arc* mRNA in CA3/DG. Our results suggest neural activity in CA3/DG is most critical to complex stimulus discrimination when stimuli are novel. This is consistent with recent data suggesting dysfunction of the medial temporal lobe-hippocampal circuit, rather than hippocampus alone, contributes to age-related deficits in object discrimination.

Poster #10

Impact of age- and stress-related neuroendocrine dysfunction on working memory and GABAergic synaptic markers in prefrontal cortex

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Normal aging is associated with impaired cognition, including working memory supported by the prefrontal cortex (PFC). Our prior work strongly implicates altered PFC glutamatergic and GABAergic signaling in age-related working memory impairment. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis also accompanies the aging process and it has been proposed that the cumulative effects of stress and concomitant glucocorticoid exposure over the lifespan exacerbate neural changes that mediate the emergence of cognitive deficits. As the PFC is enriched in glucocorticoid receptors, the present study tested the hypothesis that age-related differences in HPA function associate with working memory ability and that chronic stress recapitulates adverse effects of aging on working memory and PFC glutamatergic/GABAergic signaling protein expression. First, we evaluated the relationship between working memory and circulating corticosterone (CORT) in aged rats. Young adult (4-6 mo) and aged (22-24 mo) rats were characterized for working memory ability using a delayed response task. As in our previous work, working memory in aged rats was less accurate than young, although aged performance spanned a broad range with some aged rats performing similar to young (unimpaired) and others performing worse than young (impaired). Basal CORT measured across the diurnal cycle was greater in aged rats than in young but this elevation was not associated with working memory. When challenged with a stressor (1 h restraint), stress-induced CORT was positively correlated with working memory performance of aged rats. Next, we determined the extent to which chronic variable stress can recapitulate the behavioral and molecular consequences of advanced aging. Young adult rats were exposed to a 21-day randomized schedule of twice-daily stressors including forced swims, water in cage, restraint stress and exposure to predator urine. Accuracy of working memory declined over the course of the regimen in chronically stressed rats compared to non-stressed controls. On the 22nd day, rats were sacrificed and PFCs dissected for molecular analysis. While markers affiliated with excitatory signaling (NMDARs, VGluT1) were not reliably changed by stress, expression of GABA(B)R1a, a presynaptic GABA autoreceptor, and VGAT, the presynaptic vesicular GABA transporter, were significantly reduced in the PFC of stressed rats. Collectively, our findings identify a causal role for stress in PFC GABA signaling alterations that could contribute to impaired working memory.

Poster #11

Connectivity changes after cognitive training in young and aged rats

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Changes in large-scale neural connectivity are a hallmark of brain aging that have been linked to cognitive decline. Recent behavioral models for probing the integrity of inter-regional communication along with advances in functional MRI offer a unique opportunity to study functional connectivity in conjunction with quantification of the neurobiological mechanisms that underlie alterations in large-scale network communication. In this study, we determined how cognitive training on an object-place paired association (OPPA) task, which requires interactions between prefrontal, medial temporal and subcortical structures, altered functional connectivity in young (4 mo, n = 5) and aged (24 mo, n = 5) Fischer 344 x Brown Norway F1 hybrid rats. A resting state fMRI dataset was collected in a 11.1 Tesla Bruker system. All rats were scanned for three sessions: before cognitive training, after two weeks of training on the OPPA task in which both young and aged rats were not performing above an 80% criterion (second session), and after four weeks of OPPA training in which the young rats, but not old, were performing at criterion (third session). A 1-shot spin echo EPI sequence was acquired with acquisition parameters for a total acquisition time of 10 mins (an image was acquired every 2s). Anatomical scans for image overlay and reference-to-atlas registration were collected using a fast spin echo sequence. Time series fMRI signals were extracted from each region of interest (ROI) based on the atlas-guided seed location (150 total areas). The correlation values of the graphs were thresholded for each subject to create matrices with equal densities (e.g the top 15% correlation values). Network matrices were normalized by the highest correlation value, such that all matrices had edge weight values ranging from 0 to 1. The networks were quantified with the following graph theory metrics: *node strength* (sum of edge weights), and rich club (highly interconnected subnetwork commonly termed as hubs). Young rats did not show differences in global node strengths between the three sessions; however, the aged rats showed an increased in node strength connectivity after the first training session at high node strength values. The areas involved in increasing the node strength values in the aged group were: anterior cingulate, cortical, striatal. Particularly the rich club increased after the first session in the aged group and was maintained during the third session. This suggests an engagement in learning as rats aged in a subnetwork (comprised of anterior cingulate, striatal area, somatosensory, motor, insular, and motor cortex areas) that is not engaged in learning of young rodents.

Poster #12

Peripheral inflammation induces age-dependent attentional impairments in rats

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Aging is characterized by increased inflammation, which correlates with cognitive decline. Activation of the peripheral immune system via acute lipopolysaccharide (LPS) injection elicits deficits in learning, spatial memory, and cognitive flexibility, with middle aged rats displaying enhanced impairment. Little is known of inflammation's impact on vigilance, and more so, if systemic inflammation, which more closely models conditions in aging, impairs attentional function. Thus we examined the impact of chronic LPS injections in young and middle-aged rats on the 5-choice serial reaction time task (5-CSRTT), expecting attentional deficits to emerge with chronic LPS treatment and greater disruption in middle aged rats. Young (4mo old) and middle-aged (12-14 mo old) Fischer-344 rats were food restricted and trained on the 5-CSRTT, which requires continuous monitoring for a light cue (duration: 10, 2.5, and 0.5s) occurring in one of five holes and nose poking the lit hole. Once rats reached criterion (>50% correct on each signal duration and <10% omissions for five consecutive days) they were injected weekly with LPS (1mg/kg, i.p.) and their attentional capacity was assessed as a weekly average (four weeks total). The impact of treatment and age on attentional capacity were analyzed specifically. Rats were perfused and the prefrontal cortex (PFC), which significantly contributes to attentional performance, was assessed for activated microglia (Iba-1) and astrocytes (GFAP). After the first LPS injection, rats exhibited an exaggerated sickness response, which was observable in higher omission rates during the first week (interaction: $F_{1.64,\ 29.49}=17.46$, $p=0.00$). Average correct responses did not significantly vary by age ($F_{1,18}=3.45$, $p=0.08$) or treatment ($F_{1,18}=0.24$, $p=0.63$); however, for the shortest signal duration, aged LPS-injected rats displayed greater attentional deficits during the first week ($p=0.05$). All LPS-injected rats exhibited longer correct ($F_{1,18}=6.75$, $p=0.02$) and incorrect response latencies ($F_{1,18}=12.29$, $p=0.003$), despite no change in food retrieval latency, suggestive of LPS-induced cognitive slowing. In addition to attentional deficits, smaller, activated microglia in the PFC were observed after chronic LPS treatment ($p=0.05$), though GFAP density was comparable. Thus, peripheral inflammation impaired cognitive processing regardless of age and independently of the chronicity of treatment. As predicted, middle aged rats displayed greater attentional deficits under challenging conditions, though it arose immediately after infection and resolved with continued inflammatory activation.

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Poster #13

Mapping the spatial extent of climbing fiber-mediated spillover to cerebellar interneurons

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Excitatory synaptic transmission in the nervous system is mediated by glutamate, and is traditionally considered to occur exclusively at synapses. Under conditions of high activity or when released at a high concentration, glutamate spills out of synapses to activate extrasynaptic receptors. While extrasynaptic signaling is thought to augment synaptic transmission in several brain regions, we and others have shown that communication between climbing fibers (CFs) and molecular layer interneurons (MLI) in the cerebellar cortex occurs exclusively via glutamate spillover in the absence of anatomically-defined synapses. Glutamate released at the CF-Purkinje cell (PC) synapse spills out to activate AMPA- and NMDA-type receptors on surrounding MLIs. The actions of extrasynaptic glutamate are controlled by excitatory amino acid transporters (EAATs) that remove glutamate from the extracellular space. Although the cerebellar cortex exhibits highly stereotyped anatomical connectivity and astrocytic transporter expression, it is divided into zones based on differential expression of several proteins including the PC-specific glutamate transporter, EAAT4. We performed simultaneous whole cell voltage clamp recordings and confocal imaging of PCs and MLIs to monitor CF activation and assess spillover responses from a single CF. Post-hoc neuronal reconstruction show that the degree of dendritic overlap between the PC-MLI pairs correlates with the magnitude of spillover current in MLIs. Ongoing experiments seek to understand the spatial spread of spillover mediated MLI activation in zones of high and low EAAT4 expression. Together these results help define the anatomical and molecular factors governing spillover transmission at the CF-MLI synapse.

Poster #14

Restoration of progranulin to progranulin-deficient mice corrects lysosomal abnormalities

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Loss of function mutations in progranulin (*GRN*) are a major autosomal dominant cause of frontotemporal dementia (FTD), and likely cause disease through progranulin haploinsufficiency. Homozygous *GRN* mutations that produce complete progranulin deficiency cause the lysosomal storage disorder neuronal ceroid lipofuscinosis (NCL), revealing that progranulin is critical for proper lysosomal function. Impaired lysosomal function may also play a role in FTD due to *GRN* mutations (FTD-*GRN*), as brains from FTD-*GRN* patients exhibit elevated levels of lysosomal proteins. As in humans, progranulin-deficient mice ($Grn^{+/-}$ and $Grn^{-/-}$) exhibit lysosomal abnormalities throughout the brain, with elevated levels of lysosomal proteins, changes in lysosomal enzyme activity, and in $Grn^{-/-}$ mice accumulation of lipofuscin granules. In this study, we investigated whether brains from progranulin-deficient mice and FTD patients with *GRN* mutations exhibit similar lysosomal abnormalities, and tested whether restoration of progranulin to progranulin-deficient mice would reverse these abnormalities. $Grn^{+/-}$and $Grn^{-/-}$ mice, as well as FTD-*GRN* patients, exhibited increased activity of β-Hexosaminidase A (HEXA), which was associated with increased protein and RNA levels of the enzyme. Brains from FTD-*GRN* patients and $Grn^{-/-}$ mice had reduced activity of β-glucocerebrosidase (GBA), an enzyme with previously reported abnormal trafficking in $Grn^{-/-}$ macrophages. $Grn^{-/-}$ mice also exhibited additional enzymatic changes not present in FTD-*GRN* samples. Restoration of progranulin to $Grn^{-/-}$ mice by intracranial injection of an adeno-associated viral (AAV)-progranulin vector normalized activity of lysosomal enzymes and reduced lipofuscin levels throughout the brain. These data indicate that lysosomal dysfunction due to progranulin deficiency is reversible, which supports use of progranulin-boosting therapies for FTD-*GRN* patients, particularly in the early stages of disease.

Poster #15

Dendritic spine structural remodeling provides cognitive resilience against Alzheimer's disease pathology

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Approximately 30-50% of individuals who come to autopsy without dementia have high levels of Alzheimer's disease (AD) pathology. These cases are proposed to represent individuals who are resilient to dementia, but how cognitively normal older individuals with AD pathophysiology withstand the development of dementia has remained one of the most pivotal, unanswered questions in the field. Here we used innovative, highly optimized three-dimensional modeling of dendritic spines to analyze synapse populations from controls, cognitively normal individuals with high AD pathology, and AD dementia cases. Our analysis shows that dendritic spines undergo unique structural remodeling exclusively in patients with high AD pathology but no cognitive impairment. Samples included postmortem human prefrontal cortex tissue from age-matched pathology-free controls, controls with high levels of AD pathology (CAD), and late-onset AD cases. Methods included Golgi-Cox technique, brightfield imaging, three-dimensional digital reconstruction and morphological analysis of dendritic spines. We compared the density of dendritic spines within layers II and III pyramidal neuron dendrites in Brodmann Area 46 dorsolateral prefrontal cortex, a key area of working memory, using the Golgi-Cox technique in control, CAD, and AD cases. We developed a method to digitally trace impregnated dendrites from brightfield microscopy images, enabling accurate three-dimensional reconstruction of dendritic structure. Analysis of spine morphology revealed unique structural remodeling of synapses exclusively in CAD cases compared to controls or AD. These results bridge gaps to link non-human primate models of age-related memory loss with human dementia. Our findings support the hypothesis that spine plasticity is a mechanism of cognitive resilience that protects older individuals with AD pathophysiology from developing dementia and highlight structural plasticity as a substrate for therapeutic intervention to delay dementia onset during the preclinical phase of AD.

Poster #16

The biophysical characteristics of alpha-synuclein fibrils that dictate inclusion formation and neurodegeneration

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Lewy body diseases (LBDs) involve the spread of alpha-synuclein inclusions, composed primarily of alpha-synuclein fibrils, across much of the brain in Parkinson disease, Lewy Body Dementia, Multiple System Atrophy, and Alzheimer disease. Exposure of rodent brain tissue to pre-formed alpha-synuclein fibrils created from recombinant protein or isolated from inclusions in brains with neurodegenerative disease can result in the corruption of endogenous alpha-synuclein into additional fibrils in neurons. We have found that the development of inclusions and their spread in the brain correlates with neurodegeneration. However, the fate of fibrils immediately after injection is not clear as basic aspects like diffusion and turn-over have not been previously reported. Further, whether the injected material itself forms some types of inclusions later detected in neurons with antibody approaches is also unclear. Here, we describe how fibrils spread in the brain after initial injection, how they turn over, and what types of cells internalize the fibrils to later form inclusions. We focus on how fibril length might affect these characteristics and how local turn-over and uptake selectively dictate vulnerability to inclusion formation and neurodegeneration. Through these studies, we hope to bridge biophysical characteristics of alpha-synuclein fibrils together with neurodegenerative phenotypes in the brain.

Poster #17

Comparative analysis of the sensitivity and specificity of ser(P)-129 alpha-synuclein monoclonal antibodies

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-Synuclein (α-syn) is an abundant presynaptic protein that is the primary constituent of Lewy bodies and neurites that are major pathological hallmarks of Lewy body diseases (LBDs). The majority of α-syn in these inclusions is phosphorylated on the serine-129 amino acid (Ser(P)-129), while Ser(P)-129 levels are very low or undetectable in the cytosol of healthy neurons. There are mixed reports regarding the specificity of different monoclonal antibodies used in rodent tissues to assess α-syn related pathologies. As such, a benchmark antibody that allows cross-study analysis does not yet exist. The goal of this study is to evaluate the commercially available Ser(P)-129 α-syn monoclonal antibodies that include clones 81a, EP1236Y, MJF-R13, and pSyn64 for their application in rodent tissue immunohistochemistry and immunofluorescence. *In vivo,* Lewy body disease-reminiscent pathology was induced through the exposures of α-syn preformed fibrils (PFFs). PFFs, generated from recombinant α-syn, can corrupt and seed the recruitment of endogenous α-syn into fibrillar aggregates weeks after the initial exposures. Brain tissue from Sprague-Dawley rats and C57Bl/6J mice exposed to PFFs or control monomeric protein were compared to neurons from α-syn knockout rodents to assess antibody specificity and sensitivity. Substantial differential off-target labeling was observed between the different antibodies, and recommendations for applications towards specific protocols are given.

Poster #18

Analysis of neuropathology in PINK1 knockout rats induced by alpha-synuclein preformed fibrils

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Alpha-synuclein-immunoreactive pathology is one of the main pathological hallmarks of Parkinson's disease (PD). Mutations in the alpha-synuclein gene are causally linked to dominantly inherited forms of PD and mutations in the PTEN-induced putative kinase-1 (PINK1) gene are linked to recessively inherited forms of PD. PINK1 knockout (KO) rats develop alpha-synuclein-immunoreactive pathology in addition to locomotor deficits and age-dependent loss of dopaminergic neurons in the substantia nigra pars compacta. Because abnormal alpha-synuclein protein aggregates appear spontaneously in PINK1 KO rats around the same age that neurodegeneration begins, we hypothesize that PINK1 KO rats are more prone to alpha-synuclein aggregation compared to wild-type (WT) rats. We further hypothesize that induction of alpha-synuclein aggregation can accelerate neurodegeneration in PINK1 KO rats compared to WT controls. To test these hypotheses, we injected alpha-synuclein pre-formed fibrils (PFFs) or alpha-synuclein monomer into the striatum of PINK1 KO and WT control rats at age three months, prior to the appearance of significant pathology in PINK1 KO rats. Four weeks post-injection, animals were perfused and brains were removed, cryoprotected, and serially sectioned in the coronal plane. Systematically spaced sections were stained by immunofluorescence using antibodies specific for serine 129-phosphorylated (pS129) alpha-synuclein as a selective marker for aggregated alpha-synuclein, and antibodies specific for tyrosine hydroxylase (TH) as a marker for dopaminergic neurons. We measured total pS129 alpha-synuclein immunoreactivity in various brain regions including the substantia nigra. Additionally, we measured the number of cells immunoreactive for both pS129- alpha synuclein and TH in the substantia nigra as a percentage of the total number of TH cells in the substantia nigra. These studies are important for defining the role of alpha-synuclein aggregation in PD pathogenesis and for determining the extent to which pS129 alpha-synuclein causes or accelerates neurodegeneration in PINK1 KO rats.

Poster #19

Hippocampal circadian disruption in early senescence mouse model

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Age related cognitive decline and disruptions in circadian rhythms are growing problems as the average human life span increases. Multiple strains of the senescence-accelerated mouse (SAM), derived from the AKR/J line, show reduced life span, and the SAMP8 strain in particular has been well documented to have cognitive deficits in behavior as well as impaired long-term potentiation (LTP) in hippocampus when compared to the senescence resistant strain (SAMR1). While the SAMP8 strain of mice have been shown to have a split pattern of circadian locomotor activity, little is known about circadian regulation within hippocampus of these strains of mice. We hypothesized that the cognitive deficits in these mice are due in part to altered circadian clock function in the hippocampus. To test this hypothesis, we measured protein expression of the key molecular clock components, PER2 and BMAL1, at 4-hour intervals across the 24-hour light-dark cycle in whole hippocampus isolated from SAMP8 and SAMR1 mice at 6 months of age; immunohistochemistry in the SCN was also performed. Western blot analysis revealed a normal 24-h rhythm in PER2 and BMAL1 expression in hippocampus from SAMR1 control mice (cosinor analysis, $p < 0.05$). However, despite seemingly normal PER2 immunoreactivity in the SCN in both strains (verified by immunohistochemistry), SAMP8 mice had arrhythmic expression of PER2 and BMAL1 in whole hippocampus (cosinor analysis, $p > 0.60$). Experiments are ongoing to determine whether night restricted feeding can rescue arrhythmicity of the hippocampal molecular clock. Understanding how circadian rhythms impact cognition in aging will be important for improving quality of life in elderly populations.

Poster #20

Increased use of peripheral vision is associated with increased functional connectivity between peripheral V1 and functionally specialized visual areas

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Visual acuity in central vision is vital for everyday tasks such as recognizing faces and reading words. However, with central vision loss, such as in macular degeneration (MD), individuals must rely on peripheral vision to perform everyday tasks. Previously, our lab demonstrated that increased reliance on peripheral vision is associated with increased cortical thickness in peripherally responsive areas of primary visual cortex (V1). However, the impact of increased use of peripheral vision on the functional connectivity of V1 is unknown. Because MD patients rely heavily on peripheral vision, we hypothesized that peripheral V1 would possess enhanced functional connectivity to visual areas involved in tasks that are typically performed with central vision. For example, Fusiform Face Area (FFA) and Visual Word Form Area (VWFA) are specialized for processing faces and written language, respectively, and would both likely possess altered connectivity to peripheral V1 with increased peripheral vision use. To test this hypothesis, we used fMRI to measure resting-state functional connectivity between peripheral V1 and category-selective visual areas in 10 MD patients and matched controls. MD patients showed stronger connectivity between peripheral V1 and category-selective visual regions, compared to healthy controls. This association likely reflects increased use of peripheral vision for everyday visual tasks. Overall, these results suggest that connectivity between V1 and higher order brain regions is influenced by the degree to which certain parts of the visual field are used. Together, these findings help provide insight into the nature of visual cortical plasticity in the adult brain.

Poster #21

Enhancer RNAs as Regulators of Gene Expression and Neuronal Function

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Distal enhancer elements in DNA enable higher-order chromatin interactions that facilitate gene expression programs and thus contribute to cellular phenotype and function. In the brain, enhancer-promoter interactions help to ensure cell- and tissue-specific gene expression profiles, defining which genes are active during neuronal specification and which genes remain accessible in adult neurons. In addition to their close links to gene activation, enhancer elements are themselves subject to widespread, bidirectional transcription that yields non-coding enhancer RNA (eRNA). However, although eRNAs are correlated with overall enhancer activity, the precise function of eRNAs remains controversial. Here, we examined the function of eRNAs arising from multiple enhancers near the well-characterized immediate early gene *Fos* (also known as *c-Fos*). We show that eRNA transcription from *Fos* enhancers is dynamically modulated by various forms of neuronal activity, requires RNA polymerase II, and precedes activity-dependent induction of *Fos* mRNA. Visualization of *Fos* eRNA transcripts with single-molecule RNA FISH revealed exclusive localization within the cell nucleus. Targeted stimulation of eRNA synthesis from *Fos* enhancers using CRISPR-dCas9 fusion proteins produced corresponding increases in *Fos* mRNA expression, with limited cross-talk between enhancers. Anti-sense based *Fos* eRNA knockdown decreased *Fos* mRNA expression, whereas mRNA knockdown did not affect eRNA levels. Finally, CRISPR-targeted delivery of eRNA to a *Fos* enhancer elevated mRNA induction following neuronal depolarization. Together, these results suggest that RNAs transcribed from neuronal eRNAs are important regulators of enhancer-driven gene regulatory programs.

Poster #22

Tonic and phasic activation of GIRKs contribute to low dentate granule cell excitability

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The dentate gyrus (DG) is a main entry point for neural activity into the hippocampal formation, integrating sensory and spatial information from the cortex in a manner that generates a neural representation ("engram") of a context. This role within the trisynaptic circuit requires that only a small fraction of the principal granule cells (GCs) are active at any given time. This sparse neural activity is enforced by powerful networks of inhibitory GABAergic interneurons in combination with low intrinsic excitability of GCs. Although the cellular and circuit properties that dictate synaptic inhibition are well studied, less is known about mechanisms that confer low GC intrinsic excitability. Using an electrophysiological approach here we demonstrate that intact G-protein mediated signaling is required to maintain the characteristic low resting membrane potential that differentiates dentate granule cells from CA1 pyramidal cells and immature adult born GCs. We show that intact G-protein signaling enables constitutive G-protein gated inwardly rectifying potassium channels (GIRK) activity, resulting in part from tonic GABAB receptor-mediated stimulation of GIRKs. Perforant path electric stimulation evokes a phasic activation of GIRKs by synaptic GABAB receptors on mature GCs, but adult born new GCs completely lack functional GIRK activity, with both tonic and phasic GABAB-receptor mediated GIRK signaling developing only after 3-4 weeks of maturation. Using transgenic mice and optogenetic tools we show that GABAB evoked phasic GIRK activation is interneuron specific, arising primarily from neuronal nitric oxide synthase (nNOS)-expressing interneurons rather than parvalbumin or somatostatin-expressing interneurons, and requires expression of GIRK2 subunits. Together these results demonstrate that G-protein mediated signaling robustly contributes to the low intrinsic excitability that differentiates mature and developing dentate GCs, and suggests that nNOS-expressing interneurons are principal gate-keepers of GABAB-receptor synaptic inhibition.

Poster #23

Peripheral monocyte entry is required for alpha-synuclein induced inflammation and neurodegeneration in a model of Parkinson disease

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Accumulation of alpha-synuclein (α-syn) in the central nervous system (CNS) is a core feature of Parkinson disease (PD) that leads to activation of the innate immune system, production of inflammatory cytokines and chemokines, and subsequent neurodegeneration. Here, we used heterozygous reporter knock-in mice in which the first exons of the fractalkine receptor (CX3CR1) and of the C-C chemokine receptor type 2 (CCR2) are replaced with fluorescent reporters to study the role of resident microglia (CX3CR1+) and infiltrating peripheral monocytes (CCR2+), respectively, in the CNS. We used an α-syn mouse model induced by viral over-expression of α-syn. We find that *in vivo,* expression of full-length human α-syn induces robust infiltration of pro-inflammatory CCR2+ peripheral monocytes into the substantia nigra. Genetic deletion of CCR2 prevents α-syn induced monocyte entry, attenuates MHCII expression and blocks the subsequent degeneration of dopaminergic neurons. These results demonstrate that extravasation of pro-inflammatory peripheral monocytes into the CNS plays a key role in neurodegeneration in this model of PD synucleinopathy, and suggest that peripheral monocytes may be a target of neuroprotective therapies for human PD.

Poster #24

Amyloid-β induces dendritic degeneration by altering Rho kinase (ROCK) signaling in Alzheimer's disease

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Current estimates project that there are approximately 5.4 million Americans affected by Alzheimer's disease (AD). Cognitive decline is a clinical hallmark of AD, while accumulation of amyloid-β (Aβ) is a pathological hallmark. Aβ accumulates prior to synapse loss in AD, and synapse loss correlates more strongly with cognitive decline than classical pathologic hallmarks. Yet, there are few therapeutic strategies that target synapse loss as a mechanism to delay or prevent cognitive decline in AD. RhoA, a Rho GTPase family member, and its primary downstream effectors, the Rho-associated coiled-coil containing protein kinases (ROCK) 1 and ROCK2, are potent regulators of actin dynamics, influencing neuronal morphology and synaptic plasticity. Our previous work demonstrated that ROCK1 and ROCK2 protein levels are increased in mild cognitive impairment due to AD (MCI) and AD cases, and that Aβ activates the RhoA/ROCK pathway. We show that Aβ induces dendritic spine degeneration in primary hippocampal neurons, but treatment with Fasudil, a clinically available pan-ROCK inhibitor, prevents Aβ-induced spine loss. Moreover, we define how pharmacologic or genetic manipulation of ROCKs interacts with Aβ's negative impact on dendritic spine physiology in hippocampal neurons. Using three-dimensional modeling of dendritic structure, we define isoform-specific effects of ROCKs on dendritic spine density and morphology. Our findings highlight key role for ROCKs in dendritic degeneration and continue to support a notion for ROCK inhibition as a viable treatment for cognitive decline in AD progression.

Poster #25

Common physiological and neurochemical alterations of striatal cholinergic function in DYT-TOR1A and DYT-THAP1 knock-in mouse models of dystonia

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Dystonia is a movement disorder, which typically results in twisted postures due to abnormal muscle contraction. Clinical and experimental data point to abnormalities of striatal cholinergic function in dystonia. Two of the most common genetic forms of isolated dystonia are those resulting from mutations in the TOR1A (DYT-TOR1A) and THAP1 genes (DYT-THAP1). Knock-in (KI) mouse models for mutations underlying both DYT-TOR1A and DYT-THAP1 have been developed. We hypothesize that physiological and neurochemical alterations of striatal cholinergic interneurons may be a shared mechanism of isolated dystonias. To test this idea, we used heterozygous KI mice with the disease-causing ΔGAG mutation of the gene encoding TorsinA and with the disease-causing C54Y mutation of the gene encoding THAP1, as well as their wild-type controls. *In vivo* reverse microdialysis was employed to determine striatal acetylcholine efflux and *ex vivo* slice cell-attached electrophysiological recordings were used to examine the pacemaking activity of cholinergic interneurons. In particular, we sought to determine whether cholinergic interneurons from DYT-THAP1 KI mice displayed "paradoxical excitation" in response to the dopamine D2 receptor agonist, quinpirole, an endophenotype observed across multiple rodent models of DYT-TOR1A and proven to be a consequence of heightened cholinergic tone. Results showed that both DYT-TOR1A and DYT-THAP1 mice had elevated acetylcholine in the striatum both in the basal state and in the presence of neostigmine. Furthermore, both models also displayed dopamine D2 receptor-induced "paradoxical excitation" in the firing rate of striatal cholinergic interneurons. These data suggest that DYT-TOR1A and DYT-THAP1 have common pathophysiological and neurochemical physiology and that striatal cholinergic dysfunction may underlie both of these forms of dystonia. Further investigation of other mouse models of dystonia may further extend this common theme of striatal cholinergic dysfunction as a mechanism of dystonia.

Poster #26

Role of somatostatin and parvalbumin interneurons in 4-aminopyridine-induced epileptiform discharges in mouse cortex

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4-Aminopyridine (4-AP) induces epileptiform discharges in a variety of brain regions. These events are associated with enhanced inhibitory as well as excitatory synaptic transmission. The relative contribution of specific subclasses of GABAergic interneurons to epileptiform activity in 4-AP model has not been well characterized. We have used genetically-encoded archaerhodopsin to investigate the role of somatostatin (SST) and parvalbumin (PV) interneurons in the regulation of evoked epileptiform discharges. Whole cell patch clamp recordings were obtained from L5 pyramidal cells in somatosensory cortex of 30 to 70 day old mice. In the presence of 100 μM 4-AP, local stimulation was used to evoke epileptiform activity. Archaerhodopsin activation in SST interneurons during (Light Off: 6385.98 ± 562.1 mV*ms vs Light On: 2873.44 ± 165.2 mV*ms; $p < 0.05$, paired t-test) and after local stimulation (Light Off: 6601.67 ± 642.82 vs Light On: 4339.20 ± 431.6 mV*ms; $p < 0.05$, paired t-test) reduced the area under the curve (AUC) of epileptiform discharges. Similarly, archaerhodopsin activation in PV interneurons was effective in reducing the evoked responses when electrical stimulation occurred during (Light Off: 11029.35 ± 732.7 mV*ms vs Light On: 2234.16 ± 203.8 mV*ms; $p < 0.05$, paired t-test) or after (Light Off: 10610.44 ± 715.1 vs Light On: 3719.62 ± 288; $p < 0.05$, paired t-test) light onset. Light activation of the PV interneurons reduced responses to a significantly greater extent than that of SST interneurons both during (24.49 ± 1.2 % vs 55.19 ± 2.3 %; $p < 0.05$, paired t-test) and after (44.3 ± 1.9% vs 65.26 ± 0.8%; $p < 0.05$, paired t-test) electrical stimulation. This suggests that PV neurons may be more effective in reducing excitability in the 4-AP model. Since both types of cells were effective in reducing epileptiform activity, it raises the possibility that non-selective activation of interneurons could be more efficacious.

Poster #27

The role of infiltrating myeloid cells in alpha-synuclein neurotoxicity

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Parkinson disease (PD) is a common neurodegenerative movement disorder and results in the loss of dopaminergic neurons in the substantia nigra pars compacta. PD is diagnosed clinically by motor symptoms responsive to dopamine replacement therapies. Pathologically, PD is diagnosed by proteinaceous aggregates called Lewy bodies and neurites in the brain, which consist mainly of the PD-linked protein α-synuclein (α-syn). Analysis of post-mortem tissue in PD demonstrates the accumulation of CD4-postive immune cells from the periphery that infiltrate into susceptible brain tissue. PET-neuroimaging using TSPO ligands shows that inflammation occurs early in PD and does not rescind through the course of disease. However, the contribution of peripherally-derived immune cells in the brain and their impact on neurodegeneration in PD has been difficult to understand. Here, we examine neuroinflammation in the rodent brain after the formation of α-syn inclusions in neurons caused by intra-cranial injections of α-syn fibrils. We find evidence for peripheral immune cell invasion that occurs prior to neurodegeneration. Ex vivo, we find that macrophages readily internalize and degrade α-syn fibrils, and in the process, elicit pro-inflammatory responses that may be damaging to nearby neurons. Through correlational observations in vivo and mixed immune-cell and primary neuronal cultures in vitro, we hope to establish how different inflammatory responses may influence neurodegeneration and the spread of α-syn pathology through the brain.

Poster #28

nNOS$^+$ interneurons contribute to inhibition and neurogenesis in the dentate gyrus

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The dentate gyrus (DG) is a unique brain region that exhibits very low levels of neural activity, wherein only a small percentage of principal granule cells (GCs) are active at any time, and active GCs display low spiking frequencies. The DG is also one of only two regions in the mammalian brain where adult neurogenesis occurs. GABAergic interneurons of the DG not only maintain sparse GC firing, but also provide newly generated GCs with depolarizing GABA as a trophic factor for survival and synaptic integration into the existing network. It is well established that parvalbumin (PV) expressing DG interneurons are important for DG inhibition and neurogenesis, but here we assess how a slow-spiking interneuron family called Ivy/neurogliaform cells that express neuronal nitric oxide synthase (nNOS), contribute to inhibition and neurogenesis. We crossed nNOS-CreER mice with Ai14(RCL-tdT)-D or Ai32(RCL-ChR2(H134R)/EYFP) and gave tamoxifen chow for one week after weaning. We found that all nNOS$^+$ interneurons showed slow maximal firing rates and slow action potential kinetics. nNOS$^+$ cells often had delayed spiking phenotypes, afterhyperpolarizations, and morphology characteristic of Ivy/neurogliaform cells. In contrast, PV$^+$ interneurons had high maximal firing rates, fast action potential kinetics, and basket cell morphology. We also crossed each ChR2-expressing mouse line with POMC-eGFP reporter mice, allowing us to record synaptic responses from both mature and newborn GCs. Optogenetic activation of nNOS$^+$ interneurons generated slow-rising and decaying $GABA_A$-mediated postsynaptic currents (PSCs) in both mature and newborn GCs that were enhanced by NO711, consistent with volume transmission from Ivy/neurogliaform cells. Single light pulses also generated $GABA_B$ PSCs in mature GCs, another hallmark of Ivy/neurogliaform-mediated transmission that differs from fast synaptic signaling by PV$^+$ interneurons. The combined $GABA_A$- and $GABA_B$-mediated inhibition generated by optogenetic activation of nNOS$^+$ interneurons robustly inhibited GC spiking for hundreds of milliseconds, with a slow $GABA_B$-mediated component. Furthermore, optogenetic activation of nNOS$^+$ interneurons (5Hz for four minutes, repeated every five minutes for 60 minutes), increased the number of Ki-67 labeled proliferating progenitors. Together, these data suggest that nNOS$^+$ interneurons display characteristics of Ivy/neurogliaform cells and shape both inhibition and neurogenesis in the DG.

Poster #29

ERRα as a putative mediator of PGC-1α-dependent gene expression: relevance for the pathophysiology of Schizophrenia

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The transcriptional coactivator peroxisome proliferator activated receptor gamma coactivator-1 alpha (PGC-1α) is a known regulator of transcripts involved in neuronal function, including neurotransmission, morphology and metabolism. Importantly, polymorphisms in PGC-1α have been linked to schizophrenia and bipolar disorder. Studies from our lab indicate a reduction in the PGC-1α-dependent transcripts synaptotagmin 2, complexin 1, neurofilament heavy chain and parvalbumin in the cortex, without changes in PGC-1α expression. The mechanisms underlying these changes in gene expression are not clear. We show here that a potential mediator of PGC-1α effects in the brain is orphan nuclear receptor estrogen-related receptor α (ERRα). Promoters of PGC-1α-dependent transcripts contain binding sites for members of the ERR family, ERRα inverse agonists block PGC-1α-driven gene expression, and ERRα knockout mice exhibit reductions in PGC-1α dependent genes in cortex and hippocampus. Interestingly, while ERRα null mice do not show overt motor abnormalities seen in PGC-1α null mice, these mice show impairments in prepulse inhibition, similar to mouse models of schizophrenia. These studies highlight the cell and circuit-specific roles for ERRα in the brain and suggest that modulation of this pathway could be explored for the rescue of discrete endophenotypes in psychiatric disease.

Poster #30

Blunted prefrontal dopamine release in a NMDA receptor hypofunction mouse model

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In vivo PET imaging demonstrates an increase in psychostimulant-induced dopamine (DA) release in the striatum of patients with schizophrenia. A recent PET study also showed a deficit in amphetamine-induced DA release in PFC in schizophrenia. Such dysfunction of DA system in schizophrenia may be following to a deficit in NMDA receptor (NMDAR) function. We investigated the impact of NMDAR blockade on amphetamine-induced DA release in PFC and striatum in an NMDAR hypofunction mouse models, where NMDAR subunit GluN1 deletion occurs in a subset of GABA neurons in postnatal development or in adulthood (Belforte et al, 2010). Notably, over 80 % of parvalbumin (PV)-positive GABA neurons in the mPFC are GluN1-deleted, while less than 5% of PV local neurons are affected in the ventral striatum or VTA. We also used a PV-cre or somatostatin-cre mediated GluN1 KO mouse strain. We measured psychostimulant-induced locomotor activity, the basal levels of tissue DA and its metabolites by HPLC, and extracellular DA levels from accumbens (NAc, lateral shell) and mPFC before and after amphetamine (2.5 mg/kg, i.p.) by in vivo microdialysis technique.

Postnatal GluN1 KO mutant mice showed much higher stimulant-induced locomotor activity compared to the controls. Almost no genotypic difference was detected in tissue DA and HVA levels by HPLC. In vivo brain microdialysis showed no differences in the baseline DA levels in mPFC and NAc before the treatment. Amphetamine injection evoked 21.6-fold DA release from the baseline in the NAc of the postnatal KO mice, whereas only 5-fold increase in the control mice ($F(1, 10) = 9.4$, $p=1.9E-05$, repeated ANOVA). In a separate cohort, no amphetamine-induced DA increase was detected in mutant mPFC, whereas 3-fold increase was observed in the control mPFC ($F(1, 15) =7.1$, $p=9.3E-05$, repeated ANOVA). A similar blunted DA release in mPFC was observed in PV- GluN1 KO mutants, while the DA behavior of adult GluN1 KO mutant mice or somatostatin-cre/GluN1 KO mutant mice was similar to that in control mice.

In conclusion, postnatal NMDAR hypofunction in GABA neurons, in particular in PV neurons, confers mPFC hypo-DA and striatal hyper-DA levels, further suggesting a role of PV neuron-NMDAR hypofunction in schizophrenia pathophysiology.

Poster #31

Effect of expectation on transcranial direct current stimulation suppression of craving and eating

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Background: Transcranial direct current stimulation (tDCS) is a noninvasive brain-modulating technique being heralded as a promising new treatment for a myriad of conditions including obesity. tDCS consistently reduces food craving but reductions in eating are less reliable. A challenge for all tDCS studies is that some participants can correctly distinguish the real from the standard sham condition. This introduces the possibility that expectation related to the provision of treatment may confound efforts to isolate the true efficacy of tDCS. Hence, we conducted a study that directly pitted the effects of expectation against tDCS.

Methods: Thirty-five adults with a body mass index (BMI: kg/m^2) ≥ 25 were informed of the anti-craving/eating effects of tDCS. Once the tDCS electrodes were placed, half were told they were going to receive "real tDCS" (expectation group) and the other half were told they were going to receive "fake tDCS" (no expectation group). Within each of these two groups, half were administered real (2mA current/20 min) and half sham tDCS (2mA current/30 sec at the start and end of 20 min). Univariate ANOVAs assessed main and interaction effects of expectation and tDCS on food-photo craving and in-lab eating test outcomes.

Results: tDCS did not reduce food craving or eating, regardless of expectation. However, participants in the expectation group ate 39% less than participants in the no expectation group ($p=0.031$), regardless of tDCS condition, a reduction more than twice that reported by previous studies attributing the suppression of eating to tDCS.

Conclusions: These results suggest that expectation may be responsible for some of the reported anti-obesity effects attributed to tDCS. The results also call for improved shamming methods and revision of information provided on consent forms for all studies using tDCS.

Poster #32

Altered hippocampal inputs to the mPFC result in deficits in social behaviors in Rett syndrome mice

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Altering the excitatory/inhibitory balance in the medial prefrontal cortex (mPFC) causes autism-like social phenotypes in mice. Using an unbiased machine-learning behavioral classifier, we identified atypical social behaviors and impaired social memory in the *Mecp2* knockout (KO) mouse model of Rett syndrome (RTT), an autism-associated monogenic developmental disorder. Neuronal network activity is lower in the mPFC of *Mecp2* KO mice compared to age-matched WT mice, as estimated by c-Fos immunohistochemistry and high-speed imaging of voltage-sensitive dye (VSD) signals in acute slices. However, stimulation of ventral hippocampal (vHIP) fibers in mPFC slices of *Mecp2* KO mice results in larger amplitude and spatial spread of VSD signals. Normalized to intracortical stimulation in layer 2/3 of the same slices, there is a stronger contribution of vHIP inputs to the *Mecp2* KO mPFC compared to WT mice. In addition, high-frequency stimulation of vHIP afferents in mPFC slices from *Mecp2* KO mice fails to undergo long-term potentiation, as observed in WT slices. To identify active neurons during social memory tasks, we utilized retrobead tracing to label pyramidal neurons in area CA1 and the subiculum (SUB) that project to the mPFC and c-Fos immunohistochemistry. This approach revealed that mPFC-projecting CA1/SUB neurons are selectively activated in WT mice during social tasks. On the other hand, mPFC-projecting CA1/SUB neurons in *Mecp2* KO mice do not show heightened c-Fos levels after social memory tasks. These data suggest that mPFC-projecting vHIP pyramidal cells encode information important for social recognition, and that non-plastic, non-selective inputs from the vHIP in the mPFC of *Mecp2* KO mice may contribute to the observed deficits in social memory and underlie atypical social behaviors. We are currently testing if chemogenetic silencing of the vHIP improves social behaviors in *Mecp2* KO mice, and if vHIP chemogenetic activation in WT mice results in altered network activity and social behaviors and memory phenotypes reminiscent of those observed in *Mecp2* KO mice.

Poster #33

MRI guided drug delivery for location specific neuromodulation

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Pharmacological manipulation of neural activity is essential in both the clinic and laboratory, but current methods of drug delivery to the brain have important intrinsic limitations. Many potential neuromodulatory agents delivered systemically do not cross the blood brain barrier (BBB) and can accumulate in off target tissues. Those agents that do cross the BBB have a widespread effect throughout the entire CNS. Thus, potential treatments are confounded by both reduced efficacy and a wide range of side effects. One can overcome these problems by direct injection into the brain, however this requires highly invasive surgeries. To overcome these limitations, we have developed a non-invasive focused ultrasound drug delivery system that allows targeted neuromodulation with fewer off target effects. This system provides an MRI-visible encapsulation mechanism that is both biocompatible and stable and that can carry therapeutic concentrations of a variety of drugs. It allows the drugs to be cleared from the body without releasing a drug payload in non-target tissues. Focused ultrasound (FUS) is used to open the BBB allowing the non-invasive delivery of the drug carriers into the brain in a location specific manner. In addition, FUS can activate drug release from drug carriers into target tissue and causes a change in MRI contrast confirming location and concentration of drug release to desired tissue.

Poster #34

Inhibiting Tau-SH3 interactions protects against amyloid-β

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The microtubule-associated protein tau has been extensively studied because it aggregates into neurofibrillary tangles within neurons, which are a normal feature of aging in the medial temporal cortex, may contribute to cognitive aging, and are one of the hallmarks of Alzheimer's disease (AD). Tau reduction reverses cognitive deficits in several models of AD, making it an exciting therapeutic target for treatment of the disease. Interestingly, genetic knockout of tau also reduces seizure susceptibility in AD models, which may contribute to the neurodegeneration found in the disease. While the microtubule-binding domain of tau has been studied heavily, less is known about its proline-rich region, which is hyperphosphorylated in AD. This region of tau has several PxxP motifs that mediate binding with SH3-containing proteins, including the nonreceptor tyrosine kinase fyn. Fyn is also an important mediator of network hyperexcitability, as it is involved in NMDA, AMPA, and mGluR signaling. Exogenous amyloid-β activates fyn, leading to NMDAR phosphorylation and excitotoxicity in neurons. Interestingly, expressing a truncated form of tau excludes fyn from dendrites and protects against seizure susceptibility in mice, showing that network hyperexcitability may be influenced by tau-SH3 interactions like that with fyn. We developed a peptide inhibitor of tau-SH3 interactions that mimics the 5th and 6th PxxP motifs in tau to inhibit its interaction with SH3-containing proteins that bind to these motifs, including fyn. We first confirmed that it blocks the tau-fyn interaction through AlphaScreen and by proximity ligation. We then determined that the inhibitor protects against neurite loss and dysfunction in metabolic activity due to amyloid-β toxicity. Our results show that tau-SH3 interactions are necessary for amyloid-β induced toxicity and could be a therapeutic target for AD and other conditions with neuronal hyperexcitability.

Poster #35

CNS resident macrophage activation and peripheral immune cell infiltration in an AAV2 α-syn model of Parkinson disease

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Parkinson disease (PD) is characterized by progressive loss of dopamine producing neurons in the substantia nigra pars compacta (SNpc) and widespread intracellular inclusions of the protein alpha-synuclein (α-syn). Evidence highlights the role of the immune system in progression of PD. In both human patients and rodent models, α-syn pathology is accompanied by microglial activation, T cell infiltration, increased cytokine and chemokine release, and IgG deposition. However, the triggers responsible for initiating this immune response remain poorly understood. Additionally, many previous studies have not separated microglia from CNS resident macrophages (including perivascular, meningeal, and choroid plexus macrophages) and infiltrating cells during analysis, complicating the study of innate mechanisms. To determine the role of resident CNS macrophages in models of PD, we utilized an adeno-associated virus (AAV) that overexpresses full-length human α-syn. We injected this into the SNpc of transgenic mice in which the first exon of CX3CR1 is replaced with GFP. Using flow cytometry and immunohistochemistry, we examined tissue resident CX3CR1+ cells (CD45lo microglia and CD45hi CNS macrophages) for activation markers and proliferation. We found that α-syn led to increased microglial MHCII expression in the midbrain. Additionally, CNS resident macrophages increased in overall number and number of MHCII+ macrophages. Furthermore, α-syn expression led to robust infiltration of peripheral monocytes. These results indicate the importance of microglia and CNS resident macrophages in the initiation of neuroinflammation, recruitment of peripheral immune cells, and neurodegeneration in an α-syn PD model.

Poster #36

Abnormalities in the copper transporters ATP7A and CTR1 in postmortem schizophrenia substantia nigra

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Dysbindin is downregulated in several regions of the brain in schizophrenia. One of dysbindin's functions is to modulate copper (required for monoamine metabolism and myelination). The substantia nigra possesses one of the highest copper contents in the human brain. The current study used Western blot analysis to compare copper transporters ATP7A and CTR1, and dysbindin isoforms 1A, and 1B/C in postmortem substantia nigra in schizophrenia subjects (n=15) and matched controls (n=11); significant results are noted. The combined schizophrenia group exhibited decreased levels of CTR1 (42.6% decrease) and dysbindin isoform 1B/C (18.8% decrease) versus controls. When subdivided by medication status (medicated or unmedicated), the CTR1 decrease was similar in both groups versus controls, suggesting no medication effect. ATP7A levels were decreased in unmedicated versus medicated subjects (38.3% decrease) and controls (35.3% decrease), suggesting medication-induced rescue. When subdivided by treatment response, responders exhibited decreased CTR1 levels versus controls (47.1% decrease), while resistant subjects had decreased dysbindin 1B/C levels versus controls (32.1% decrease). A positive correlation between dysbindin 1B/C and CTR1 was observed in controls that was absent in schizophrenia subjects ($p=0.029$) and medicated subjects ($p=0.03$). A positive ATP7A/dysbindin 1A relationship was observed in unmedicated subjects that was absent in medicated subjects ($p=0.007$) and controls ($p=0.003$). Unmedicated subjects exhibited a negative relationship between dysbindin 1A and 1B/C that was lacking in medicated subjects ($p=0.048$). These results provide the first evidence of disrupted copper transport into and within nigral cells in schizophrenia, potentially related to isoform specific abnormalities of dysbindin and antipsychotic treatment.

Poster #37

Proteasome activity and expression in Schizophrenia brain

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Schizophrenia is a complex neuropsychiatric illness that affects 1% of the population and abnormalities in neurotransmission are a hallmark of the illness. However, the myriad changes of numerous different systems suggests that rather than being a disorder of a given neurotransmitter system (e.g. dopamine, glutamate, GABA), schizophrenia may instead be a disturbance of core intracellular processes that underlie regulation of these systems. Proteasome-regulated degradation is well-placed to impact these pathways, and abnormalities in transcript and protein expression of proteasome-associated proteins implicate dysfunction of this system in schizophrenia. The proteasome is a multicatalytic complex that consists of a core particle (20S) that performs proteolytic activity and regulatory complexes (RP) that recognize substrates and facilitates access to the 20S. The primary regulatory complex associated with the proteasome is the 19S RP. When the 19S RP is bound to the 20S, referred to as the 26S complex, the proteasome is able to recognize ubiquitinated substrates and degrade fully-folded proteins. This primarily occurs in the cytosol and has long been the best characterized function of the proteasome. However, recent work has demonstrated an essential role for the uncapped-20S complex in degrading damaged and oxidated proteins and smaller peptides. As these complexes perform separate activities, the current study seeks to determine how the proteasome may impact schizophrenia pathophysiology by measuring total and complex-specific proteolytic activity in human postmortem brain tissue from the superior temporal gyrus (STG) of subjects with schizophrenia and comparison subjects. Additionally, a novel neuron-specific function of the proteasome has been shown in which the 20S associates with the membrane, degrades intracellular proteins, and produces peptides that are released into the extracellular space where they can modulate neurotransmission. An abnormality in this process is consistent with the current literature in schizophrenia, and so the current study seeks to determine whether novel function and localization of proteasomes in neurons can be seen in human cortex and if it is altered in the STG in schizophrenia.

Poster #38

Early synapse vulnerability targets dentate gyrus in the novel TgF344-Alzheimer's disease model

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The earliest and most insidious stages of Alzheimer's disease (AD) are characterized by altered brain function at the level of the synapse, where pathology begins in the entorhinal cortex (EC) and spreads via functionally connected synapse to the hippocampus. As soluble toxic species of amyloid beta oligomers and hyper-phosphorylated tau rise, EC-to- hippocampal synaptic weakening results and occurs decades prior to clinical presentation of cognitive symptoms. Therefore, there is great need for disease-modifying therapies that can slow or halt disease progression before debilitating symptoms arise. The newly developed TgF344-AD rat model is recognized as the most comprehensive and clinically relevant rodent model of AD to-date. This model fully recapitulates progressive age-dependent AD pathology with key features including early rise in soluble A□□, soluble hyper-phosphorylated tau, and gliosis at 6 months of age. These deficits occur prior to plaques, tangles, cellular loss, and behavioral impairment on hippocampus-dependent learning tasks, which begin between 12-15 months. Whether synaptic alterations occur in hippocampus at 6, 9 and 12 months of age is not known. Furthermore, it is not known if hippocampal subfields are differentially affected by progressing AD pathology, or if gender differences exist during presymptomatic pathogenesis in TgF344-AD rats. Here, we investigated the time-course of synaptic changes in basal transmission, presynaptic release probability, long-term potentiation (LTP) using extracellular dendritic fEPSP recording and spine density by Golgi impregnation in two hippocampal sub-regions in both male and acutely-ovariectomized female TgF344-AD rats and wildtype littermates. Longitudinal studies reveal that the TgF344-AD rat model has hippocampal synaptic alterations that precede documented appearance of plaques and tangles. Basal synaptic transmission is impaired in TgF344-AD rats at medial perforant path-dentate granule cell (MPP-DGC) MPP-DGC synapses prior to CA3-CA1 synapses. Interestingly, impaired basal synaptic transmission at CA3-CA1 begins earlier in TgF344-AD males than females. Paired-pulse ratio and dendritic spine density is unchanged at MPP-DCG and CA3-CA1 synapses in TgF344 AD rats during the presymptomatic phase (6-12 months of age) suggesting a postsynaptic mechanism for altered basal synaptic strength. Finally, LTP magnitude is unaltered at CA3-CA1 synapses during the presymptomatic phase, yet is pathologically enhanced at MPP-DCG synapses in TgF344-AD rats at 6 months of age. Together these data confirm presymtomatic synaptic function is altered prior to the onset of reported behavioral deficits and bolsters the use of TgF344-AD rat model for investigations into disease-modifying therapies.

Poster #39

Elevated O-GlcNAcylation modulates inhibitory neurotransmission hippocampal area CA1

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Studies from our lab have begun to characterize the role of protein O-GlcNAcylation on hippocampal synaptic transmission and learning and memory. This post-translational modification involves the O-linkage of β–N-acetylglucosamine to Ser/Thr residues on target proteins. O-GlcNAcylation is as dynamic as protein phosphorylation and is carried out by the enzyme O-GlcNAc transferase (OGT), which attaches the O-GlcNAc moiety, and O-GlcNAc (OGA) transferase, which catalyzes its removal. Together, this enzymatic set represent the final step of the Hexosamine Biosynthetic Pathway, the sole metabolic pathway for all O-GlcNAcylation in the body. Immunohistochemical staining for O-GlcNAcylated proteins in rat and human hippocampus shows pronounced immunoreactivity in all regions of hippocampus, with expression in excitatory pyramidal cells, GABAergic interneurons, and astrocytes. Using brain slice electrophysiology, we previously reported that acutely increasing O-GlcNAcylation, using either the substrate glucosamine or the OGA inhibitor Thiamet-G, induces a novel NMDAR-independent form of LTD at CA3-CA1 synapses that requires O-GlcNAc modification of GluA2 AMPAR subunits (Taylor et al., 2014). In more recent studies, we have found that increasing O-GlcNAcylation dampens ongoing epileptiform activity at these same synapses. To date, there have been no studies investigating whether GABAergic inhibition is modulated by O-GlcNAcylation, or whether this is specific for excitatory transmission. Using whole-cell voltage-clamp recordings from CA1 pyramidal cells, we investigated whether increasing O-GlcNAcylation using the OGA inhibitor Thiamet-G modulates the frequency or amplitude of spontaneous IPSCs. Preliminary experiments show a reduction in IPSC amplitude following bath application of Thiamet-G, with no change in IPSC frequency, suggesting a possible postsynaptic site of action. Further experiments will examine possible changes in evoked IPSCs onto CA1 pyramidal cells. As the balance of excitatory to inhibitory input controls the final output of CA1 pyramidal cells, E/I ratios will be measured in the presence of elevated O-GlcNAcylation. Collectively these data will further characterize the role of protein O-GlcNAcylation in modulating hippocampal function.

Poster #40

Spread of synuclein pathology following synuclein fibril injection in murine models

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Parkinson disease (PD) is the second most common neurodegenerative disease. Cardinal features include rigidity, resting tremor, bradykinesia, and postural instability. Although current treatments can temporarily improve motor symptoms, no current treatments stop disease progression. Insoluble inclusions known as Lewy bodies (LB) and Lewy neurites (LN), composed mostly of α-synuclein (α-syn), are diagnostic histopathological findings of PD. They are found throughout the nervous system including the substantia nigra pars compacta, cerebral cortex, and hippocampus; these aggregates correlate with onset and progression of PD and related synucleinopathies. We hypothesize preventing formation and spread of α-synpathology will prevent disease progression. Studying α-syn pathology is important for understanding the mechanisms of PD and can contribute to our understanding of disease progression. Injection of α-syn fibrils in animal models can induce robust inclusions that resemble the LB and LN found in diseased brains. Here, we describe the effect of injection location on inclusion formation at the site of injection and in interconnected brain regions. We evaluated injections in the striatum, cortex, and substantia nigra of C57BL/6J mice and found distinct patterns of inclusion formation. Striatal injections produced the most robust, consistent pathology with inclusions found in brain regions relevant for synucleinopathies.

Poster #41

The role of Gadd45b in DNA demethylation and cocaine action

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Introduction: Epigenetic mechanisms are central regulators of the function and information storage capacity of neuronal systems. Methylation of cytosine nucleobases in DNA is a multifunctional epigenetic regulatory modification capable of exerting powerful control gene. In the brain, activity-dependent changes in DNA methylation are critical for synaptic plasticity and memory formation, and have been implicated in a broad range of neuropsychiatric disease states, including drug addiction. However, although activity-related DNA demethylation requires the *Gadd45* (*Growth arrest and DNA-damage-inducible*) protein family, very little is known about how DNA demethylation regulates the function of brain reward circuits or the role that *Gadd45* family members play in behavioral responses to drugs of abuse.

Methods: Here, we combined unbiased genome-wide transcriptional profiling, pharmacological tools, shRNA, and CRISPR/dCas9 transcriptional activation with traditional knockout and behavioral approaches in rodent model systems (both *in vitro* and *in vivo*) to dissect the role of *Gadd45b* in dopamine-dependent epigenetic regulation.

Results: We show that acute cocaine administration induced upregulation of *Gadd45b* mRNA in rat nucleus accumbens, but did not alter expression of other methylation-related transcripts. Similarly, acute dopamine treatment in striatal neuron cultures increased expression of *Gadd45b* and *Gadd45g* mRNA. This effect was mimicked by the Drd1 agonist SKF-38393, suggesting upregulation in Drd1-containing neurons. *In vitro*, CRISPR-targeted transcriptional activation of either *Gadd45b* or *Gadd45g* with a dCas9-VP64 fusion construct was capable of unsilencing a methylated reporter gene, suggesting a mechanistic link between *Gadd45* induction and DNA demethylation. Finally, we show that both dopamine treatment (*in vitro*) and cocaine administration (*in vivo*) induce DNA demethylation, and that *Gadd45b*$^{-/-}$ mice exhibited impaired conditioned place preference for cocaine.

Conclusions: These results suggest that striatal *Gadd45b* functions as a dopamine-dependent immediate early gene to coordinate demethylation of DNA at downstream target genes, and that this action is important for cocaine-related behavioral plasticity.

Poster #42

Temperature-sensitive outward currents through two-pore domain K^+ channels in nociceptive-like primary afferent neurons

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Two-pore domain K^+ channels (K2P) play important roles in setting resting membrane potentials and neuronal excitability. Activity of K2P channels has been found to be highly temperature-dependent, raising a possibility that these channels may be involved in setting neuronal excitability at different temperatures in primary afferent neurons. In the present study we seek to characterize K2P channels in nociceptive type of primary afferent neurons in rat dorsal root ganglia (DRG) to determine their temperature sensitivity and pharmacological properties. Under the condition when cations flowing through voltage-gated ion channels were inhibited, we measured outward currents to determine K2P channel activity in nociceptive-like DRG neurons acutely dissociated from adult rats. The outward currents were recorded using whole-cell patch-clamp recordings with a Cs^+-based intracellular recording solution, which had reversal potentials near -80 mV. Based on the current amplitude and thermal sensitivity of the outward currents, cells could be classified into three types. In the first type (type I), outward currents had large amplitude at the temperature of 22^{o}C, and the amplitude of the outward currents increased when temperature increased to 30^{o}C and reduced when temperature dropped to 14^{o}C. In the second type (type II), outward currents had large amplitude at the temperature of 22^{o}C, and the amplitude of the outward currents did not increase when temperature increased to 30^{o}C but reduced when temperature dropped to 14^{o}C. In the third group (type III), outward currents had small amplitude at the temperature of 22^{o}C, and the amplitude of the outward currents did not increase when temperature increased to 30^{o}C but increased when temperature dropped to 14^{o}C. Pharmacological properties of the temperature sensitive outward currents in these three types of cells were examined. Outward currents in type 1 cells but not type 2 and type 3 cells could be inhibited by PGF2α, a compound that has recently been shown to have effects on K2P channels. Gd^{3+} and riluzole, two compounds that can inhibit K2P channels, were also tested and they appeared to produce inhibitory effects on the outward currents of type I and type II cells. Taken together, this study may suggest that different types of K2P channels are present in functionally distinct groups of nociceptive neurons, and their functions in setting nociceptive neuron excitability need to be determined in future studies.

Poster #43

Regulation of static plasma membrane tension and Piezo2 channel activity by Rho-associated protein kinase in DRG neurons

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Primary afferent neurons can sense their physical environment using mechanically activated (MA) channels that convert mechanical force to electrical signals. Piezo2 channel is a newly identified MA channels expressed on primary afferent neurons of the dorsal root ganglia (DRG) and its activation generates rapidly adapting mechanically activated (RA-MA) currents. We have recently shown that actin filament, a main type of cytoskeleton, plays an important role in regulating Piezo2-mediated RA-MA currents via its impact on static plasma membrane tension in DRG neurons. Since Rho-associated protein kinase (ROCK) is a key regulator of actin organization, in the present study we hypothesized that ROCK also plays a key role in regulating static plasma membrane tension and Piezo2 channel activity in DRG neurons. We used the laser tweezers optical trapping technique to determine static plasma membrane tension of cultured DRG neurons, and examined effects of ROCK activation on static plasma membrane tension of DRG neurons. We further examined RA-MA currents using the whole-cell patch-clamp recording technique and determined effects of ROCK activation on RA-MA currents. The static plasma membrane tension was 52.3 ± 0.8 pN/μm ($n = 7$) in control DGR neurons and was increased to 123 ± 0.2 pN/μm ($n = 7$, $P < 0.05$) following the treatment with Narciclasine to activate ROCK via RhoA pathway. The increase was blocked by fasdile, a ROCK inhibitor. Concurrent with the increases of static plasma membrane tension, we found that the activation of ROCK also significantly enhanced RA-MA current amplitude in DRG neurons. Taken together, our findings suggest that ROCK regulates static plasma membrane tension and Piezo2 channel activity in DRG neurons.

Poster #44

BIN1 loss in inhibitory neurons increases network hyperexcitability

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Alzheimer's Disease (AD) affects about five million Americans, who receive only a very modest benefit from current treatment options. Multiple treatment trials have failed in the past, raising interest in identifying new targets to treat AD. GWAS studies have recently identified bridging integrator 1 (*BIN1*) as the second leading genetic risk factor in AD after only *APOE*. Neurons express a unique BIN1 isoform, and growing body of evidence indicates loss of the neuronal isoform of BIN1 in AD. However, the function of neuronal BIN1 remains unclear and its contribution to AD is critical to investigate. Network hyperexcitability has been repeatedly observed in AD: patients with mild cognitive impairment or dementia due to AD have epileptiform activity. Such aberrant activity is recapitulated in multiple rodent models of AD. Multiple lines of evidence suggest that increased network hyperexcitability results from inhibitory neuron dysfunction in AD patients. Network synchrony is tightly regulated by the activity of inhibitory GABAergic interneurons that coordinate synchronous excitatory neuron firing required for proper brain oscillatory activity. Therefore, interneuron impairment may play an important role in AD pathogenesis. Here, we generated mice lacking BIN1 in interneurons, by crossing mice in which BIN1 exon 3 is flanked by loxp sites to mice expressing Cre recombinase under *Viaat* (vesicular inhibitory amino acid) promoter. We found that loss of BIN1 in inhibitory neurons increases susceptibility to pharmacologically-induced seizures, a phenomenon we have also observed in mice deficient in BIN1 brain-specifically. Mice lacking BIN1 in inhibitory neurons have age-dependent behavioral deficits, as well as decreased survival. These data generate fundamental insight about the mechanistic role BIN1 plays in AD to provide promising therapeutic strategies for targeting inhibitory neuron dysfunction and network hyperexcitability in AD.

Poster #45

Stimulus-evoked cortical physiology identifies corticospinal tract activation by subthalamic deep brain stimulation

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Background: Although DBS is effective for motor symptoms of Parkinson's disease, improvement varies substantially in individuals. Motor side effects constrict the therapeutic window, limit efficacy, and can worsen speech and gait. Non-invasive methods to identify capsular activation could be used to tailor outcomes and guide directional steering, adaptive stimulation, and other emerging technologies.

Aims: We evaluated whether the latency of scalp potentials elicited by subthalamic DBS predicts motor side effect thresholds at a given stimulation site.

Methods: We measured event related potentials elicited by 20 Hz DBS with high density electroencephalography in 7 participants (8 hemispheres, 32 electrodes). We reversed bipolar DBS contact pairings to minimize the stimulus artifact, calculated event related potentials, and correlated response latency with motor side effect thresholds during 160 Hz stimulation using one-way ANOVA at alpha of 0.05.

Results: DBS elicits cortical activation at approximately 1 millisecond after stimulus onset at sites with and without motor side effects. In a voltage-dependent manner, cortical activation occurs at shorter latencies at sites with capsular side effects versus those chosen for clinical therapy ($F=12.2$ and $p<0.001$, ANOVA).

Conclusions: The precise timing of cortical activation by DBS predicts clinically relevant motor side effects, suggesting distinct cortical projections into effective versus ineffective stimulation sites. These findings provide a non-invasive framework to guide emerging technologies such as directional and closed loop stimulation.

Poster #46

Autophosphorylated LRRK2 in exosomes for predicting Parkinson disease: evaluation of the Norway LRRK2 cohort

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Biomarkers that reliably predict Parkinson disease susceptibility and progression are sought for successful clinical trials for disease modifying therapies. Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene are the most common known genetic cause of late-onset of PD, increasing lifetime risk for PD 30 to ~100% depending on the mutation. These pathogenic mutations cause an upregulation of the pSer1292-autophosphorylation site in model systems. Previously, we demonstrated that pSer1292-LRRK2 in urinary exosomes is upregulated in male G2019S-LRRK2 mutation carriers from biobanked samples in the LRRK2 Consortium. Here, in a new cohort of subjects collected in Trondheim, Norway, we analyzed exosomes from both cerebral spinal fluid (CSF) and urine collected at the same clinic visit. pSer1292-LRRK2 was upregulated in urinary exosomes from both male and female G2019S-LRRK2 mutation carriers. In CSF exosomes, the proportion of autophosphorylated pSer1292-LRRK2 was much higher than in urinary exosomes, and these levels were not different between mutation carriers and controls. Thus, there is a poor correlation between pSer1292-LRRK2 levels in urinary versus CSF exosomes. These results establish the feasibility of measuring autophosphorylated LRRK2 in CSF for tracking LRRK2 kinase inhibition in the brain in a clinical setting, and that urinary exosome analysis may be more promising for biomarker development and patient stratification than CSF exosome analysis.

Poster #47

Induction of activated T cells in brain and peripheral lymph nodes in an AAV synuclein model of Parkinson disease

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Alpha-synuclein (α-syn) accumulation is a hallmark of Parkinson disease (PD). Recently, this accumulation has been shown to lead to an immune response producing a pro-inflammatory environment in the CNS which includes infiltration of CD4 and CD8 T cells. In other CNS inflammatory disorders such as MS, the infiltration of activated T cells into the brain and spinal cord after priming in peripheral lymph nodes is important for the initiation and progression of the disease process. We sought to determine whether a similar process was at work in PD. Using an adeno associated virus (AAV) to over-express α-syn in mice and a combination of immunohistochemistry and flow cytometry, we examined the effect of abnormal brain α-syn on brain and lymph node T cell populations. AAV expressing either full-length human α-syn or GFP as a control was injected into the substantia nigra of mice. T cell populations were assessed in the brain and lymph nodes four weeks later. We found that *in vivo,* overexpression of full-length human α-syn does indeed induce substantial infiltration of activated CD3/TCR+ T cells into the substantia nigra, an effect not seen with the AAV-GFP control virus. Additionally, we observed an increase in activated CD44+ CD4 and CD8 T cells in the deep cervical lymph nodes which drain from the CNS in response to α-syn. These observations suggest that overexpression of α-syn in the brain leads to an immune response that involves α-syn dependent priming of T cells in the lymph nodes and subsequent migration into the brain parenchyma. Better understanding of this T cell response could lead to more targeted and effective immunotherapies to stop or slow the progression of PD.

Poster #48

Dissection of motivated behavior and reward: analysis of neural activity in the nucleus accumbens

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Purpose: Addiction is an increasingly prevalent problem in the United States, associated with progressively higher rates of morbidity and mortality. Exposure to drugs of abuse leads to reorganization of neural circuits and alteration of synapses, which outlive the direct effects of the drug and may contribute to addiction. The nucleus accumbens (NAc) has a significant role in motivation, pleasure, and reward, and has been identified as a key area in the development and maintenance of addiction. The present study aims to determine how neuronal activity in the NAc is altered in response to cocaine. Our central hypothesis is that administration of cocaine will increase neuron firing in the NAc, and that optogenetic photoactivation of neurons in the NAc will elicit reward-seeking behavior and drug-evoked neuroplasticity.

Methods: In order to assess how neuronal activity in the NAc is altered as a result of drug exposure, cell firing was recorded *in vivo* from electrode microarrays bilaterally implanted in the NAc of naive male Sprague Dawley rats that have been exposed to either cocaine (10mg/kg) or saline. In an additional group of animals, channelrhodopsin (ChR2) was virally expressed in the NAc and optogenetic guides were surgically implanted to determine if photostimulation of neurons in this area is sufficient for reward-related behavior.
Results: As predicted, acute cocaine exposure increased activity of a subpopulation of neurons in the NAc, independent of environment or context. Additionally, preliminary data show that photostimulation of ChR2 in the NAc core, but not in the NAc medial shell, drives motivated behavior as measured by real-time place preference.
Conclusions: By elucidating how cocaine exposure alters the activity of specific cell populations and specific neuronal circuitry involving the NAc, we may identify important mechanisms underlying the etiology of addiction and relapse, as well as propose novel targets for preventive and therapeutic interventions.

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Poster #49

Network covariance of hippocampal subfield volumes associated with healthy aging and the risk for Alzheimer's disease

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It is well established that healthy aging is associated with regional brain atrophy, which may be exacerbated by an increased risk for Alzheimer's disease (AD) with the apolipoprotein E (APOE) ε4 allele. We have previously reported regionally distributed network patterns of gray matter volume throughout the brain associated with healthy aging and APOE risk for AD (Alexander et al., 2006, 2012; Bergfield et al., 2010) using magnetic resonance imaging (MRI) and a multivariate model of regional covariance, the Scaled Subprofile Model (SSM; Alexander and Moeller, 1994). In this study, we sought to evaluate the effect of aging on the SSM network pattern of hippocampal subfield volumes in a cohort of healthy, community-dwelling middle-aged to older adults, who were screened to exclude common medical conditions of aging, including hypertension and diabetes. T1-weighted 3T volumetric MRIs were obtained in 81 healthy adults (45F/36M, mean±sd age = 66.2±10.1, mean±sd Mini-Mental State Exam = 29.2±0.9, APOE ε4 status = 22 carriers/59 non-carriers), 50 to 89 years of age. Image processing was performed using Freesurfer (v6.0) software to obtain bilateral hippocampal sub-region volumes of CA1, CA3, CA4, dentate gyrus granule cells (DG-GC), molecular layer, subiculum, presubiculum, and hippocampal tail. Total intracranial volume (TIV) was computed for each participant's native scan using SPM12. Regional network analysis was performed with SSM bootstrap re-sampling and 10,000 iterations on the TIV-adjusted hippocampal subfield volumes using the Akaike information criterion. A linear combination of the first eight SSM components was associated with increasing age in the sample ($R^2 = 0.27$, $p \leq 2.49E\text{-}3$). This regional pattern was characterized by volume reductions in bilateral DG-GC and molecular layer sub-regions with relative increases in bilateral CA3. Univariate regional analyses showed that each of the bilateral DG-GC and molecular layer sub-regions were inversely correlated with age ($p's \leq 2.86E\text{-}5$), whereas CA3 regions did not reach significance ($p's \geq 0.07$). After we controlled for age and gender, expression of the SSM pattern was greater in the APOE ε4 carriers than non-carriers ($p \leq 0.004$). The results indicate a regionally specific pattern of hippocampal subfield volumes with reductions in the vicinity of the dentate gyrus and relative preservation in the region of CA3 that is associated with healthy aging, and is further expressed to a greater extent in APOE ε4 carriers. Together, these findings support selective regional vulnerability of the dentate gyrus in the context of healthy aging and in relation to genetic risk for late onset AD.

Poster #50

Socioemotional and neural correlates of off-task thinking in young and old adults

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Recent years have brought a growing appreciation that the human mind has a propensity to wander away from the task at hand. Adults spend upwards of half their waking day cognitively disengaged from the task at hand, yet despite this high frequency, the correlates and consequences of off-task thought are poorly understood. Off-task thought may facilitate problem solving and contribute to one's sense of self-identity, but it can also fuel unhappiness and associate with psychiatric disorders. Further, little is known about how on- and off-task thoughts change in aging. Despite the well-established cognitive "positivity effect" in old age, the elderly are highly vulnerable to depression and social isolation. These gaps call for a deeper understanding of influences on cognitive and socioemotional well-being across the lifespan.

Toward this end, we explored the frequency, content, and correlates of on- and off-task thought in young (N = 42, ages 25-35, mean = 28.5) and older adults (N= 115, ages 60 – 88, mean = 70) across two contexts. First, we developed a trait questionnaire to estimate thought patterns in daily life. Second, we developed a retrospective self-report questionnaire to assess thought content during a 5 minute resting state paradigm while acquiring fMRI data to explore neural correlates of cognitive changes. Results reveal numerous differences between young and older adults, with broad consistency across the two contexts outlined above. Older adults reported less frequent internally-focused off-task thoughts (i.e., mind-wandering), but greater focus on the fixation crosshair and distraction by irrelevant external stimuli. They also displayed greater present-focused and reduced past-focused content and biases toward more positive and other-focused thoughts. Among older adults, better well-being was associated with fewer internally-focused off-task thoughts (especially negative thoughts), fewer external distractions, and more goal-oriented content and imagery. Importantly, resting state functional connectivity analyses revealed group differences in the default and frontoparietal control networks, which have been implicated in off-task thought in young adults. Overall, these findings shed light on the content, mental health correlates, and neural underpinnings of off-task thinking in young and older adults.

Poster #51

Enhanced Nrf2 expression improves neural stem cell function during a critical aging period

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Our recent studies have examined the function of rat subventricular zone (SVZ) neural stem and progenitor cells (NSPCs) during aging. This work indicates that although NSPC function continuously declines with advancing age, there is a critical time period during middle-age (13-15 mos) when a prominent reduction in NSPC survival, regeneration, and associated behavioral function (fine olfactory discrimination), occurs. We also find that this specific temporal pattern of NSPC deterioration is mediated via the reduced expression of the redox-sensitive transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2). Based on these data, in this study, we investigated whether increasing Nrf2 expression could potentially mitigate the decline in NSPC function across the identified critical middle-age period. First, we generated recombinant adeno-associated viral (rAAV2/1) vectors, to overexpress Nrf2 within endogenous NSPCs in the aging SVZ niche, and characterized their efficiency. Subsequently the Nrf2 vectors (or eGFP vectors as controls) were administered into the SVZs of aging rats, at time-points either before or after the critical period. Results indicate that animals that had received rAAV2/1-Nrf2-eGFP, before the advent of the critical middle-age period (at 12 mos), exhibited substantially improved fine olfactory discrimination abilities in comparison to animals receiving the control rAAV2/1-eGFP virus. Striatal function, measured via a beam task, was also enhanced in the Nrf2 overexpressing animals compared to controls. Additionally, histological analysis revealed that NSPC survival, proliferation, and neurogenesis in the SVZ had significantly increased upon Nrf2 overexpression. Early data also show greater NSPC migration through the rostral migratory stream, and their subsequent integration into the olfactory bulb, in Nrf2 overexpressing rats. On the other hand, Nrf2 overexpression in SVZ NSPCs after the completion of the critical period (at 21 mos) did not result in a significant improvement of NSPC activity at either cellular or behavioral levels. In summary, these data support Nrf2 pathway modulation as a potential approach to enhance aging NSPC function, and have important implications towards developing stem cell-based therapeutics for age-related neurological disorders.

Poster #52

Regional covariance patterns of white matter microstructure in healthy aging

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Diffusion tensor imaging (DTI), a non-invasive method for characterizing microstructural white matter, has been used to evaluate white matter differences in aging. Previous studies have primarily applied univariate approaches for evaluating relations between age and DTI metrics of white matter integrity, with prominent results showing associations between advancing age and decreases in fractional anisotropy (FA) and increases in mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). We applied a multivariate method, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994), to identify separate white matter regional network patterns for each diffusivity measure that optimally predicted age in a sample of 196 neurologically healthy community-dwelling older adults, ages 50-89. Additionally, we assessed the contributions of common vascular risk factors, including white matter hyperintensities (WMH), hypertension, and homocysteine, to each covariance pattern. We used TRACULA for automated probabilistic tractography to reconstruct 18 major white matter pathways and to generate estimates of FA, MD, RD, and AD. We used a multivariate model of regional network covariance, SSM, to identify regional patterns of white matter integrity associated with aging. We found distinct age-related regional patterns of white matter tracts for each diffusivity metric ($5.3E\text{-}9 \leq p \leq 0.001$). Additionally, there were no interactive effects of vascular risk factors and age on the covariance patterns. Only WMH volume showed an additive effect on the white matter integrity network patterns for FA, MD, and AD ($0.019 \leq p \leq 0.029$), whereas hypertension and homocysteine did not show contributory effects. Together, these findings suggest that in the context of healthy aging, damage to white matter microstructural tracts may differentially predict advancing age through region-specific effects and may be further influenced by macrostructural white matter lesion load.

Poster #53

Multimodal neuroimaging reveals white matter microstructure related covariance networks of subcortical gray matter volumes in healthy aging

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Healthy aging preferentially affects selected gray matter (GM) and white matter (WM) brain regions and has been widely studied using univariate analysis methods. Multivariate network analysis of multimodal magnetic resonance imaging (MRI) data may potentially improve regional characterization of age-related differences by combining information from complementary imaging modalities. Here we use this framework to investigate how differences in global WM microstructural integrity relate to regional network covariance of subcortical grey matter (SGM) volumes, including the hippocampus, amygdala, thalamus, pallidum, putamen, caudate and nucleus accumbens, and further assess how this pattern is related to age and regional white matter hyperintensity (WMH) load. T1-weighted volumetric, diffusion weighted imaging (DWI), and T2 FLAIR 3T MRI scans were obtained in 196 healthy community dwelling older adults, 50 - 89 years of age (mean±sd age = 69.8 ± 10.6; 95F/101M). Freesurfer v5.3 was used for segmenting T1 scans and extracting SGM volumes. DWI scans were processed with TRACULA and global fractional anisotropy (FA) and mean diffusivity (MD) were computed as the average of 18 major WM tracts. WMH maps were produced by automated multispectral segmentation using SPM12's Lesion Segmentation Toolbox. A lobar atlas template was used to obtain regional WMH volumes from the four major lobes. The Scaled Subprofile Model was applied to the SGM volumes to derive their regional covariance networks in relation to global mean FA and MD. The FA-related SGM network pattern accounted for 9.8% of the variance in FA, included relative reductions in bilateral thalamus with preservation of the right caudate, but was not related to age ($p = 0.73$). The MD-related SGM network pattern accounted for 18.6% of the variance in MD, exhibited volume reductions bilaterally in hippocampus and putamen with relative preservation of left caudate and right pallidum, and was positively related to age ($r^2 = 0.29$, $p = 1.1E-16$). After adjusting for age, gender, years of education and hypertension status, the FA-SGM pattern was not related to regional WMH (FDR $p > 0.14$), while the MD-SGM pattern was positively related to WMH load in the frontal ($r^2 = 0.078$, FDR $p = 9.0E-6$), temporal ($r^2 = 0.06$, FDR $p = 7.5E-5$) and parietal ($r^2 = 0.045$, FDR $p = 4.9E-4$) lobes. Together, these findings demonstrate the regionally varying impacts of differential aspects of WM integrity on subcortical GM in the context of healthy aging, providing further support for using multimodal, multivariate network analyses to more fully characterize the regionally distributed effects of brain aging.

Poster #54

Mechanistic role of brain hypometabolism and mitochondrial uncoupling in perimenopausal hot flash

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The goal of the current study is to determine the mechanism of the signature symptom of the menopausal transition, the perimenopausal hot flash. We hypothesized that loss of ovarian hormone regulation of bioenergetics in brain induces a series of adaptive responses in the brain, which are initiated by decline in glucose metabolism, followed by activation of alternative fuel sources, ketone bodies and free fatty acids, which lead to mitochondrial uncoupling and temperature dysregulation. We used the ovariectomy (OVX) rat model as a reliable and predictive inducer of temperature dysregulation. Loss of ovarian hormones in the OVX rats led to decreased uterine weight, increased body weight and a significant increase in peripheral (tail skin) temperature. Further, our analyses in the OVX rat model indicated that peripheral temperature dysregulation coincided with systemic glucose intolerance and decreased cerebral glucose metabolism (FDG-PET). We further tested our hypothesis that loss of ovarian hormones leads to disruption and uncoupling of the proton motive force-dependent energy conservation systems and the consequent dissipation of energy as heat. Results of these analyses indicated that mitochondrial respiratory control ratio (RCR) was decreased in OVX rats accompanied by increased mitochondrial uncoupling, the upregulation of mitochondrial uncoupling proteins (UCPs), and enhancement of mitochondrial fragmentation in multiple brain regions. These OVX-induced changes were completely or partially prevented by 17beta-estradiol treatment, suggesting an obligatory role of estrogen signaling in these events. Finally, to investigate the relationship between mitochondrial uncoupling in the brain and the increase in peripheral temperature, mitochondrial uncoupling was induced by 2,4-dinitrophenol (2-DNP), a mitochondrial uncoupler. Our analyses indicate that intracerebroventricular injection of 2-DNP induced sequential fluctuations in brain temperature, core temperature and tail skin temperature, with the endogenous mitochondrial uncouplers (UCP2 and UCP3) downregulated in the brain, likely a negative feedback to the 2-DNP-induced mitochondrial uncoupling. Collectively, we established the physiological and bioenergetic phenotype of a rat model of hot flash, and our findings provide new mechanistic details of hot flash by connecting loss of ovarian hormones, brain hypometabolism, mitochondrial uncoupling and dysfunction, and peripheral temperature dysregulation. This work was supported by NIA 5P01AG026572 to RDB; Project 5 to RDB.

Poster #55

Dissociation of performance in hippocampus- and prefrontal cortical-dependent tasks in aging fisher 344 rats

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It is well established that cognition and cognitive performance declines with age-related diseases, but it also declines during normative aging. Even within normal aging, there is a spectrum of performance levels at any given chronological age, where people show differing levels of behavior within a specific age, as well as across ages. This spectrum of decline is also observed in animal models. In this study, we use Fisher 344 (F344) rats of three different ages (young 6mo, middle-aged 15mo, and aged 23mo) in attempt to identify behavioral and molecular markers that may reveal clues to successful cognitive aging. All animals are tested on a thorough cognitive assessment battery to identify their level of performance on multiple domains of behavior that rely on the functional integrity of different brain regions. The first tests are the spatial and cued versions of the Morris water maze, the former relying on the function of the hippocampus, the latter is a test of visual and motor competence. These tests are followed by a spontaneous object recognition task, which relies on the function of the perirhinal cortex. A delayed-match-to-place version of the Morris water maze is then given, to test working memory that is dependent on the prefrontal cortex. Additionally, hippocampus subregion functionality is then assessed using a spatial and temporal ordering task with differing levels of interference. We used the performance level on the spatial version of the Morris water maze task to categorize each animal into a cognitive performance level of low, average, or high, within the young, middle-aged and old age groups. When we used this categorization scheme to group performance on the working memory task, this grouping did not correspond to low, average, and high performance for working memory in the middle aged and older animals, but did correspond to low, average, and high performance for working memory in the young animals. Taken together, these data suggest that beginning in middle-age, the relationship between spatial and working memory performance begins to change: different animals can exhibit a high hippocampal and low frontal cortex performance, low hippocampal and high frontal cortex performance, high performance in both, or low performance in both tasks. This is reminiscent of other data in rats (Bizon et al., 2009) and human studies (Glisky & Kong, 2008) where correlations between hippocampus- and prefrontal cortical-dependent performance is often only weakly related within individuals (Alexander et al., 2012). This suggests that more work is needed to elucidate intervention targets that will be effective for personalized optimization of cognitive aging.

Poster #56

Brain region-specific changes in melanocortin receptor expression in aged rat brain

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It has been reported that the human melanocortin 4 receptor (hMC4R) is involved in neurodegenerative disease (Shen et al., 2016). Melanotropins may protect against the progression of Alzheimer's disease (Giuliani et al., 2014). Furthermore, administration of α-MSH or its more stable analog [Nle4,D-Phe7]-α-MSH (NDP-α-MSH) has been observed to enhance learning and memory (Beckwith, et al. 1975). However, the impact of age with respect to melancortin receptor expression remains unexplored. Here we systematically investigated the expression of melanocortin receptors in brain of young (9 months) and aged (23 months) rats, who were assessed for their cognitive status in memory tasks. Six regions of the brain were extracted from each animal, including the frontal cortex + anterior midbrain, parietal cortex, cerebellum, posterior midbrain, hippocampus and occipital lobe. We collected the membrane fragments from each region of all animals in each age group, then ran a specific binding assay using iodine labelled NDP-α-MSH on a high throughput Micro Beta II radiation counter. Six samples were measured from each animal for each region, and then averaged to produce a single count for each animal in each region. All measurements were collected in a blind fashion. We discovered that melanocortin receptor expression was reduced in the aged rats in four of the six regions studied. This finding potentially opens a new window of discovery for exploring and developing new treatments for cognitive changes that arise in normal aging and in neurodegenerative disease.

Poster #57

Sparser representation of experience by aged rat lateral entorhinal cortex

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The hippocampus undergoes biological changes with age that are related to changes in memory function. Subregions of the hippocampus receive major inputs from and send backprojections to superficial and deep layers of Lateral Entorhinal Cortex (LEC), respectively. In contrast to the well-studied Medial Entorhinal Cortex (MEC), LEC neurons do not show substantial spatial selectivity in their firing patterns. Rather, LEC is thought to be involved in representing non-spatial features of experiences, such as objects and odors. The role of LEC in odor discrimination and how the corresponding neural activity may change with age remain unknown. In this study, we examined whether LEC neuronal populations are selectively activated in response to distinct odors during track running, and hypothesized that aging may alter these activity patterns and contribute to memory dysfunction. To test this, adult and aged rats were trained to run laps on a circular track in a constant environment. After training, one behavioral group (AA) experienced the same set of 6 odors around the track during two run sessions, separated by 20 minutes. A second group (AB) also had two run sessions, but the odor stimuli were distinct between the two epochs. In principal neurons, the mRNA of the immediate-early gene *Arc* is localized to discrete cellular compartments based on the time since activation. We used cellular compartment analysis of temporal activity by fluorescence *in situ* hybridization (catFISH) and confocal microscopy to visualize this time-dependent subcellular distribution of *Arc* mRNA. We identified neurons activated during the first, second, or both run sessions in superficial and deep LEC. We found that AA and AB behaviors elevated activity in LEC compared to a non-behavioral control condition. However, the population activity failed to distinguish between the distinct A and B odor experiences. This suggests that LEC neural population activity stably represents higher order features of the track-running experience regardless of altered odor input. Surprisingly, more cells reached *Arc* activation thresholds during the second epoch than the first. This may indicate that LEC circuits are sensitive to priming by similar past experience. Additionally, we report that a lower proportion of LEC neurons participated during the behavior in aged rats than in adult rats. This latter result might be explained in at least two ways: the representation of multimodal experience by LEC is either refined or reduced by aging. The question of whether a sparser network representation results in maintained, improved, or reduced behavioral function across the lifespan awaits future investigation.

Poster #58

Age-associated changes in awake hippocampal sharp-wave ripples during spatial eyeblink conditioning

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Sharp-wave ripples are brief (~70 ms) high-frequency oscillatory events that are generated in the hippocampus. Ripples that occur during rest periods following a learning experience are believed to support memory consolidation. Normal aging reduces the rate of occurrence of ripple events and reduces the oscillatory frequency of ripples during rest (Wiegand et al., 2016). Although ripples during rest have been implicated in memory consolidation, waking ripples may also be involved in short-term planning and memory recall. It is unknown how normal aging alters features of waking ripples. Accordingly, we investigated whether characteristics of waking ripple oscillations and associated single-unit activity undergo age-dependent changes in rats. Local-field and single-unit activity were recorded from the CA1 region of the hippocampus. Sharp-wave ripple events were examined in old (n = 5) and young (n = 6) F344 male rats as they performed a place-dependent eyeblink conditioning task. Comparisons between ripples occurring during rest and waking behavior and between aged and young animals revealed two effects. First, although ripples in aged rats had a significantly lower oscillatory frequency relative to young rats during rest ($p < 0.01$, t-test, n aged = 5, n young = 6), there was no difference between aged and young rats on this measure during behavior ($p = 0.83$). Second, the modulation of principal neuron firing activity by waking ripples was reduced in aged animals when compared to young rats (aged: n = 233 neurons, young: n = 167 neurons, Wilcoxson rank sum test, $p < 0.001$). Modulation was measured as the difference between the mean firing rate during the ripple compared to the mean firing rate during 100 ms intervals that preceded and followed each ripple (+/- 350 to 450 ms). Even though ripple oscillatory frequency was normalized in aged rats during behavior, modulation of single cell activity within a ripple was reduced. Given the involvement of waking ripples in memory recall, these changes in the dynamics of waking ripples could contribute to age-associated memory loss.

Poster #59

Relation of physical sport activity to regional white matter integrity in older adults

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Physical activity (PA) may have an important role in maintaining cerebral white matter (WM) integrity in healthy aging. We sought to determine whether high levels of self-reported physical sport activity are associated with better WM integrity. Self-report ratings of physical sport activity were obtained from 210 healthy older adults (M ± SD age = 70.0 ± 10.4 yrs). Participants reporting high sport activity (n=38) were compared to those with low sport activity (n=172). T1 and diffusion weighted 3T MRIs were processed using Freesurfer v5.3 and TRACULA for tractography to compute fractional anisotropy (FA) and mean (MD), radial (RD), and axial (AD) diffusivity for 18 WM tracts. ANCOVA tested age group (young-old group (YO) = 50-69 yrs; old-old group (OO) = 70-89 yrs), PA group, and interaction effects after controlling for hypertension status. No main effects for PA group (p's > 0.05) were observed across all four diffusion metrics. For FA, results revealed main effects for age group for three WM tracts ($0.003 \leq p \leq 0.006$) such that, for two tracts, the OO had lower values. All age group effects for MD, RD, and AD revealed that the OO had higher diffusion than the YO. For MD, we found age effects for all but one bilateral WM tract ($2.0E\text{-}5 \leq p \leq 0.039$). For RD, we found age effects for all but one bilateral and two individual WM tracts ($0.002 \leq p \leq 0.048$). For AD, effects for all but two bilateral and two individual WM tracts ($4.0E\text{-}7 \leq p \leq 0.047$) were observed. We found age by PA interactions for two tracts for FA, left inf. longitudinal fasciculus (ILF; $p = 0.045$) and right uncinate (UNC; $p = 0.025$). Interactions were observed for the same three tracts, ant. thalamic radiation (ATR), sup. longitudinal fasciculus-parietal (SLFP), and temporal (SLFT) bundles, bilaterally for MD ($0.016 \leq p \leq 0.04$) and in left tracts of AD ($0.007 \leq p \leq 0.037$). An interaction was observed for left ILF for MD ($p = 0.011$) and right cingulum cingulate gyrus (CCG) for AD ($p = 0.035$). For RD, interactions were observed for bilateral SLFT, left ILF, right ATR, SLFP, and UNC ($0.007 \leq p$'s ≤ 0.043). Simple effect analyses showed that within the OO, those with lower PA had lower FA for the ILF tract ($p = 0.011$). For the UNC tract, among those with low PA, the OO had lower FA ($p = 0.012$). Effects for MD, RD, and AD showed that among those with low PA, the OO had higher diffusion ($p \leq 0.002$). In the OO, those with low PA had higher diffusion in all but one tract for MD and RD and two tracts for AD ($0.002 \leq p$'s ≤ 0.043). After adding gender as an additional covariate for main and interaction effects, the regional findings were consistent. These findings suggest that high levels of PA may be an important lifestyle factor that can help to maintain WM integrity in old age.

Poster #60

Pharmacokinetics and safety profile of a single-dose administration of an estrogen receptor β-selective phytoestrogenic formulation (PhytoSERM) in peri and postmenopausal women

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Background: Of all victims of Alzheimer's disease (AD) 68% are postmenopausal women. Estrogen and hormone replacement therapies (HRT) begun at the time of menopause transition have been associated with reduced risk and delayed onset of AD. However, adverse outcomes of HRT have led to an increasing number of women declining its use but seeking non-pharmaceutical alternatives. The search for a safe approach to promote estrogenic signaling in the brain, without eliciting adverse effects, has focused on the development of tissue-selective estrogen receptor modulators (SERMs). Selective estrogen receptor-β (ER-β) targeting has been attempted in the development of therapies for a range of conditions including cognitive impairment and menopausal symptoms. PhytoSERM, a preparation of genistein, daidzein, and S-equol, has an 83-fold selective affinity for (ER-β) and may promote neuronal survival and estrogenic mechanisms in the brain without having feminizing activity in the periphery.
Objective: To assess the safety, tolerability and single-dose pharmacokinetics of the phytoSERM formulation in peri- and postmenopausal women.
Methods: Eighteen women aged 45-60 years from a 12-week clinical trial evaluating cognitive performance and vasomotor symptoms were randomly assigned to placebo, 50mg, or 100mg phytoSERM treatment groups. Plasma levels of the 3 parent phytoestrogens and their metabolites were measured before and at 2, 4, 6, 8 and 24 hours after ingestion by isotope dilution HPLC electrospray ionization tandem mass spectrometry.
Results: Plasma concentrations of genistein, daidzein and S-equol peaked at 9, 6 and 4 h, respectively for the 50mg dose, and at 6, 6 and 5 h, respectively for the 100 mg dose. The maximum concentration (C_{max}) and area under the curve (AUC) for the 3 parent compounds were greater in the 100 mg dose group indicating a dose-dependent change in concentration with the phytoSERM treatment. No adverse events were elicited.
Conclusion: The phytoSERM combination was well tolerated, appeared without adverse effects, and exhibited a favorable pharmacokinetic profile. After single oral administration of 50 and 100mg tablets of the phytoSERM formulation, the phytoestrogens genistein, daidzein and S-equol were rapidly absorbed, reached high plasma concentrations, and showed a dose proportional increase in concentration exposures in its pharmacokinetics. The formulation may prove to be advantageous in future clinical trials for several peri- and postmenopausal conditions.

Poster #61

Deficits in aged rats on the W-track continuous spatial alternation task suggest impaired hippocampal-prefrontal interactions

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The hippocampus and the PFC are part of a functional system involved in memory-guided decision making, a cognitive process particularly vulnerable to age-related decline in human and animal models of aging. Groups of young and old rats were tested on a continuous spatial alternation task (Frank *et al.,* 2000) in which they learned to alternate arm visits on a W-shaped track in order to receive a food reward. There are two interleaved components of this task: (1) an "outbound" or alternation component (working-memory) and (2) an "inbound" component, requiring the animal to remember to return to the center arm (spatial memory). The inbound component is primarily hippocampus dependent. The outbound component, in contrast, likely utilizes both the PFC to maintain a working memory of the previously visited arm, as well as the hippocampus to localize the currently rewarded position in absolute space. Rats with hippocampal lesions are impaired in learning both components of the task and show a pattern of perseverative inbound errors during initial learning (Kim & Frank, 2009). Although lesioning the hippocampus results in slower learning rates, animals are still able to reach learning criterion with time, suggesting adaptive compensation among parallel cognitive networks. Additionally, both aged rats and those with lesions to the mPFC show delayed learning on a T-maze spatial alternation task which also requires rats to maintain a working memory of the previously visited feeder (Ramos *et al.,* 2003 , Divac & Wikmark, 1975). In the present study, aged rats made more outbound errors throughout testing, resulting in significantly more days to reach learning criterion, as compared to young rats. Furthermore, while all animals were able to learn the hippocampus-dependent inbound component of the task, 4 of 6 aged animals remained at or near chance level on the outbound component, even after extended testing days. Aged rats may be more impaired on the outbound part of the task because it requires cooperation of both the hippocampus and mPFC, each of which is compromised with age. In addition, there are striking individual differences among aged animals in their ability to learn this task. The next step in the study will be to perform dual-region ensemble recordings from both the hippocampus and the mPFC while animals complete the alternation task in order to answer how age impacts network dynamics between these two regions, as well as identify the source of significant variation in performance among aged rats.

Poster #62

Temporal contiguity predicts reward association learning in bonnet macaques

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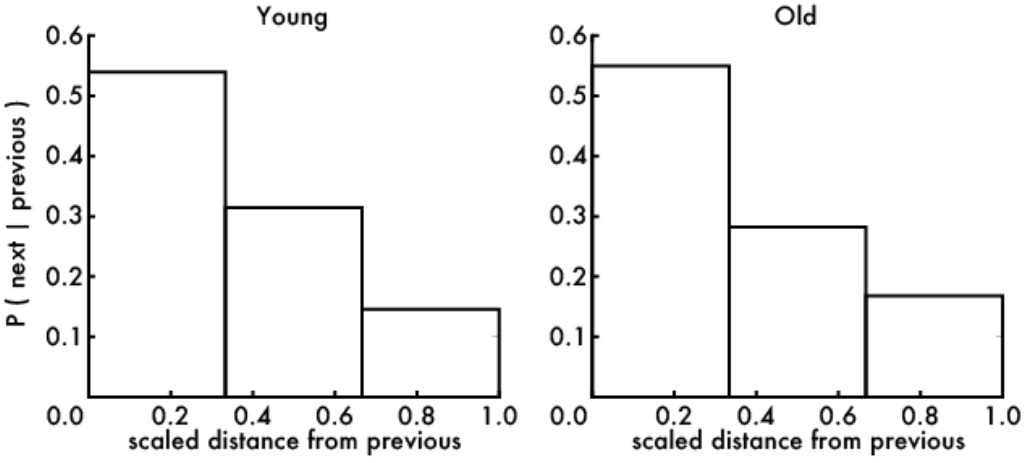
When human subjects freely recall items from a list, they are more likely to name a neighbor of the item they last recalled. This finding, known as the temporal contiguity effect, has led to the development of the "temporal context model" of memory which theorizes that temporally neighboring events share similarity in the underlying neural representations (Howard and Kahana, 2002). While this model is supported by studies examining brain activity using local field potential or functional MRI measurements in humans (Hsieh et al., 2014, Kyle et al., 2015, Manning et al., 2011), because only humans can perform free recall, the scope of research on this topic has remained limited. However, state-space models, which through Bayesian statistics can uncover the precise timing of learning, make it possible to investigate temporal contiguity in tasks that do not rely on verbal responses. Here we utilize a state-space model and new methods to calculate the conditional probabilities in a fixed-sequence, forced-choice reward association task performed by 16 bonnet macaques. The results suggest that during multiple days of association-pair learning, newly-learned pairs tend to be more temporally contiguous to recently-learned pairs than to more distant pairs in both young (10 yrs, n=7) and old (23 yrs, n=9) monkeys {see figure below}. To our knowledge, our data represent the first evidence that temporal contiguity can underlie reward association learning and extends the study of contiguity using conditional probabilities to non-verbal tasks.



Poster #63

Preserved overall basal firing rates in aged rat basolateral complex of the amygdala, but neurons from aged rats are more engaged in anticipation of rewards compared to young rats

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Decision making abilities change across the lifespan as a result of altered brain networks and the accumulation of knowledge and experience. One structure known to be important for detecting changes in value, is the basolateral complex of the amygdala (BLA). Cell numbers in BLA are preserved in aging, but there is a decrease in dopamine transmission as well as receptor density. We recently reported an increase in oscillatory power in the beta-band frequency (~20 Hz) in the BLA, coinciding with the expectation of large rewards in aged rats. We investigated the possibility that the activity of BLA neurons also differs in aged rats during discrimination learning or decision making. To better characterize the activity of BLA neurons in aging, we recorded the single-unit activity of young and aged rats during rest and as they acquired and performed decision making tasks in which reward probabilities and magnitudes were manipulated. Firing properties of BLA neurons during a 30-min rest period before the task was initiated preserved between young and aged rats. During task performance, however, we found that a greater proportion of neurons in the aged rat BLA modulated their firing following entry to the food area (about 2 seconds before reward delivery), whereas the proportion of cells was similar across age groups for all other task events (light cue, lever press and reward). The evoked activity of single neurons was then visualized using peri-event time histograms, and patterns of activation were found to vary in duration, amplitude, sign and onset time. To characterize the firing rate modulation with respect to trial parameters such as reward magnitude and probability, we applied robust statistics to assess the change in firing rate for each neuron individually (at peak firing rate). Using this method, we found that after food cup entry and reward onset, over 20% of BLA neurons in young and aged rats modulated their firing rate to reward size or reward probability, but not trial type (free vs forced choice) nor recent choice history (win/stay-lose/shift). This proportion was greater in aged rats after food cup entry (~35% vs 25%), whereas the proportions were similar across age groups after reward onset (~25%). Finally, we found that more aged rat's BLA neurons displayed greater duration evoked responses following food cup entry (mean 550ms in young and 1650ms in old) and reward onset (mean 1400ms in young and 2700ms in old). Further analyses will investigate the properties of these extended evoked responses. Overall, our results suggest that aging impacts the activity of BLA neurons primarily when animals anticipate or expect rewards, but not as they experience actual rewards.

Poster #64

A separable state-space model of learning across trials and days in an aging study in macaque monkeys

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Understanding how learning and memory changes with normal aging is increasingly important as the aged population grows. Obtaining objective measures of behavioral changes associated with aging is challenging since learning is dynamic, varies considerably between individuals, and observations are frequently binary. We introduce a method for analyzing binary response data from young and aged macaque monkeys performing tasks across multiple days that enables us to compare within-day and across-day performance. The data set comprises 14 female bonnet macaques–6 young and 8 old animals–performing a reversal learning task in the form of a modified Wisconsin Card Sort Task. Conventional methods to analyze these data are unable to capture their inherent two-dimensional nature, fail to distinguish groups, and cannot adequately assess inter-individual differences in performance. We propose a separable two-dimensional (2D) random field (RF) model of the binary data from these experiments, wherein the joint probability of a monkey's correct performance as a function of task and trial depends on two latent Markovian state sequences that evolve separately but in parallel. In this instantiation of the model, we use a Laplacian random walk prior for the monkey-dependent latent process that characterizes the dynamics of a monkey's learning across days. This captures abrupt transitions and allows the detection of change points in the observations across days due to reversal. A Monte Carlo Expectation-Maximization (EM) algorithm is used to maximize the marginal likelihood of the data from the separable 2D RF, followed by a Maximum a Posteriori estimation algorithm for change point detection. The method results in an estimate of performance within a day for each age group, and a learning rate across days for each monkey. We show that as a group the older monkeys find the tasks harder than the young monkeys, and that the cognitive flexibility of the younger group is higher. We further demonstrate the efficacy of the model by using the resulting estimates of performance as features for clustering the monkeys into two groups. The clustering results in two groups that, for the most part, coincide with those formed by the age groups. Simulation studies suggest that clustering based on the model's results captures inter-individual differences in performance levels, which allows us to identify "high performing" old monkeys. These analyses, therefore provide a method to estimate an animal's behavioral/cognitive age independent of chronological age.

Poster #65

Associations between cardiovascular risk factors and cognition in aging Hispanics compared to non-Hispanic whites

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The presence of one or more cardiovascular risk factors is associated with poorer cognitive abilities (e.g., processing speed, executive functions). In cohorts of Hispanics and non-Hispanic Whites with cardiovascular risk factors, Hispanics tended to live longer than Whites. This finding, known as the Hispanic paradox, is robust. However, it is unclear whether the Hispanic paradox confers protection on cognitive processes. The present study compared relationships between cardiovascular risk and cognition in late-middle age and older Hispanics (n = 67) and non-Hispanic Whites (n = 67) selected from the National Alzheimer's Coordinating Center (NACC)* database. Participants included healthy controls (n = 90) and individuals with mild cognitive impairment (n = 44). Hispanics and non-Hispanic Whites were matched on age (50-94 years, mean age = 72 years), gender, cognitive status (i.e., cognitively healthy versus MCI), hypertension, and apolipoprotein e4 status. Hispanics had higher body mass index (BMI) and fewer years of education, on average, than Non-Hispanic Whites. A neuropsychological battery of tests was administered to all participants. Tests of interest were Forward Digit Span, Backward Digit Span, Logical Memory Long Delay Recall, phonemic fluency (F-A-S), semantic fluency (Animals), and the Boston Naming Test. In SPSS, the general linear models tested if cardiovascular risk factors influenced cognition differentially for Hispanics compared to Non-Hispanic Whites, controlling for age and education. Associations between cardiovascular risk and cognition differed between Hispanics and Non-Hispanic Whites. These risk factors predicted poorer cognition in Hispanic individuals but not Non-Hispanic Whites, particularly on measures of executive functions, including working memory (Backward Digit Span) as well as semantic fluency (Animals). No main effects of hypertension or BMI were detected. Taken together, cardiovascular health influenced cognition among Hispanics to a greater degree than non-Hispanic Whites. This finding is contrary to the notion of a Hispanic Paradox-like protection on cognitive processes.

Poster #66

PhytoSERM for the management of menopause-associated vasomotor symptoms: effect of APOE genotype and mitochondrial haplogroup

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PhytoSERM is a selective estrogen receptor beta (ERβ) modulator comprised of three clinically relevant phytoestrogens: genistein, daidzein, and equol. Earlier *in vitro* and *in vivo* studies demonstrated neuroprotective effect of PhytoSERM, without side effect on the reproductive system. In a mouse model of hot flash, 8-week PhytoSERM diet prevented surgical menopausal-induced rise in tail temperature. In the present study evaluating safety and efficacy of PhytoSERM for menopause-associated hot flashes (ClinicalTrial.gov ID: NCT01723917), 44 post-menopausal women aged 48 to 58 years old with a vasomotor symptom such as hot flash and a memory complaint were included. Participants were randomized into placebo (N=16), 50mg (N=17), or 100mg (N=11) daily dosage groups. Frequency and severity of hot flash were self-reported throughout the 12-week trial period. Changes in hot flash frequency within each treatment group were analyzed using non-parametric paired t-test between week 1 and week 12, and changes among treatment groups were analyzed using non-parametric ANOVA followed by unpaired t-test. Results were then stratified based on the APOE genotype and mitochondrial haplogroup of the participants. At week 12, participants on both the 50mg and the 100mg PhytoSERM groups had significantly lower hot flash frequencies compared to week 1. However, only the 50mg group demonstrated significant reduction compared to the placebo group, supporting 50mg daily as a more effective dosage for management of hot flash. When stratified by APOE genotype, non-APOEε4 carriers on 50mg group had significantly reduced hot flash frequencies compared to those from the placebo group. APOEε4 carriers on 50mg of PhytoSERM also had a trend of reduced hot flash frequency, but failed to reach statistical significance, likely due to limited sample size. When stratified by mitochondrial haplogroups, haplogroup H on 50mg of PhytoSERM had significantly reduced hot flash frequency compared to those on placebo, whereas non-H haplogroups had a trend of reduction but failed to reach statistical significance. Collectively, daily treatment of PhytoSERM at 50mg significantly reduced hot flash frequency in post-menopausal females, with non-APOEε4 carriers and haplogroup H more responsive to the treatment. A larger cohort is necessary to further identify and confirm responders based on APOE genotype and mitochondrial haplogroups.

Poster #67

Dynamic expression of RNA stress granule components in aging brains: from flies to rats

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RNA stress granules are dynamic cytoplasmic structures that assemble in response to various cellular insults. In the process, these non-membrane bound organelles sequester specific mRNAs causing inhibition of translation initiation, with the goal of protecting the cell from spending precious resources during times of stress. Upon stress removal, RNA stress granules disassemble and translation is reinitiated. These dynamic changes in RNA stress granules have been linked mechanistically to age-related neurodegenerative diseases suggesting that they may be playing key roles in the aging process. Despite some existing reports that translation inhibition changes with aging, it remains unclear whether RNA stress granules are undergoing dynamic changes as organisms grow older. To shed light on this question, we began by profiling the expression of RNA binding proteins associated with RNA stress granules including TIAR, PABP, FMRP, Gcn2 as well as the translation initiation factor eIF2alpha in aging fly and rat brains. Analyses of both transcript and protein expression of these RNA stress granule/translation initiation markers indicate dynamic changes in aging fly and rat brains. While Gcn2 and phosopho-eIF2alpha expression decline, there is an increase in TIAR levels with age. In addition, the expression of TAR DNA binding protein (TDP-43), a key RNA binding protein implicated in neurodegeneration exhibits a reduction in expression in both fly and rat brains, during aging. These findings support the hypothesis that RNA stress granules undergo dynamic changes during aging. Current experiments including polysome fractionations and expression profiling are aimed at elucidating the role of cellular stress responses in aging brains from the perspective of RNA stress granules.