The Evelyn F. McKnight Brain Research Foundation Poster Reception

The Westin San Diego Gaslamp Quarter
San Diego Ball Room
910 Broadway Circle
San Diego, CA 92101

Sunday, November 4th, 2018
5:00 p.m. – 7:00 p.m.

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

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MBRF Poster Session Author and Title List

University of Miami

Poster #1) J. BARTER, A. RANI, A. KUMAR, T. C. FOSTER. "Adulthood infections alters synaptic gene transcription and contributes to age-related memory loss"

Poster #2) M. PINTO, U. D. VEMPATI, F. DIAZ, S. PERALTA, C. T. MORAES. "Lack of cytochrome c in adult forebrain neurons in vivo leads to a decrease in cytochrome c oxidase, increased oxidative stress but no overt cell death"

Poster #3) A. P. RAVAL, W. J. MORENO, O. FURONES-ALONSO, T. RUNDEK, W. D. DIETRICH, H. M. BRAMLETT. "Monitoring post-stroke frailty in nicotine exposed female rats"

Poster #4) J. RICE, L. CAHALIN, D. CORP, A. SWAROWSKY, B. E. LEVIN, T. RUNDEK, J. GOMES-OSMAN, K. MCINERNEY. "Timed up-and-go performance and dual-task effects are correlated with distinct neuropsychological measures of executive function in healthy older adults"

Poster #5) J. RICE, D. CORP, A. SWAROWSKY, J. GOMES-OSMAN. "Dual-task performance is related to a neurophysiological measure of plasticity in individuals with memory disorders"

Poster #6) J. RICE, K. MCINERNEY, B. E. LEVIN, T. P. MORRIS, D. CABRAL, T. RUNDEK, J. GOMES-OSMAN. "Effects of a 4-week aerobic exercise intervention on TMS neuroplasticity measures and cognition in healthy sedentary adults: an ongoing pilot study"

Poster #7) A. CHOI, H. ZHONG, A. BARRIENTOS. ""Biogenetic features and function of the mitochondrial ribosome in health and mitochondrial encephalomyopathies"

Poster #8) K. M. SANDERS, T. AKIYAMA. "Anxiety-like behavior and Fos expression in amygdala elicited by itch mediators in mice"

University of Florida

Poster #9) A. R. HERNANDEZ, C. M. HERNANDEZ, K. T. CAMPOS, L. M. TRUCKENBROD, Q. P. FEDERICO, B. M. MOON, J. A. MCQUAIL, A. P. MAURER, J. L. BIZON, S. N. BURKE. "Nutritional ketosis enhances cognitive resilience in young and aged rats"

Poster #10) C. M. HERNANDEZ, C. A. ORSINI, C. C. LABISTE, A. WHEELER, T. W. TEN EYCK, M. M. BRUNER, S. M. SINGHAL, C. J. FRAZIER, B. SETLOW, J. L. BIZON. "Aged rats do not use basolateral amygdala during outcome evaluation in an intertemporal choice task"

Poster #11) S. A. JOHNSON, S. M. TURNER, K. N. LUBKE, K. E. FERTAL, A. P. MAURER, J. L. BIZON, S. N. BURKE. "Hippocampal, perirhinal, and lateral entorhinal contributions to mnemonic discrimination in young and aged rats"

Poster #12) A. KUMAR, T. C. FOSTER. "Both GluN2A and GluN2B contribute to the induction of the redox-mediated potentiation of NMDA receptor synaptic function at CA3-CA1 hippocampal synapses of aged animals"

Poster #13) D. G. LAMB, T. S. GARMAN, S. RAMIREZ, A. CRIDER, M. M. BRUNER, E. W. DIRR, F. DELGADO, K. P. OLCZAK, A. P. MAURER, K. J. OTTO, S. N. BURKE, B. SETLOW, J. L. BIZON. "Effects of vagus nerve stimulation on selective attention in Brown Norway rats"

Poster #14) G. SMITH, A. RANI, A. KUMAR, T.C. FOSTER. "Investigation of age-related impairment in pattern separation employing modified version of water maze beacon task"

Poster #15) T. W. TEN EYCK, C. M. HERNANDEZ, J. A. MCQUAIL, M. M. BRUNER, C. C. LABISTE, A. WHEELER, B. SETLOW, J. L. BIZON. "Altered GABAB receptor signaling in basolateral amygdala may contribute to age-associated differences in intertemporal choice"

Poster #16) L. M. TRUCKENBROD, A. R. HERNANDEZ, J. E. REASOR, K. T. CAMPOS, Q. P. FEDERICO, K. E. FERTAL, K. N. LUBKE, S. A. JOHNSON, B. J. CLARK, A. P. MAURER, S. N. BURKE. "Dissociable effects of advanced age on prefrontal cortical and medial temporal lobe ensemble activity"

Poster #17) A. WHEELER, C. M. HERNANDEZ, C. A. ORSINI, T. W. TEN EYCK, C. C. LABISTE, B. SETLOW, J. L. BIZON. "Female rats show greater impulsive choice than males in an intertemporal choice task"

Poster #18) B. YEGLA, T. FOSTER, A. KUMAR. "Frontal upregulation of serine racemase alters cognitive flexibility in middle age rats"

University of Alabama at Birmingham

Poster #19) K. ABIRAMAN, L. T. STEWART, L. L. MCMAHON. "Elevated O-GlcNAcylation depresses inhibitory transmission recorded from granule cells in the rat dentate gyrus"

Poster #20) A. E. ARRANT, A. J. FILIANO, A. R. PATEL, M. Q. HOFFMANN, N. R. BOYLE, S. N. KASHYAP, V. C. ONYILO, A. H. YOUNG, E. D. ROBERSON. "The role of neuronal and microglial progranulin deficiency in FTD- and NCL-like pathology"

Poster #21) A. F. BARTLEY, K. ABIRAMAN, L.T. STEWART, M. IQBAL HOSSAIN, D. M GAHAN, A. KAMATH, M. K. BURDETTE, S. ANDRABE, S. H. FOULGER, L. E. DOBRUNZ, L. L. MCMAHON. "Inorganic scintillators are biocompatible with neuronal and circuit function"

Poster #22) D. BHATTACHARYA, A. F. BARTLEY, Q. LI, L. E. DOBRUNZ. "Reducing inhibition improves E/I balance and hippocampal circuit function in PGC-1α null mice"

Poster #23) N. V. N. CARULLO, R. C. SIMON, K. D. BUNNER, A. SALISBURY, J. S. REVANNA, K. E. SAVELL, F. A. SULTAN, J. J. DAY. "Enhancer RNAs are necessary and sufficient for gene transcription and neuronal function"

Poster #24) R. B. CREED, L. L. MCMAHON, M. S. GOLDBERG. "Analysis of cortico-striatal glutamatergic transmission in PINK1 KO rats"

Poster #25) L. L. FLEMING, W. K. BURGE, D. K. DECARLO, K. M. VISSCHER. "Visual network modularity in patients with central vision loss"

Poster #26) S. FOX, L. VOLPICELLI-DALEY, R. COWELL. "Defining Cellular identity and cell-specific expression changes in the pre-formed fibril model of Parkinson Disease"

Poster #27) A. M. GOODMAN, L. L. MCMAHON. "Noradrenergic denervation-supersensitivity in the TgF344-AD rat driven by β-adrenergic receptors"

Poster #28) K. M. GREATHOUSE, B. D. BOROS, M. GEARING, J. H. HERSKOWITZ. "Dendritic spine remodeling accompanies Alzheimer's disease pathology and genetic susceptibility in cognitively normal aging"

Poster #29) R. M. HAUSER, C. E. WALLS, K. MCINERNEY, S. C. SINT JAGO, R. G. SANCHEZ, F. D. LUBIN. "G9a-mediated heterochromatin rearrangement in the dentate gyrus during epileptogenesis"

Poster #30) B. W. HENDERSON, S. V. BACH, J. J. DAY, J. H. HERSKOWITZ. "RhoA-associated kinases ROCK1 and ROCK2 mediate amyloid-β induced synaptic degeneration in Alzheimer's disease"

Poster #31) K. JOYCE, K.PATEL, L. MCMEEKIN, D. CROSSMAN, R. COWELL. "Erralpha mediates pgc1alpha regulation of metabolism targets in neuronal culture"

Poster #32) Q. LI; L. E. DOBRUNZ. "Endogenous neuropeptide Y release attenuates long-term potentiation in the temporoammonic pathway of hippocampus"

Poster #33) S. J. MABRY, J. I. AGUILAR, A. SHEKAR, H. MATTHIES, A. GALLI. "Phosphatidylinositol (4,5)-bisphosphate coordinates functional interactions in the dopamine transporter to promote amphetamine preference"

Poster #34) N. MCCARTHY, W.LI, L. POZZO-MILLER. "Dopaminergic fibers from the locus coeruleus indirectly modulate cerebellar Purkinje cells through Bergmann glia activation"

Poster #35) M. PHILLIPS, L. POZZO-MILLER. "Ventral hippocampal inputs to the mPFC regulate social memory"

Poster #36) M. RICH, J. SHERWOOD, Y. BAO, F. D. LUBIN, M. BOLDING. "Focused ultrasound blood brain barrier opening mediated delivery of MRI-visible nanoclusters for noninvasive neuromodulation with spatiotemporal precision"

Poster #37) J. R. ROTH, T. J. RUSH, S. J. THOMPSON, O. A. STATON, J. N. COCHRAN, E. D. ROBERSON. "Tau-SH3 interactions are critical for amyloid-β toxicity in primary neurons"

Poster #38) R. G. SÁNCHEZ, R. R. PARRISH, R. LOCKHART, S. BUCKINGHAM, K. NAKAO, T. EID, D. ROSS, R. ROBERTS, R. MCCULLUMSMITH, J. KING, K. RILEY, F. D. LUBIN. "Increasing O-GlcNAc levels alters DNA methylation and reduces epileptiform activity"

Poster #39) K.E. SCHOONOVER, S. L. QUEERN, S. E. LAPI, R. C. ROBERTS. "Impaired copper transport in schizophrenia results in a copper-deficient brain state: a new side to the dysbindin story"

Poster #40) S. C. SINT JAGO, F. D. LUBIN. "Exercise effects on an experimental rodent model of temporal lobe epilepsy"

Poster #41) R. UNDERWOOD, B. WANG, T. YACOUBIAN. "Rab27b modulates alpha-synuclein release and toxicity"

Poster #42) Y. VOSKOBIYNYK, J. COCHRAN, T. RUSH, J. ROTH, M. WAQAS, E. D. ROBERSON. "The Alzheimer's disease risk gene BIN1 regulates network hyperexcitability"

Poster #43) C. K. WALKER, B. D. BOROS, K. M. GREATHOUSE, K. A. CURTIS, R. RAMDAS, J. H. HERSKOWITZ. "Dendritic spine pathology links tauopathy mouse models to Alzheimer's disease"

University of Arizona

Poster #44) P. K. BHARADWAJ, L. A. NGUYEN, G. A. HISHAW, T. P. TROUARD, J. R. MOELLER, C. G. HABECK, G. E. ALEXANDER. "Relation of white matter lesion load to cortical gray matter thickness in healthy aging"

Poster #45) R. D. BRINTON, L. DO, A. S. BERNSTEIN, A. MISHRA, F. YIN, M. K. DESAI, T. P. TROUARD. "Effect of sex and ApoE genotpye on regional brain volumes and white matter integrity in mice using high resolution MR imaging"

Poster #46) L. M. BUSTOS, A. CACCAMO, C. BRANCA, I. S. PIRAS, E. FERREIRA, M. J. HUENTELMAN, W. S. LIANG, B. READHEAD, S. ODDO. "RIPK1 regulatory activity in Alzheimer's disease"

Poster #47) N. J. CAREY, M. A. ZEMPARE, C. J. NGUYEN, K. M. BOHNE, M. K. CHAWLA, S. SINARI, M. J. HUENTELMAN, D. BILLHEIMER, C. A. BARNES. "Age-dependent correlation between spatial and working memory does not extend to object recognition"

Poster #48) S. CHEN, N. KUMAR, Z. MAO, T. WANG, R. SITRUK-WARE, R. D. BRINTON. "Chronic exposure to the therapeutic progestin nestorone promotes neurogenesis: Implications for sustaining regeneration in female brain"

Poster #49) A. COMRIE, J. P. LISTER5, M. K. CHAWLA, C. A. BARNES. "Lateral but not Medial Entorhinal Cortex population representations become more sparse with age"

Poster #50) N. M. DE LA PENA, D. T. GRAY, L. UMAPATHY, S. N. BURKE, T. P. TROUARD, C. A. BARNES. "Tract-specific white matter correlates of age-related reward devaluation deficits in macaque monkeys"

Poster #51) M. K. DESAI, R. W. IRWIN, M. PRAJAPATI, K. PATHAK, P. PIRROTTE, R. D. BRINTON. "Allopregnanolone restores cognitive function in APOE4+ females and males and promotes metabolism of fuels required for ATP generation"

Poster #52) R. J. ECK, M. K. CHAWLA, B. SIDDEGOWDA, N. J. CAREY, M. A. ZEMPARE, C. J. NGUYEN, C. A. BARNES, D. C. ZARNESCU. "Dynamic expression of RNA stress granule components in behaviorally characterized young, middle aged and old rats"

Poster #53) M. FRANCHETTI, P. K. BHARADWAJ, L. A. NGUYEN, Y. C. KLIMENTIDIS, G. HISHAW, T. P. TROUARD, D. A. RAICHLEN, G. E. ALEXANDER. "Relation between physical sport activity and white matter hyperintensity volume in older adults"

Poster #54) D. T. GRAY, S. N. BURKE, J. R. ENGLE, L. UMAPATHY, T. P. TROUARD, C. A. BARNES. "Thalamocortical white-matter integrity and the relationship between auditory function and cognitive decline in aged macaque monkeys"

Poster #55) S. V. KOEBELE, J. M. PALMER, B. HADDER, R. MELIKIAN, C. FOX, I.M. STROUSE, D. DENARDO, C. GEORGE, E. DAUNIS, H. A. BIMONTE-NELSON. "Hysterectomy with ovarian conservation uniquely impacts cognition and serum hormone profiles in a rat model"

Poster #56) C. KYLE, J. STOKES, J. MELTZER, M. R. PERMENTER5, J. A. VOGT, A. D. EKSTROM, C. A. BARNES. "Convolutional neural networks for fast and accurate 3D reconstruction of histological sections"

Poster #57) A. W. LESTER, C. J. BLUM, A. J. KAPELLUSCH, C. A. BARNES. "Aged-related impairments in spatial reference frame updating"

Poster #58) Z. MAO, F. YIN, Y. SHANG, R. BRINTON. "Hormone loss and intervention initiated at different endocrine status differentially regulate brain bioenergetic function: Implications for Alzheimer's disease"

Poster #59) A. MISHRA, F. YIN, Z. MAO, Y. SHANG, L. DO, T. P. TROUARD, R. D. BRINTON. "Sex differences in metabolic and inflammatory aging in humanized APOE-ε4 knock-in rat brain"

Poster #60) J.-M. MIZELL, S. WANG, M. FRANCHETTI, W. KEUNG, M. H. SUNDMAN, Y.-H. CHOU, G. E. ALEXANDER, R. C. WILSON. "Differential effects of healthy aging on directed and random exploration"

Poster #61) I. S. PIRAS, M. D. DE BOTH, A. L. SINIARD, L. IANOV, M. K. CHAWLA, A. RANI, A. J. KENNEDY, J. J. DAY, A. KUMAR, J. D. SWEATT, T. C. FOSTER, C. A. BARNES, M. J. HUENTELMAN. "Changes in whole transcriptome in hippocampus sub-regions of aged rats"

Poster #62) A. V. PRAKAPENKA, R. NEELEY, C. BERNS-LEONE, S. NORTHUPSMITH, V. L. PEÑA, A. A. GEORGE, R. MELIKIAN, S. PATEL, D. S. LADWIG, R. HIROI, A. L. MANN, M. J. VALENZUELA SANCHEZ, R. W. SIRIANNI, H. A. BIMONTE-NELSON. "Behavior and brain: uncovering relationships between 17-beta-estradiol dose, spatial memory performance, and protein expression in the brain of middle aged ovariectomized rats"

Poster #63) W. PYON, D.T. GRAY, S. ASHFORD, C.A. BARNES. "A direct comparison of dye- and imaging-based removal of lipofuscin-induced autofluorescence from primate brain tissue"

Poster #64) Y. SHANG, J. BERGHOUT, Y. LUSSIER, F. YIN, R. D. BRINTON. "Perimenopausal aging brain is characterized by a bioenergetic-inflammatory transition state that indicates Alzheimer's vulnerability"

Poster #65) J. S. TALBOOM, A. K. HABERG, M. DE BOTH, M. NAYMIK, A. L. SINIARD, L. RYAN, E. L. GLISKY, M. J. HUENTELMAN. "First degree family history of Alzheimer's disease influences paired associates performance and is modified by apolipoprotein e genotype, heart disease, and smoking"

Poster #66) A. TERRAZAS, M. ZEMPARE, N. J. CAREY, K. M. BOHNE, L. DO, T. P. TROUARD, P. F. WORLEY, C. A. BARNES. "NPTX2 knockout rats: a novel model for protection of synaptic function in aging and disease"

Poster #67) E. VAN ETTEN, P. K. BHARADWAJ, L. A. NGUYEN, G. A. HISHAW, T. P. TROUARD, G. E. ALEXANDER. "Hippocampal mediation of subjective memory complaints differs by hypertension status in healthy older adults"

Poster #68) T. WANG, J. YAO, C. M. SOLINSKY, S. CHEN, R. D. BRINTON. "Allopregnanolone rescues mitochondrial dysfunction in ovariectomized triple-transgenic Alzheimer's mouse brain and familial Alzheimer's neural stem cells"

Poster #69) Y. WANG, C. SOLINSKY, G. HERNANDEZ, L. SCHNEIDER, R. D. BRINTON. "Combining mitochondrial haplogroup, APOE genotype, and sex as a predictive responder identifier to regenerative therapeutic allopregnanolone for Alzheimer's disease"

Poster #70) V. E. Woner, J. M. Palmer, S. V. Koebele, I. M. Strouse, M. N. Willeman, V. L. Pena, W. Winslow, A. Caccamo, A. Oddo, H. A. Bimonte-Nelson. "An evaluation of short-term and long-term ovarian hormone deprivation in the APP/PS1 mouse model of Alzheimer's disease"

Poster #71) T. YE, M. J. BARTLETT, T. FALK, S. L. COWEN. "L-DOPA-induced striatal gamma oscillations split into low- and high-frequency components following ketamine exposure in an animal model of L-DOPA-induced dyskinesia"

Poster #72) F. YIN, M. DESAI, Y. SHANG, Y. WANG, Z. MAO, A. MISHRA, R. D. BRINTON. "Impact of APOE genotype on the sex differences in bioenergetics and Alzheimer's risks in aging mouse brain"

Inter-Institution

Poster #73) D. A. RAICHLEN, P. K. BHARADWAJ, M. K. FRANCHETTI, S. SIMS, R. F. REZAEI, S. MERRITT, C. J. JESSUP, E. S. PORGES, D. GELDMACHER, G. A. HISHAW, N. ALPERIN, T. P. TROUARD, V.G. WADLEY, B. E. LEVIN, A. J. WOODS, T. RUNDEK, K. VISSCHER, R. A. COHEN, G. E. ALEXANDER. "Relation of physical activity to regional maps of cortical gray matter volume in the healthy oldest old: findings from the McKnight Brain Aging Registry"

MBRF Sponsored Abstracts at the 2018 Society for Neuroscience Conference

Ralph Sacco, M.D.
Executive Director

Tatjana Rundek, M.D., Ph.D.
Scientific Director
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Poster #1

Adulthood infections alters synaptic gene transcription and contributes to age-related memory loss

J. BARTER, A. RANI, A. KUMAR, T. C. FOSTER.
University of Miami, Miami, FL

Early-life events (inflammation, stress) can act through epigenetic mechanisms to promote the emergence of pathological phenotypes, later in life. As such, early-life events may contribute to individual variability in age-related cognitive decline. This study was designed to determine if infections during adulthood confers cognitive vulnerability with advancing age. For this study, male 6 month old Fischer 344 X Brown Norway hybrid rats were injected once a week for 7 weeks with lipopolysaccharide (LPS; 1 mg/kg) or control (n=8 per group). At 12 months of age, animals were tested on the episodic version of the spatial water maze task. At this time point (i.e. 6 months post-treatment), no effect of treatment was observed for cognitive performance. In contrast at 18 months of age, a tendency (p=0.061) for a treatment effect was observed for episodic spatial memory. A trend (p=0.06) for an LPS mediated impairment was also observed for another hippocampal-dependent task, inhibitory avoidance, at 18 months of age. Following behavioral characterization at 18 months of age, we performed next-generation sequencing on the CA1 region of the hippocampus to understand the mechanisms behind these behavioral differences. Transcriptional analysis revealed that 202 genes were upregulated with LPS treatment. Gene cluster analysis indicated upregulation of genes for biosynthetic process (1.2E-2). There were 372 genes that were downregulated due to prior LPS treatment. Specific genes that were downregulated with treatment included Camk2b, mTOR, and Nsmf, which are known to mediate neuronal plasticity. Further, enrichment analysis for downregulated genes indicated decreased expression of genes linked to the glioma KEGG pathway (4E-02), the dendrite (29 genes; 5.9E-3), postsynaptic density (16 genes; 2.1E-3), and histone modification (21 genes; 2.8E-2). This data suggests that infections during adulthood can interact with aging leading to long-term negative effects on transcription and/or cognitive performance. Due to the long-term nature of the effects, as well as altered gene expression linked to histone modification, we speculate that the differential expression of mRNA may occur through an epigenetic mechanism. Current studies are increasing the number of animals in the study and testing the idea that the interaction of age and inflammation on gene expression involves epigenetic mechanisms.

Poster #2

Lack of cytochrome c in adult forebrain neurons in vivo leads to a decrease in cytochrome c oxidase, increased oxidative stress but no overt cell death

M. PINTO, U. D. VEMPATI, F. DIAZ, S. PERALTA, C. T. MORAES.
University of Miami, Miami, FL

Background: Cytochrome c (Cyt c), a heme-containing protein present in the mitochondria, has a critical function in both respiration and apoptosis. Consistent with these vital functions, somatic Cyt c mouse knockout is embryonically lethal.Methods: In order to investigate the sensitivity of postnatal neurons to Cyt c functions, we developed a conditional neuron-specific knockout model. Neuron-specific Cyt cKO mouse (nCytcKO) was created by crossing the floxed Cyt c mouse with a CamKII-a cre transgenic mouse, which deletes the floxed alleles post-natally.Results: nCytcKOmice were normal at birth but developed an abnormal phenotype at 2 months of age with weight loss, tremor, decreased sensorimotor coordination and early death between 3-4 months. Histological analysis did not show major neuronal degeneration. Analyses of oxidative phosphorylation showed a specific reduction in complex IV levels. Markers of oxidative stress were also increased suggesting reverse electron transfer involvement in the pathomechanism. Conclusions: This novel model showed that complex IV levels are modulated by Cyt c levels. It also showed that decreased Cyt c in neurons lead to severe behavioral abnormalities and premature death without neuronal loss or inflammation.

Poster #3

Monitoring post-stroke frailty in nicotine exposed female rats

A. P. RAVAL, W. J. MORENO, O. FURONES-ALONSO, T. RUNDEK, W. D. DIETRICH, H. M. BRAMLETT.
University of Miami, Miami, FL

Cigarette smoking is a preventable risk factor for stroke, which is a leading cause of death and disability worldwide. Stroke disproportionately kills more women than men. Among women smokers, the risk of stroke remains high even at a young age. Smoking is a predictor of frailty, and pre-stroke smoking is associated with increased post-stroke frailty and even transient ischemic attacks that are characterized by mild ischemic episodes can result in a woman becoming frail. Frailty is characterized by an increased vulnerability to acute stressors and the reduced capacity of various bodily systems due to age-associated physiological deterioration. Although frailty is associated with increased in-hospital mortality, poorer outcome at discharge, and decreased likelihood of being discharged to the home, the prevention and treatment of smoking and stroke-associated frailty remains unaddressed. The ability to quantify frailty before and after stroke in an animal model will add to our understanding of frailty-related precursors to vascular disease. Studies performed in laboratory animals and humans support that whole body vibration (WBV) reduces or reverses pathological remodeling of bone and lessens frailty-related physiological deterioration. Adult female rats were exposed to nicotine (16 days) and to stroke by transient middle cerebral artery occlusion (tMCAO) and randomly assigned to either WBV(40 Hz; for twice a day, 5 days/week for 30 days) or control groups. We monitored the frailty index (FI) prior to and 1 month after tMCAO alone or in combination with WBV. The FI was composed of the following criteria: 1) activity levels, 2) hemodynamic measures, 3) basic metabolic status, and 4) cognitive performance of rats. Animals were sacrificed on the 30th day of WBV treatment, and brain tissue was harvested for histopathological analysis. The post-ischemic WBV intervention improves frailty parameters, reduces brain damage, and reduces frailty in control female rats, but not in the nicotine-exposed group. This suggests that WBV may be a potential therapy to reduce post-ischemic frailty and improve functional and cognitive outcomes after stroke in women. Results of this study define the frailty criterion that can be employed for future studies.

Poster #4

Timed up-and-go performance and dual-task effects are correlated with distinct neuropsychological measures of executive function in healthy older adults

J. RICE, L. CAHALIN, D. CORP, A. SWAROWSKY, B. E. LEVIN, T. RUNDEK, J. GOMES-OSMAN, K. MCINERNEY.
University of Miami, Miami, FL

Background:
Performance on the timed up-and-go (TUG), a measure of functional mobility, is related to mental function in healthy active adults. The single-task TUG is associated with general cognition, while a cognitive dual-task TUG is uniquely related to executive function and attentional capacity. However, it is not clear how different speeds (self-selected vs fast) and patterns of dual-task effects (DTE) during the TUG are related to neuropsychological tests of executive function, in sedentary adults.
Purpose:
The primary purpose of this study was to investigate the relationship between neuropsychological performance and TUG performance under normal, fast, and dual-task (DT) conditions in healthy sedentary adults. The secondary purpose was to investigate the relationship between DTE on both the cognitive and motor tasks in the TUG-DT condition and neuropsychological performance.
Methods:
We enrolled 13 sedentary older adults (59.2±5.2 years, 5 males) with sedentary defined as performing physical exercise < twice in the past two months. Attention and executive function were assessed using the Stroop, Delis-Kaplan Executive Function System (DKEFS) verbal fluency, and the Repeated Battery for the Assessment of Neuropsychological Status (RBANS) digit span and coding. The TUG battery included 2 trials each of a self-selected pace, fast pace, and dual-task TUG (TUG-self, TUG-fast, and TUG-DT respectively). The secondary cognitive task was serial-7 subtractions, with correct response rate measured in sitting to assess baseline single-task performance. The DTE was calculated for both motor and cognitive performance (DTE-TUG, DTE-response) with a negative value indicating a decrement in performance (DT-cost). Spearman's rho was used to investigate the relationship between cognitive performance measured by neuropsychological testing and TUG scores.
Results:
As expected the TUG-DT had the longest duration (M=10.35, SD ±2.63) followed by the TUG-self (M=8.9sec, SD ±1.2) and TUG-fast (M=6.8sec, SD±0.79). The mean DTE-TUG was -37.63% (SD±51.6%) and DTE-response -16.29% (SD±24.02%) with no significant differences between the DTE (p=.19) measured by paired t-test.
The TUG-self and TUG-fast were correlated with processing speed tasks embedded in the Stroop, specifically with Stroop Color (rs (12)=601, p=.001) and Stroop Word (rs =-.669, p=.012) respectively. The TUG-DT was correlated to DKEFS phonemic fluency (rs =-.648, p=.017), DKEFS switching fluency (rs =-.808, p=.001), DKEFS switching accuracy (rs =-.714, p=.006), and RBANS coding (rs=-.663, p=.014). The DTE-TUG was correlated to DKEFS phonemic fluency (rs =.651, p=.016) and DTE-response to Stroop Color-Word (rs=.721, p=.005), and Stroop Interference (rs =.599, p=.030).

Conclusions:
TUG-DT performance shows moderate to high correlations with multiple measures of verbal fluency, mental switching and attention, while the TUG-self and TUG-fast were moderately correlated with processing speed tasks. The cognitive DTE was moderately correlated to response inhibition measured by the Stroop Interference score while motor DTE was correlated to phonemic fluency.

Implications:
This study suggests that TUG-DT relies on different elements of executive function compared to the single-task TUG. Additionally, raw performance measured by different TUG tasks and overall DTE seem to utilize unique elements of cognition.

Acknowledgements: Dr. Gomes-Osman was funded by an Evelyn F. McKnight Brain Institute Pilot award.

Poster #5

Dual-task performance is related to a neurophysiological measure of plasticity in individuals with memory disorders

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Background and Purpose:
Successful aging requires the nervous system to adjust and adapt to a multitude of environmental demands. Given that falls are a major source of accident related injury in the elderly, the adaptability of motor and cognitive systems allows older adults to safely navigate their environment. This adaptability can be measured by appropriate allocation of attention and effort to the performance of dual-task behaviors, such as walking while performing a mental task. In neurophysiological studies, 'adaptability' within the nervous system can be also be measured non-invasively by using transcranial magnetic stimulation (TMS). Theta-burst stimulation of the motor cortex using TMS induces a modulation of motor evoked potentials (MEPs) that can be used to assess plasticity (i.e., adaptability) within intracortical circuits. It is not clear if adaptability assessed via dual-task performance is related to adaptability measured neurophysiologically (i.e., TMS plasticity). Given that there is evidence supporting that individuals with memory disorders demonstrate alterations in both dual-task performance and responses in TMS plasticity, the aim of this study is to explore whether these two phenomena are related.
Case Description:We enrolled 6 individuals with diagnoses of mild cognitive impairment (MCI) and mild Alzheimer's Disease (AD) aged 71 to 87 years (5 female), with a mean score on the Montreal Cognitive Assessment (MoCA) of 17.6±6. Inclusion criteria were: ability to walk independently, sufficient comprehension of study procedures and no contraindications to TMS. Exclusion criteria were: neurologic or psychiatric condition compromising study participation and any unstable or uncontrolled medical condition.
Outcomes:Participants engaged in a single study visit. For the plasticity assessment, intermittent theta-burst was applied to the primary motor cortex, and pre and post MEP responses were recorded from the first dorsal interosseous muscle. Plasticity was quantified by computing the percent change in the amplitude of MEPs from baseline to post theta-burst at various intervals with T10 used as the primary outcome. Dual-task walking was assessed using a 90-sec walk while performing a cognitive task (serial 7-subtractions), and the accuracy was computed.
Half of the participants exhibited facilitation of MEPs at T10, and the other half demonstrated a suppression of MEPs at T10. Individuals exhibiting modulation of MEPs at T10 also demonstrated greater accuracy during the dual-task walking assessment (85%, 89% and 92%), while individuals who showed suppression of MEPs at T10 showed poorer accuracy (0%, 25% and 67%). An exploratory analysis revealed a non-significant moderate correlation between modulation of MEPs at T10 and dual-task accuracy ($r^2=0.52$, $p=0.1$).
Discussion:Although the generalizability of these results is limited by the small sample, they provide preliminary evidence suggesting a link between adaptability measured by dual-task walking and by a TMS assessment of plasticity, in individuals with memory disorders.

Acknowledgements: Dr. Gomes-Osman was funded by an Evelyn F. McKnight Brain Institute Pilot award.

Poster #6

Effects of a 4-week aerobic exercise intervention on TMS neuroplasticity measures and cognition in healthy sedentary adults: an ongoing pilot study

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Background:
There is evidence supporting improved cognitive performance following regular aerobic exercise (delivered usually over a period of 9-12 months), but it is not clear if shorter interventions can influence cognitive performance in sedentary adults. Exercise-mediated cognitive improvements can be at least partly attributed to neuroplastic changes that occur at the cortical level. Transcranial magnetic stimulation (TMS) with intermittent theta-burst stimulation (iTBS) (TMS/iTBS) provides insights into neuroplasticity within intracortical circuits that may be useful in further elucidating the relationship between exercise and cognitive improvements in aging adults.

Purpose:
The purpose of this study was to evaluate the effects of a 4-week exercise intervention on cognition and TMS/iTBS neuroplasticity in sedentary healthy adults. We hypothesized that regular aerobic exercise would be associated with improvement in cognitive performance measures and increased neuroplasticity measured with TMS/iTBS.

Methods:
Sedentary adults >45 years are being recruited. All participants completed 4 weeks of 35-minute sessions of aerobic exercise on a treadmill 4x/week. Participants were randomized into two intensity groups (moderate=55-64%, high=65-90% age-predicted maximal heart rate [Karvonen equation]). Attention and executive function were assessed using the Stroop, Delis-Kaplan Executive Function System (DKEFS) verbal fluency, and the Repeated Battery for the Assessment of Neuropsychological Status (RBANS) digit span and coding. For the TMS/iTBS neuroplasticity assessment, stimulation targeted the primary motor cortex and motor evoked potentials (MEPs) were recorded from the first dorsal interosseous muscle. The neuroplasticity assessment consisted of quantifying TMS/iTBS-induced modulation of MEPs 5 mins post-iTBS (T5). Paired sample t-tests were used to make comparisons between pre-intervention and post-intervention outcome measures.

Results:
Thus far, nine sedentary adults (mean=58.7 ± 6.1, 6 females) have completed the study. Irrespective of intensity group, we found a significant difference in DKEFS phonemic fluency ($t[8]=-2.46$, $p=.03$) post-exercise. TMS/iTBS neuroplasticity data has been collected on 5 participants (3 moderate group, 2 high group). Irrespective of group, there appeared to be an increase in TMS/iTBS neuroplasticity from pre-intervention to post-intervention (mean pre=-8.74±23.8%, mean post=11.97±31.6%).
Conclusions: We found four weeks of aerobic exercise to improve executive control (phonemic fluency) in sedentary aging adults. In addition, there appeared to be an increase in TMS/iTBS neuroplasticity. As enrollment progresses, future analyses will be conducted with a greater sample size, and will additionally examine the role of intensity (moderate versus high).
Acknowledgements:

Dr. Gomes-Osman was funded by an Evelyn F. McKnight Brain Institute Pilot award for this study.

Poster #7

"Biogenetic features and function of the mitochondrial ribosome in health and mitochondrial encephalomyopathies"

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Defects in oxidative phosphorylation (OXPHOS) cause a heterogeneous and often devastating group of disorders known as mitochondrial diseases which commonly feature central nervous system dysfunction and neuropathy. Mitochondrial diseases are poorly understood, and treatment options are almost-entirely symptomatic. A subset of these diseases is caused by mutations in essential components of the mitochondrial translation machinery, which is maintained exclusively for the synthesis and co-translational insertion of thirteen protein components of the OXPHOS enzymatic complexes into the inner-mitochondrial membrane (IMM). This machinery includes the mitochondrial ribosome, which has diverged substantially from its better understood cytosolic and bacterial counterparts through major structural and compositional modifications. Despite apparent importance for productive assembly of the OXPHOS complexes, little is known about how mitoribosome specific adaptations regulate its function. The **objective** of this project is to expand our understanding of how mitoribosome biogenesis, composition, and structure affect its function in the context of health and disease. Our research focuses on a unique aspect of the mitoribosome: its tethering to the IMM. Based on high resolution mitoribosome structures, this tethering is thought to be mediated by the mitoribosome large-subunit (mt-LSU) protein mL45, which we hypothesize functions in appropriate insertion of nascent polypeptides into the IMM making it critical to OXPHOS complex assembly. We will test this hypothesis with both an exploratory and confirmatory approach to the following aims: **Aim I)** Characterize the role of mL45 in mitoribosome assembly and function; **Aim II)** Define structural determinants of the mL45-mediated anchorage to the IMM; **Aim III)** Define components of the mL45 mitoribosome anchoring site. Our **methodology** involves examination of the structure-function relationship of mL45 in terms of mitoribosome assembly and function through expression of strategically modified versions of mL45 in human cancer cell lines deficient in mt-LSU assembly or ablated for mL45. We will search for additional mitoribosome tethering mediators by identifying the mL45 interactome using co-ImmunoPrecipitation approaches and BioID proximity labeling followed by mass spectrometry. All experiments will be performed at least in triplicate. Early results show that mL45 is necessary for the stability of mt-LSU proteins, mt-LSU assembly, and translational function of the mitoribosome. Ongoing work will reveal a more detailed picture of mL45's contribution to mitoribosome assembly and function.

Poster #8

Anxiety-like behavior and Fos expression in amygdala elicited by itch mediators in mice

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Chronic itch is typically accompanied by negative emotional states. Itch intensity is linked to anxiety, and in turn anxiety and stress can exacerbate itch, leading to a vicious cycle that impacts quality of life for chronic itch patients. However, the central mechanisms underlying this cycle are poorly understood. We aimed to measure anxiety-related behavior and neuronal activity following acute intradermal injection of three pruritogens: histamine, the major inflammatory pruritogen released by mast cells; chloroquine, a nonhistaminergic pruritogen that induces itch through MrgprA3 receptors; and serotonin, a nonhistaminergic pruritogen that induces itch through multiple 5-HT receptor subtypes. Adult male C57BL/6 mice (n = 9-15/group) received an intradermal injection of histamine, chloroquine, serotonin, or phosphate-buffered saline (PBS) vehicle into the rostral back skin and were recorded on the elevated plus maze (EPM) or open field test (OFT) for 10 min. Open arm time on the EPM and the percent of center square entries on the OFT were used as measures of anxiety-like behavior. Mice displayed significantly reduced open arm time on the EPM following histamine, chloroquine, or serotonin injection compared to PBS control. Similarly, mice displayed significantly reduced percent center square entries in the OFT following histamine or chloroquine injection compared to PBS control. Next, we used immunohistochemistry to label c-Fos, a marker of neuronal activity, in several anxiety-related brain regions. Mice received an intradermal injection of histamine, chloroquine, serotonin, or PBS to the rostral back, and after 2 hr, they were perfused and dissected. c-Fos was labeled and quantified in the amygdala, parabrachial nucleus, and midcingulate cortex. Pruritogens evoked significantly a greater number of c-Fos+ neurons in these areas compared to PBS control. These results suggest that the amygdala, parabrachial nucleus, and midcingulate cortex may be part of a brain circuit that processes the affective component of itch and contributes to itch-induced anxiety-like behavior.

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Poster #9

Nutritional ketosis enhances cognitive resilience in young and aged rats

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As the number of individuals living beyond the age of 65 is rapidly increasing, so is the need to develop strategies to combat the age-related cognitive decline that may threaten independent living. The incomplete link between cognitive decline and the neurobiological changes that accompany normative aging is further complicated by the existence of bidirectional changes in neural activity levels observed within aged subjects. This factor impedes the development and implementation of potential therapeutic strategies to combat age-related cognitive decline. Therefore, potential strategies must focus on mitigating the effects of aging by targeting processes ubiquitous to the entire brain, such as impaired glucose utilization and the neurometabolic deficits that commonly accompany the aging process. To do this, this study utilized a ketogenic diet as a metabolic strategy to switch the primary fuel source from glucose to ketone bodies, a process known as ketosis. Calorically and nutritionally equivalent ketogenic (KD) and control (CD) diets were utilized for a minimum of 3 months in 4- and 24-month old male and female Fisher 344 x Brown Norway rats prior to behavioral testing and hippocampal (HPC) and prefrontal cortical (PFC) protein quantification. An elevated figure-8 maze, with one closed arm and one open arm, was utilized to test anxiety-like behavior within the context of a spatial alternation task. Rats on the KD learned to alternate throughout this asymmetrical maze in fewer training sessions relative to rats on the CD. Within the same testing apparatus, KD rats required fewer training sessions to acquire an object-in-place association than CD rats. Furthermore, CD rats selected the correct object significantly fewer times in the open arm relative to the closed arm, but the KD group did not differ in performance across arms. Together, these data demonstrate the potential of a KD to mitigate anxiety- and age-related cognitive deficits. Age- and region-specific changes were found in vesicular transporters for GABA and glutamate within PFC and HPC tissue, indicating changes in neuronal signaling properties within these regions following ketosis. Furthermore, glucose and monocarboxylate transporters were also differentially affected, suggesting metabolic capacities were also altered. While there were no changes in motor tests, positive changes in peripheral health markers including visceral adipose tissue and improved resting glucose levels were observed. Together, these data suggest utilizing a ketogenic diet to alter metabolic processes within the brain may confer resilience against the cognitive and neurobiological effects of advanced age.

Poster #10

Aged rats do not use basolateral amygdala during outcome evaluation 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 (prior experience) with valuation of the organism's current wants and needs (incentive motivation). Moreover, evaluation of the outcome received (is it more or less than expected) is critical for driving future choices. 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 changes that mediate these age differences in intertemporal choice are unknown, lesion and electrophysiological studies consistently implicate the basolateral amygdala (BLA) in motivation and affective decision making. The current experiments used optogenetic approaches to determine the effects of temporally discrete BLA inactivation on choice behavior during an intertemporal choice task. Young adult (6 mo) and aged (24 mo) Fischer 344 x Brown Norway F1 hybrid rats were surgically implanted with guide cannulae targeting BLA through which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered and optic fibers were implanted. Rats were subsequently trained on an adjustable-delay intertemporal choice task in which preference for small vs. large rewards was evaluated in the presence of increasing delays to large rewards. Upon reaching stable performance, light-induced BLA inactivation was performed using a within-subjects design such that BLA was inactivated at discrete phases of the task: the period before choice (deliberation), the delay interval prior to large reward delivery (delay), a 4 s period during reward (outcome) or the intertrial interval (ITI). BLA inactivation during the ITI, delay interval or large reward delivery had no effect on behavioral performance. In contrast, BLA inactivation during deliberation increased young rats' choice of the large, delayed reward, whereas BLA inactivation during the small reward outcome decreased their choice of the large, delayed reward. The effects of BLA inactivation during deliberation were replicated in aged rats, while there was no effect of BLA inactivation during the outcome phase of the task in aged rats. These data indicate that in young adults, there are multiple BLA circuits that exert opposing influences on decision making. Importantly, however, aged rats fail to use the BLA to process information about outcome to guide future choices. These data may help explain the robust age-associated differences in intertemporal choice evident across aging populations.

Poster #11

Hippocampal, perirhinal, and lateral entorhinal contributions to mnemonic discrimination in young and aged rats

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Memory requires that similar episodes be represented distinctly. Notably, many symptoms of age-related memory loss appear to derive from a decreased ability to distinguish between similar events (e.g., Stark et al. 2013). In a rodent version of the mnemonic similarity task that tests this ability, we have shown aged rats are selectively impaired in distinguishing a learned target object from similar lure objects (Johnson et al. 2017), and that disrupting neural activity in the dorsal CA3 in young adult rats impairs mnemonic discrimination. Given work in animal models and, more recently, human functional neuroimaging studies, implicating the perirhinal and entorhinal cortices in age-related decline in mnemonic discrimination (Berron et al. 2018; Maurer et al. 2017; Reagh et al. 2018; Ryan et al. 2012), the present study investigated activation of neural ensembles across medial temporal lobe and hippocampal regions during mnemonic similarity task performance in young and aged rats. F344 x Brown Norway F1 hybrid rats (young adult 6-8 m, aged 26-30 m) were behaviorally characterized and trained 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). To assess neural ensemble activation as it relates to mnemonic discrimination performance, rats completed two behavioral epochs with distinct versus similar objects, then brain tissue was rapidly extracted and prepared for fluorescent in situ hybridization (FISH) against the immediate early gene Arc. The proportion of neurons expressing Arc was systematically counted from regions of interest across the lateral entorhinal cortex (LEC), perirhinal cortex (PRC), CA3, and CA1. Consistent with previous studies, aged rats showed a reduction in the proportion of neurons active during mnemonic discrimination in superficial layers of PRC. This effect was also observed in output layers of LEC. In contrast to medial temporal lobe regions, aged rats showed a greater proportion of neurons active in hippocampus, particularly in CA3 and the proximal portion of CA1. Of note, while the size of neural ensembles active across regions did not correlate with performance on behavioral epochs immediately prior to tissue collection, a greater proportion of neurons active in the proximal CA1 was observed in rats that showed better abilities discriminating similar objects over the course of initial behavioral training. Our results directly parallel findings from older adults and support the emerging view that circuit level dysfunction across the medial temporal lobe and hippocampus contributes to age-related memory loss.

Poster #12

Both GluN2A and GluN2B contribute to the induction of the redox-mediated potentiation of NMDA receptor synaptic function at CA3-CA1 hippocampal synapses of aged animals

A. KUMAR, T. C. FOSTER.

A decrease in N-methyl-D-aspartate (NMDA) receptor synaptic responses during aging contributes to impaired synaptic plasticity and is associated with impaired cognition. Electrophysiological studies have described NMDA receptor hypofunction during aging, due to an oxidized redox state of neurons. The current studies employed extracellular field potential recordings to investigate contribution of GluN2A and GluN2B subunits in the induction of redox-mediated potentiation of NMDA receptor synaptic responses at CA3-CA1 hippocampal synapses in aged animals. Acute hippocampal slices were prepared from aged (~25 mo) male F344 rats. NMDA-mediated synaptic field potentials were isolated by addition of picrotoxin (20 µM) and DNQX (30 µM). In most cases, a control slice was recorded in a separate chamber (n = 19 slices). To determine if NMDA receptor activity was required for reducing agent, dithiothreitol (DTT)-induced potentiation of the NMDA receptor response, baseline field potentials were recorded followed by bath application of various antagonists (NVP-AAM077, 0.4 µM, n = 5; ifenprodil, 5 µM n = 8; RO-6981, 4 µM, n = 5, or zinc, 1 µM, n = 3). An ANOVA indicated a treatment effect [$F(4,36) = 3.87$, $p < 0.05$]. Post hoc tests indicated that GluN2A receptor antagonist, NVP decreased the synaptic response (85 ± 8 mean percent decrease ± SEM) relative to vehicle, ifenprodil, or zinc. A new baseline was recorded, DTT (0.5 mM) was bath applied, and the DTT-mediated potentiation of the NMDA response was examined. A treatment effect was observed for the DTT-mediated growth of the NMDA receptor synaptic response ($p < 0.001$). DTT increased the synaptic response 63 ± 9% for control slices. The magnitude of DTT-mediated increase in the NMDA receptor response was reduced by NVP (8 ± 7%), and by GluN2B receptor antagonist, ifenprodil (20 ± 3%) or RO-6981 (21 ± 10%). The responses under antagonist conditions were not different from each other and were significantly ($p < 0.001$) decreased relative to vehicle. Zinc had no effect on the ability of DTT to increase the response (61 ± 9%). The results suggest that GluN2A and GluN2B are involved in the induction of DTT-mediated growth of the NMDA receptor mediated synaptic response.

Poster #13

Effects of vagus nerve stimulation on selective attention in Brown Norway rats

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Selective attention is a prefrontal cortical-mediated executive function that serves as a building block for many aspects of higher-order cognition. Enhancement of selective attention may offer broad functional benefits across a range of cognitively challenging circumstances and for the treatment of cognitive disorders. Prefrontal cortical acetylcholine and norepinephrine have been particularly implicated in attentional processes, and vagus nerve stimulation (VNS) can modulate cortical levels of these neurotransmitters via projections through the nucleus tractus solitarius. In the current studies, the effects of VNS were tested in Brown Norway rats (~4 mo.) using a 5-choice serial reaction time task in which rats had to respond to brief presentations of visual stimuli in a touchscreen operant chamber. Within each test session, five stimulus durations (ranging from 0.7-0.05s) were presented in a randomized fashion. Under baseline conditions, rats showed a systematic reduction in accuracy with decreasing stimulus durations. On test days in which VNS (60μs pulse width, 500μA, 50Hz, 0.8s train duration) followed correct choices, rats showed a reliable improvement in accuracy at short stimulus durations compared to baseline (no stimulation) conditions. VNS further produced a reduction in trial omissions as well as an increase in premature responses, consistent with greater task vigilance. In contrast to these enhancing effects on performance, VNS impaired accuracy at long stimulus durations relative to baseline. The effects of VNS were compared with those resulting from systemic administration of either donepezil (an acetylcholinesterase inhibitor, 0.1, 0.3, 1.0 mg/kg) or atomoxetine (a noradrenergic transporter blocker, 0.3, 1.0, 3.0 mg/kg), which were assessed using a within-subjects design. In agreement with previous literature, both drugs enhanced accuracy relative to vehicle conditions, suggesting that the beneficial effects of VNS may act through these modulatory neurotransmitter systems. Funding: This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) BTO under the auspices of Dr. Douglas Weber and Dr. Tristan McClure-Begley through the DARPA Contracts Management Office Grant No. HR0011-17-2-0019.

Poster #14

Investigation of age-related impairment in pattern separation employing modified version of water maze beacon task

G. SMITH, A. RANI, A. KUMAR, T.C. FOSTER.

Previous studies inspecting transcriptional changes within the brain during aging indicate that cognitive impairments are associated with differentially expressed genes, linked to defined neural systems (e.g. episodic memory-CA1, executive function-prefrontal cortex). These studies found that behavior was not correlated with gene expression in regions that are not the primary locus of the cognitive process (e.g. executive function-CA1). These studies provide information on possible molecular mechanisms for age-related cognitive decline. Aging is associated with a decline in pattern separation (PS), a process often measured by individuals' ability to distinguish whether a given image is identical or merely similar to previously viewed images. The dentate gyrus (DG) is implicated in PS. While a number of changes occur in the DG during aging (decline in neurogenesis, impaired synaptic plasticity, loss for afferent input), it remains unclear what specific changes may occur in the DG with age that lead to a decline in PS performance. We hypothesize that aged animals with impaired PS ability may express a distinct transcriptional profile relative to unimpaired animals, specifically within the DG. In order to examine PS, we have modified the water maze version of the beacon task in an attempt to test PS between similar spatial locations. Two groups of male F344 rats were tested with the target and decoy platforms separated by 45 or 73 cm. Preliminary findings suggest that both young (4 mo, n=10) and middle-age (12 mo, n=24) rats make significantly more errors when beacons are 45cm apart compared to 73cm apart (4 mo, $p=0.0001$, 12 mo, $p<0.0001$). First choice accuracy was found to be impaired in middle-age animals relative to young animals, regardless of beacon separation, but only when trials began at the position equidistant between the two beacons (73cm, $p=0.0001$; 45cm , $p=0.011$). Following the beacon discrimination test, rats were tested for spatial reference memory and no age-related differences were observed. These results suggest that the beacon task may be sensitive to an age-related impairment in PS. At the completion of behavioral testing, hippocampal subregions will be isolated and transcriptomic information will be derived from the DG and CA1 in order to investigate possible molecular contributors to a decline of PS with advancing age.

Poster #15

Altered GABAB receptor signaling in basolateral amygdala may contribute to age-associated differences in intertemporal choice

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The ability to choose adaptively among options that vary in time to arrival (i.e., intertemporal choice) is critical for navigating many aspects of everyday life. Most individuals will choose a large over a small reward in the absence of delays, but reliably "discount" the subjective value of the large reward if there is a delay imposed between the choice and its delivery. Greater discounting of large, delayed rewards (i.e., greater impulsive choice) is a hallmark of several neuropsychiatric disorders. In contrast, older adults exhibit less discounting of delayed rewards compared to young adults (i.e., less impulsive choice). Impulsive choice is mediated by a network of limbic cortico-striatal brain structures, and recent findings indicate that the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) are particularly critical for regulating impulsive choice in young adults. Previous optogenetic and biochemical studies from our lab and others implicate altered excitability of BLA and mPFC in age-associated changes in intertemporal choice. The objective of the current study was to investigate specifically how changes in signaling at the extrasynaptic GABAB receptor contribute to age differences in intertemporal choice in Fischer 344 × Brown Norway F1 hybrid rats. In a first cohort of young and aged behaviorally naïve rats, RNA was extracted from tissue punches of the BLA and mPFC in order to evaluate expression of transcripts associated with excitatory and inhibitory signaling molecules using RT-qPCR. Transcripts for GABAB receptor subunits were significantly reduced in the aged BLA but not the aged mPFC relative to young adults. In additional experiments, cohorts of young and aged rats received surgically implanted guide cannulae targeting either the BLA or mPFC. After recovery from surgery, rats were trained on the intertemporal choice task. Using a within-subjects design, choice performance was evaluated following intra-cerebral infusion of either the GABAB receptor agonist, baclofen (0.03, 0.1, 0.3 µg/0.5 µl/hemisphere), or the GABAB receptor antagonist, CGP55845 (0.05, 0.15, 0.5 µg/0.5 µl/hemisphere). Baclofen infused into the BLA increased impulsive choice in both young and aged rats, whereas CGP did not alter choice performance in either age group. The effects appeared specific to the BLA as neither baclofen nor CGP55845 targeted to mPFC altered choice performance in either age group. Taken together, these data suggest that reduced GABAB receptor expression, particularly in the BLA, may contribute to age-associated decreases in impulsive choice.

Poster #16

Dissociable effects of advanced age on prefrontal cortical and medial temporal lobe ensemble activity

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The link between age-related cellular changes within brain regions and larger scale neuronal ensemble dynamics critical for cognition has not been fully elucidated. The current study measured neuron activity within medial prefrontal cortex (PFC), perirhinal cortex (PER), and hippocampal (HPC) subregion CA1 of young and aged rats by labeling expression of the immediate-early gene Arc (Guzowski et al., 2001). 4- and 24-month old male Fisher 344 x Brown Norway rats were trained on an object-place paired association (OPPA) task that is dependent on this PFC-PER-HPC circuitry as well as an alternation task within the same testing apparatus. Although aged animals required more training to learn the object-in-place rule (Hernandez et al., 2015), all animals were trained to equivalent performance. The proportion of cells expressing Arc was quantified at baseline in a subset of rats sacrificed directly from the home cage, and following the OPPA and alternation behaviors in another subset. Additionally, the retrograde tracer cholera-toxin subunit B was injected into the prelimbic (PL) and infralimbic (IL) cortices within the PFC to identify cells within PER and CA1 that project to the medial PFC. Baseline Arc expression did not differ across age groups within CA1 or PER, but was elevated in aged rats relative to young within the PL and IL regions of the PFC. Within the CA1 of task-performing rats, no age-related differences in neuronal activity were observed in the entire neuron population or within CA1 pyramidal cells that project to PFC. Although behavior was comparable across age groups, behaviorally driven Arc expression was higher in the deep layers of both PER and PFC, and lower in the superficial layers of these regions in aged rats. Moreover, age-related changes in activity levels were most evident within PER cells that project to PFC. These data suggest that the PER-PFC circuit is particularly vulnerable in advanced age.

Poster #17

Female rats show greater impulsive choice than males in an intertemporal choice task

A. WHEELER, C. M. HERNANDEZ, C. A. ORSINI, T. W. TEN EYCK, C. C. LABISTE, B. SETLOW, J. L. BIZON.

Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. All other things being equal, individuals prefer large over small rewards; however, individuals tend to more readily choose small over large reward options the longer they have to wait for the large reward (i.e., the value of the large reward is “discounted” by the delay to its delivery). Marked individual differences in intertemporal choices exist across the population, with preferences for small, immediate rewards (greater “impulsive choice”) associating with many psychiatric disorders. While data from our lab (Orisini et al, 2016) and others strongly implicate sex and gonadal hormones in other aspects of decision making, such differences are poorly elucidated in the context of intertemporal choice. The goal of the current study was to characterize adult (4 mo.) male and female Fischer 344 x Brown Norway F1 hybrid (FBN) rats on an intertemporal choice task in which rats make discrete trial choices between a small, immediate reward and a large, delayed reward using a block task design. Estrous cycle was evaluated in female rats after stable baseline performance was achieved. Choice preference (% choice of the large, delayed reward) was used as the primary performance measure, and latency to respond during intermixed forced choice trials was analyzed as a measure of motivation to obtain the rewards. Compared to males, female rats showed significantly greater preference for the small, immediate over the large, delayed reward (i.e., females showed greater “impulsive choice” than males). Consistent with less incentive motivation for the large, delayed reward, females also showed longer latencies to choose this option relative to males. Overall task motivation was not affected by sex, however, as males and females completed similar numbers of trials. These sex differences in intertemporal choice were also not secondary to differences in reward magnitude perception, as males and females showed equivalent preference for the large reward when there was no delay to its delivery. Finally, choice behavior in females was not altered across the estrous cycle. Considered together, these data demonstrate that female rats show greater impulsive choice than males, and suggest that sex differences in decision making may be a contributing factor to gender disparities across a range of neuropsychiatric disorders.

Poster #18

Frontal upregulation of serine racemase alters cognitive flexibility in middle age rats

B. YEGLA, T. FOSTER, A. KUMAR.

Aging is characterized by hippocampal- and prefrontal-mediated cognitive deficits. A decrease in N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic function contributes to impaired synaptic plasticity and is associated with cognitive impairments. Given NMDAR hypofunction in aging, D-serine, a NMDAR co-agonist, is a promising target for maintaining cognitive function in aging. Levels of serine racemase (SR), which synthesizes D-serine, decline with age. Thus, enhancing NMDAR function via increased SR expression in middle age, when subtle declines in cognition emerge, was predicted to enhance performance on a prefrontal-mediated task sensitive to aging. Male Fischer-344 rats (12 mo; N=7) were injected bilaterally in the medial prefrontal cortex with 2µL of lentivirus (LV) for SR upregulation (LV-SR) or control (LV-GFP). Rats were 85% food restricted and trained on the operant attentional set-shift task to examine cognitive flexibility. This task includes visual discrimination (VD), where rats select one of two levers based on the location of a light cue. Correct responses resulted in food rewards. Rats then made an extradimensional shift to an egocentric response strategy, selecting a lever based on its location (right or left) irrespective of the light. An intradimensional shift required selection of the opposite lever from the previous trial type (from right to left). Rats had to reach criterion (8 consecutive correct responses) before advancing to the next phase. Trials to criterion, errors, omissions, and percent correct responses were collected and analyzed. Following completion, rats were perfused to evaluate location of viral infection. All rats required more trials to criterion for VD than the extra- or intra-dimensional shift ($F_{1,5}=12.68$, $p=0.02$). Based on the reduced omission rate ($t_5=14.13$, $p=0.01$) and trials to criterion ($t_5=2.23$, $p=0.07$) during VD, LV-SR rats exhibited a faster learning rate compared to controls. Their capacity for the extradimensional shift was not impacted, though performance on the intradimensional shift was impeded in LV-SR rats, whereby correct performance was lower ($t_5=4.70$, $p=0.04$) due to greater errors ($t_5=3.39$, $p=0.06$) compared to controls. Immunohistochemical analyses displayed expression of LV-SR in the cortex and white matter. LV-SR significantly increased SR expression ($t_5=2.53$, $p=0.05$), with an approximate 26% upregulation in the prefrontal cortex. Thus, prefrontal SR upregulation in middle age rats improved attentional selection during VD but impaired flexibility, suggesting NMDAR activity acts as a gate or switch between maintaining and shifting attention.

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Poster #19

Elevated O-GlcNAcylation depresses inhibitory transmission recorded from granule cells in the rat dentate gyrus

K. ABIRAMAN, L. T. STEWART, L. L. MCMAHON.

O-GlcNAcylation is crucial for protein function, and involves the addition and removal of an O-linked N-acetylglucosamine (O-GlcNAc) to serine or threonine residues by the enzymes O-GlcNAc transferase (OGT) and OGlcNAcase (OGA), both of which are highly expressed in the hippocampus. We have previously shown that acutely increasing O-GlcNAcylation using the substrate glucosamine or the OGA inhibitor, thiamet-G (TMG), induces long-term depression (LTD) at CA3-CA1 hippocampal synapses that requires O-GlcNAc modification of GluA2 AMPA type glutamate receptor (AMPAR) subunits. Additionally, we found that increasing O-GlcNAcylation dampens epileptiform activity at these same synapses. Because function of GABAA receptors (GABAARs) is modulated by serine phosphorylation, we have begun to ask whether the strength of GABAAR mediated synaptic inhibition is modulated by O-GlcNAcylation. We have found that pharmacologically increasing O-GlcNAc levels in acute slices decreases the amplitude and frequency of spontaneous IPSCs (sIPSCs) but only the amplitude of miniature IPSCs recorded from CA1 pyramidal cells. This indicates that much like phosphorylation, O-GlcNAcylation affects postsynaptic GABAAR function. To assess if this is general mechanism by which inhibition is modulated in the brain, we used whole-cell voltage-clamp recordings from dentate granule cells (DGCs) to investigate whether increasing O-GlcNAcylation modulates the frequency and/or amplitude of spontaneous IPSCs (sIPSCs) onto DGCs. Preliminary experiments found a reduction in both sIPSC amplitude and frequency following pharmacologically increasing O-GlcNAcylation. Collectively, these data will help us parse the effects of O-GlcNAcylation on the input and output stages of hippocampal processing.

Poster #20

The role of neuronal and microglial progranulin deficiency in FTD- and NCL-like pathology

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Loss of function mutations in progranulin (GRN) are a major cause of dominantly-inherited frontotemporal dementia (FTD), and individuals homozygous for GRN mutations develop a lysosomal storage disorder, neuronal ceroid lipofuscinosis (NCL). In the brain, progranulin is expressed primarily by neurons and microglia. Progranulin exerts neurotrophic effects on neurons, regulates inflammation in microglia, and is thought to maintain normal lysosomal function in both cell types. A major unanswered question in FTD due to GRN mutations is the extent to which loss of progranulin's neurotrophic and anti-inflammatory effects contributes to disease. We and others have reported that mice with selective knockout of neuronal or microglial progranulin recapitulate some, but not all, of the pathology of global Grn-/- mice, which develop lipofuscinosis, gliosis, and accumulation of lysosomal proteins that may model the pathology of NCL. In this study, we tested whether knocking progranulin out of both neurons and microglia would recapitulate the pathology of global Grn-/- mice. We crossed Grnfl/fl mice expressing Cre recombinase under promoters targeting neurons (CaMKII, N-KO) and myeloid cells/microglia (LysM, Mg-KO) to generate dual neuronal/microglial progranulin knockout mice (D-KO), and assessed the pathological phenotypes of the mice at age 24 months. Cortical progranulin levels were reduced by roughly 50% in N-KO mice and 60% in DKO mice, though Mg-KO mice did not exhibit a significant reduction in cortical progranulin levels. While knockout of both neuronal and microglial progranulin produced some pathologic abnormalities, the D-KO mice did not exhibit synergistic effects of progranulin knockout from both cell types. Unlike global Grn-/- mice, D-KO mice failed to develop lipofuscinosis, the hallmark pathology of NCL. These data show that partial progranulin insufficiency is sufficient to produce some deficits, and indicate that progranulin from other cell types is sufficient to prevent NCL-like pathology in neuronal/microglial progranulin knockout mice.

Poster #21

Inorganic scintillators are biocompatible with neuronal and circuit function

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Optogenetics is widely used in neuroscience research to control neural circuits. However new strategies for light delivery into the brain that are non-invasive and generate less physical damage caused by heat generation and implantation of probes are needed. One potential strategy could employ x-ray activation of radioluminescent particles (RPLs), enabling localized generation of light within the brain. Radioluminescent particles can be made from inorganic scintillators, which emit light of different wavelengths depending upon their composition. Whether inorganic scintillators themselves negatively impact neuronal processes and synaptic function is unknown. Cerium doped lutetium oxyorthosilicate (LSO:Ce), an inorganic scintillator that emits blue light in response to x-ray or UV stimulation, could potentially be used to activate channelrhodopsin-2 (ChR2), a light-gated cation channel. Here we used molecular, cellular, and electrophysiological techniques to investigate effects of LSO:Ce particles on neuronal health and synaptic function. As proof of principle that light emitted from LSO:Ce particles can activate ChR2 and excite neurons, we applied UV stimulation to LSO:Ce particles on acutely prepared hippocampal slices from mice that expressed ChR2 in glutamatergic neurons. This caused an increase in the frequency and amplitude of spontaneous excitatory postsynaptic currents (EPSCs) in CA1 pyramidal cells, indicating activation of ChR2. We investigated biocompatibility, and find that LSO:Ce particles have no effect on neuronal survival in culture, even after 24 hours of exposure. We tested for effects of LSO:Ce particles on synaptic transmission, and find that electrically evoked basal synaptic transmission measured in extracellular dendritic field potentials (fEPSPs) is unaltered, even with incubation times up to 3 hours. However, there was a slight but statistically significant decrease in the frequency of spontaneous EPSCs and inhibitory postsynaptic currents (IPSCs) measured onto CA1 pyramidal cells, with no change in current amplitudes. Finally, we tested for effects of LSO:Ce particles on long term potentiation (LTP), a synaptic modification believed to underlie learning and memory, and thus is a robust measurement of synaptic health and integrity. We found that LTP induction was not impaired, although there was a slight but significant reduction in LTP amplitude. Together, these results show that LSO:Ce particles are biocompatible even though there are modest effects on baseline synaptic function and plasticity. Importantly, we show that that light emitted from LSO:Ce particles is able to activate ChR2 and modify synaptic function. Therefore, LSO:Ce inorganic scintillators are potentially viable for use as a new light delivery system for optogenetics.

Poster #22

Reducing inhibition improves E/I balance and hippocampal circuit function in PGC-1α null mice

D. BHATTACHARYA, A. F. BARTLEY, Q. LI, L. E. DOBRUNZ.

Alterations in the excitation/inhibition (E/I) balance are thought to contribute to dysfunction in neuropsychiatric and neurodevelopmental brain disorders such as schizophrenia and autism. E/I imbalance can be caused by dysfunction of GABAergic interneurons, leading to enhanced or reduced GABAergic inhibition. As a result, pharmacological modulation of GABAA receptors could potentially normalize E/I function. Because E/I imbalances can be frequency dependent due to synaptic short-term plasticity, it is not clear whether the same dose that rescues baseline synaptic function would also normalize the E/I balance at higher frequencies. Our lab has previously shown alterations in E/I ratio and hippocampal circuit function in a mouse model of interneuron transcriptional dysregulation. We use mice with deletion of PGC-1α (peroxisome proliferator activated receptor γ coactivator 1α), a transcriptional co-activator that in hippocampus is localized to GABAergic interneurons. Loss of PGC-1α reduces the expression of the calcium binding protein parvalbumin, which mimics molecular aspects of some complex brain disorders. We have previously shown that there is enhanced inhibition, reduced E/I balance, and impaired CA1 circuit function in PGC-1α null mice. Importantly, the E/I imbalance and circuit dysfunction are frequency-dependent, in that the magnitude of the effects are reduced by paired-pulse stimulation at short intervals. Here we tested the extent to which reducing inhibition can restore the dynamic E/I balance and rescue the deficits in circuit function. We used acute CA1 hippocampal slices from young adult PGC-1α wildtype and null mice, and reduced inhibition by partially blocking GABAAreceptors with a low concentration of bicuculline (BIC). Surprisingly, we found that low dose BIC rescued the E/I balance during paired-pulse stimulation as well as at baseline. BIC also increased the paired pulse ratio of disynaptic inhibition in PGC-1α null slices, suggesting that it is altering interneuron recruitment. BIC improved CA1 output in slices from PGC-1α null mice to levels comparable to wildtype, as measured by E-S coupling. Our results show that modulation of GABAA receptors can potentially rescue E/I imbalances even when they are frequency-dependent.

Poster #23

Enhancer RNAs are necessary and sufficient for gene transcription and neuronal function

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Distal enhancer elements in DNA enable chromatin reorganization and facilitate gene expression programs to regulate cell fate and function. A significant fraction of regulatory DNA regions, like enhancer sites, are subject to bidirectional, RNA polymerase II-dependent transcription that results in non-coding enhancer RNAs. While evidence suggests that eRNAs are involved in the regulation of gene expression through interactions with transcription factors and epigenetic modifiers, their potential role in neuronal function and development remains unclear. Here, we used cortical neuronal cultures to investigate five different enhancer-promoter pairs. For example,¬ we determined the regulation and localization of specific eRNAs arising from enhancers surrounding Fos (also known as c-Fos), an immediate early gene that codes for a transcription factor implicated in neuronal plasticity and cognitive processes. We show that eRNA transcription from Fos enhancers is dynamically modulated by various forms of neuronal activity, requires RNA polymerase II, and precedes induction of Fos mRNA. To investigate the localization of eRNAs at the single-neuron level, we employed single-molecule RNA FISH with multiplexed probes to identify eRNA and mRNA transcripts. smFISH revealed nuclear localization of eRNAs, activity-dependent increases in Fos eRNA-1 and Fos mRNA transcripts, as well as a positive correlation between Fos eRNA-1 and mRNA within the same cells. Anti-sense based Fos eRNA knockdown decreased Fos mRNA expression, whereas mRNA knockdown did not affect eRNA levels. 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. Similarly, CRISPR-targeted delivery of eRNA to a Fos enhancer elevated mRNA induction following neuronal depolarization. Finally, we show that knockdown of a single Fos eRNA is sufficient to alter neuronal firing in vitro using a Multi Electrode Array system. Overall, these findings indicate that eRNAs directly modulate gene expression and neuronal physiology.

Poster #24

Analysis of cortico-striatal glutamatergic transmission in PINK1 KO rats

R. B. CREED, L. L. MCMAHON, M. S. GOLDBERG.

PTEN induced kinase 1 (PINK1) targets dysfunctional mitochondria for degradation via autophagy, and PINK1 mutations cause autosomal recessive Parkinson's disease (PD). The main pathological hallmarks of PD are loss of dopaminergic neurons in the substantia nigra pars compacta, which are required for normal movement, and the formation of α-synuclein-rich aggregates termed Lewy body inclusions. Accordingly, PINK1 knockout (KO) rats have mitochondrial dysfunction, locomotor deficits, and α-synuclein aggregates in multiple brain regions including the substantia nigra, striatum, and cortex. The appearance of α-synuclein aggregates in idiopathic PD and the genetic linkage of α-synuclein mutations to inherited PD both implicate α-synuclein abnormalities in PD pathogenesis. How and why α-synuclein-immunoreactive aggregates appear in PINK1 KO rats remains uncertain. α-Synuclein is one of the most abundant synaptic proteins and is important for synaptic vesicle movement and synaptic transmission. Thus, decreased spontaneous excitatory postsynaptic currents (EPSCs) in medium spiny neurons appear in α-synuclein transgenic mice even at early ages when α-synuclein aggregates are first appearing. The α-synuclein abnormalities in PINK1 KO rats leads us to predict that defects in excitatory transmission will occur in PINK1 KO rats. To test this hypothesis, we conducted whole-cell, voltage-clamp recordings of medium spiny neurons in acute slices of dorsal striatum from PINK1 KO and wild-type (WT) littermate controls at various ages. We measured spontaneous and mini excitatory postsynaptic currents (sEPSC and mEPSCs, respectively) and paired pulse ratios of evoked glutamatergic transmission to assess the efficacy of corticostriatal synaptic transmission. This work advances the characterization of PINK1 KO rats as a model of PD and can provide important insight into the mechanisms by which PD-linked loss-of-function mutations in PINK1cause dysfunction and neurodegeneration.

Poster #25

Visual network modularity in patients with central vision loss

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Several lines of evidence have shown that the adult brain has the ability to change itself in response to changes in sensory experience. Central vision loss is one major change in sensory experience that has been shown to have some impact on both brain structure and function. Here we ask how this loss influences the networks involved in processing vision. Given that the brain functions as a network, understanding how vision loss influences those networks is crucial to understanding the plasticity of the brain during altered sensory experience in adulthood. Here, we examine the visual network changes associated with macular degeneration (MD), a disease that results in loss of high resolution central vision, requiring individuals to rely on the much lower resolution of peripheral vision to perform everyday tasks. Specifically, we examined how the community structure of the visual network is different in individuals with central vision loss compared to those with healthy vision. We performed eyes-open, resting state fMRI in nine MD patients and nine matched controls in order to examine whether central vision loss is associated with changes in a measure of network structure called modularity. Modularity is defined as the extent to which a given network can be broken down into smaller clusters, known as “modules”, and the degree to which these modules possess more within- vs. between-module connections. In healthy vision, studies suggest that the modularity of visual cortex reflects the functionally distinct, hierarchical organization of the brain’s visual system. Here we examined whether loss of central vision in macular degeneration disrupts this modularity in the visual network. Standard preprocessing procedures were performed, including motion scrubbing, and assessment of motion parameters between groups, confirming movement was not significantly different between the two groups. Overall, we found that macular degeneration is associated with decreased visual network modularity compared to healthy controls. This finding suggests that there is less segregation of the visual network in participants with macular degeneration, possibly due to an overall decrease in retinal inputs to the visual system. Future studies need to further explore the extent to which this change in modularity reflects overall vision loss vs. a compensatory mechanism to more effectively process deprived vision. Nevertheless, our findings show that the structure of the visual network may be related to long term differences in the type of visual input being processed.

Poster #26

Defining Cellular identity and cell-specific expression changes in the pre-formed fibril model of Parkinson Disease

S. FOX, L. VOLPICELLI-DALEY, R. COWELL.

Parkinson Disease (PD) is a neurodegenerative movement disorder that is characterized by post-mortem observation of two pathological hallmarks including loss of dopaminergic (DAergic) neurons of the substantia nigra (SN) and alpha-synuclein aggregates (Lewy bodies and Lewy neurites). Current therapies for PD focus on managing symptoms after substantial loss of DAergic neurons with no current method of prevention of neurodegeneration. Elucidation of the underlying causes of neuronal cell dysfunction has the potential to provide new therapeutic targets to prevent loss of DAergic neurons. Post-translationally modified alpha-synuclein is the major component of filamentous inclusions in neurons throughout the brain in PD. It is not known how DAergic neurons respond to inclusion formation; defining their transcriptional profile during the cell death process could identify pathways for preventing cell death. To understand how levels of gene transcription change in neurons with Lewy pathology, we use the fibril model. According to this model, addition of alpha-synuclein preformed fibrils in vivo or in culture leads to corruption of endogenous alpha-synuclein over time, resulting in inclusions, defects in neuronal function, and cell death. To enable quantification of transcripts in cells containing alpha-synuclein aggregates, we optimized a new technique combining RNAscope fluorescent in situ hybridization with immunofluorescence for phosphorylated alpha-synuclein. With this protocol, we demonstrate that neurons with inclusions always express mRNA for alpha-synuclein, consistent with the model that inclusion formation requires cell-autonomous endogenous alpha-synuclein expression. Interestingly, inclusions were only observed in glutamatergic neurons and were not observed in GABAergic neurons, which express very low levels of alpha-synuclein mRNA. In the future, we will use this method to track transcriptional changes in a cell-specific manner during the process of inclusion formation and cell death.

Poster #27

Noradrenergic denervation-supersensitivity in the TgF344-AD rat driven by β-adrenergic receptors

A. M. GOODMAN, L. L. MCMAHON.

The locus coeruleus (LC) is the sole source of norepinephrine (NE) for most of the brain and is critical for the maintenance of late-life cognitive abilities. Damage to this central noradrenergic (NA) system causes deficits in learning and memory and age-related alterations may explain deficits in an aged organism's ability to adapt to changing environments (Weiss et al., 1980). The LC is particularly susceptible to hyperphorphorylated tau (pTau) deposition and toxicity and is one of the first regions to be damaged in prodromal Alzheimer's disease (AD). While this has been known for decades, a suitable model for study has only recently been developed, the TgF344-AD rat model. Previous murine models have been unable to recapitulate the diverse spectrum of pathology seen in human AD such as pTau inclusions, neurodegeneration, and cognitive deficits. The TgF344-AD rat harbors the APPSwe and PSEN1DeltaE9 mutations driven by a mouse prion promoter and displays the most comprehensive convergence of AD pathology in any rodent model of AD, and includes tau pathology, neurodegeneration, and cognitive deficits (Cohen et al., 2013). The spread of pathology in this model remarkably mirrors that of human AD and includes pTau deposition in the LC as early as 6-months that worsens with age (Rorabaugh et al., 2017). This pTau-mediated toxicity of the LC is thought to cause the robust NA denervation of all hippocampal subfields that begins at 6-months and worsens with age. Denervation of the NA system causes upregulation of adrenergic receptors (ARs) in central nervous tissue (Bannister et al., 1981) leading to supersensitivity of several AR subtypes (Deguchi and Axelrod, 1973; Dyer et al., 2009). Importantly, soluble Aβ also interacts with AR and convolutes the functional changes of these receptors(Wang et al., 2011). Our lab's prior electrophysiological investigation of the TgF344-AD rat demonstrated reduced synaptic transmission in hippocampal pathways: medial perforant path (MPP) to dentate granule cell (DGC) as early as six months, followed months later in CA3-CA1 (Smith and McMahon, 2018). Perhaps paradoxically, long-term potentiation (LTP) in these regions was increased in transgenic compared to non-transgenic littermates(Smith and McMahon, 2018). Since differential AR activation changes fEPSPs and the strength of potentiation or depression (Bramham et al., 1997; Izumi and Zorumski, 1999; Scheiderer et al., 2004) we propose that these modifications play a role in the aforementioned changes to synaptic properties, and cognition. Application of NE to hippocampal slices produced faster responses in Tg animals was blocked with the β-AR antagonist, propranolol. We suspect these changes to the NA system are critical to the progression of synaptic and cognitive dysfunction in early AD.

Poster #28

Dendritic spine remodeling accompanies Alzheimer's disease pathology and genetic susceptibility in cognitively normal aging

K. M. GREATHOUSE, B. D. BOROS, M. GEARING, J. H. HERSKOWITZ.

Subtle alterations in dendritic spine morphology can induce marked effects on connectivity patterns of neuronal circuits and subsequent cognitive behavior. Past studies of rodent and non-human primate aging revealed reductions in spine density with concomitant alterations in spine morphology among pyramidal neurons in the prefrontal cortex. In this report, we visualized and digitally reconstructed the three-dimensional morphology of dendritic spines from the dorsolateral prefrontal cortex in cognitively normal individuals aged 40-94 years. Linear models defined relationships between spines and age, Mini–Mental State Examination (MMSE), APOE ε4 allele status, and Alzheimer's disease (AD) pathology. Similar to findings in other mammals, spine density correlated negatively with human aging. Reduced spine head diameter associated with higher MMSE scores. Individuals harboring an APOE ε4 allele displayed greater numbers of dendritic filopodia and structural alterations in thin spines. The presence of AD pathology correlated with increased spine length, reduced thin spine head diameter, and increased filopodia density. Our study reveals how spine morphology in the prefrontal cortex changes in human aging and highlights key structural alterations in selective spine populations that may promote cognitively normal function despite harboring the APOE ε4 allele or AD pathology.

Poster #29

G9a-mediated heterochromatin rearrangement in the dentate gyrus during epileptogenesis

R. M. HAUSER, C. E. WALLS, K. MCINERNEY, S. C. SINT JAGO, R. G. SANCHEZ, F. D. LUBIN.

There are currently no treatment options available to halt or prevent the development or epileptogenesis of temporal lobe epilepsy (TLE). The process of epileptogenesis involves large-scale changes in gene transcription contributing to the restructuring of synapses associated with increased hyperexcitability in the hippocampus. Recently, epigenetic mechanisms, including histone lysine methylation (HKM), have gained interest as regulatory mechanisms of gene expression dysregulation during epileptogenesis. HKM is an epigenetic modification that can result in either gene repression or activation depending on the histone lysine residue methylated and the degree of methylation (mono-, di- or tri-methylation). Alterations in synaptic function and abnormal neuronal gene regulation in the dentate gyrus (DG) region of the hippocampus contributes to TLE pathophysiology. Using the kainate (KA) unilateral intra-hippocampal experimental mouse model of TLE, we found that the heterochromatin mark histone H3 lysine 9 di-methylation (H3K9me2) is significantly decreased in the ipsilateral DG of KA infused mice as compared to saline infused controls. We found no significant changes in H3K9me2 levels in the DG of the contralateral hemisphere of KA infused animals. Next, we determined if manipulating the H3K9 histone methyltransferases G9a/GLP (EHMT2/1) in the DG alone was sufficient to effect seizure susceptibility. Using transgenic G9a floxed mice and intra-DG hSyn-Cre AAV viral infusions, we have confirmed knockdown of G9a and subsequent decreases in H3K9me2 levels in DG cell-type specific neurons. In addition, CRISPRa approaches were used to overexpress G9a, which resulted in significant increases in H3K9me2 levels. Chromatin immunoprecipitation analysis revealed changes in H3K9me2 levels at genes associated with TLE, like Bdnf, which is overexpressed during epileptogenesis. Video-EEG monitoring suggest that demethylation of H3K9me2 increases spiking frequency and methylation of H3K9me2 dampens epileptiform activity in KA infused mice. Moreover, hippocampus-dependent memory testing suggest that H3K9me2 changes strongly correlate with memory deficits in KA-infused mice. Collectively, our data suggest that G9a mediates H3K9me2 levels in the epileptic hippocampus that are diminished in DG neurons and may lead to regulation of seizure susceptibility genes and epileptiform activity. By manipulating the heterochromatin mark, H3K9me2, we have identified a putative target for novel anti-epileptogenic therapeutics.

Poster #30

RhoA-associated kinases ROCK1 and ROCK2 mediate amyloid-β induced synaptic degeneration in Alzheimer's disease

B. W. HENDERSON, S. V. BACH, J. J. DAY, J. H. HERSKOWITZ.

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 accumulation induces cellular mechanisms that drive synapse loss in AD, resulting in abnormal neuronal firing and network de-synchronicity. Yet, there are few therapeutic strategies that target synapse loss to delay or prevent cognitive decline and detrimental network alterations 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 and influence 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 hypothesize that Aβ-induced ROCK1 and ROCK2 activity promotes dendritic spine degeneration, reducing neuronal firing in primary hippocampal cultures. By coupling genetic or pharmacologic manipulation of ROCK signaling pathways with highly innovative three-dimensional modeling of dendritic structure and microelectrode array (MEA) analyses, we highlight key roles for ROCKs in synaptic degeneration that may contribute to cognitive decline in AD progression.

Poster #31

Erralpha mediates pgc1alpha regulation of metabolism targets in neuronal culture

K. JOYCE, K.PATEL, L. MCMEEKIN, D. CROSSMAN, R. COWELL.

Mitochondrial loss of function is a critical factor in multiple neurological disorders including amyotrophic lateral sclerosis (ALS) and Parkinson Disease (PD). One of the regulators for mitochondrial function is peroxisome proliferator activator receptor co-activator gamma-1 alpha (PGC-1α). It is a transcription co-activator that drives multiple gene programs related to mitochondrial function and is localized to neurons. In general, a reduction in PGC-1a expression and/or function associates with disease progression and cell loss. However, PGC-1α does not bind to the DNA itself, rather it relies on DNA binding co-factors, such as the estrogen related receptor family (ERRs). ERRs are a family of orphan nuclear receptors that have been implicated in many neurological disorders such as schizophrenia. Our lab has shown that one in particular, ERRα, is related to the control of both neuronal and metabolism genes through a series of neuronal conditional knockout experiments. In this study we examine the possible particular mechanism of ERRα's interaction with PGC-1α. Using an adenovirus to overexpress PGC-1α we also introduce in varying doses an ERRα inverse agonist, XCT790 and show reduced expression of target genes. We also analyzed RNA-seq data from an PGC-1α overexpression study and show that there is a significant number of genes are enriched for ERR binding sequences showing the applicability of examining this interaction.

Poster #32

Endogenous neuropeptide Y release attenuates long-term potentiation in the temporoammonic pathway of hippocampus

Q. LI; L. E. DOBRUNZ.

Neuropeptide Y (NPY) is one of the most abundantly expressed neuropeptides in the central nervous system, and it has emerged as an important mediator of stress, neuroplasticity and memory processes. Multiple studies using acute or chronic administration of NPY receptor agonists and antagonists have supported a role for NPY in different functions of learning and memory. However, far less is known about how endogenous NPY release affects long-term synaptic plasticity.

We have previously shown that release of endogenous NPY can modulate short-term plasticity at temporoammonic (TA) synapses onto hippocampal CA1 pyramidal cells. In particular, endogenous NPY release can be detected by observing NPY receptor dependent changes in short-term plasticity during stimulation with a physiologically-based spike train (PST). To test whether endogenous NPY release can also affect long-term potentiation (LTP), we first tested whether PST stimulation can induce LTP in the TA pathway. We find that PST stimulation induces robust potentiation of TA synapses that is maintained for at least 1 hour, indicating that it is LTP. In addition, the selective NMDA receptor antagonist AP5 prevents the induction of TA LTP by PST stimulation, indicating this type of LTP is NMDA receptor dependent.

To improve the efficiency of NPY release, we used NPY Cre/ChR2 mice that express channelrhodopsin 2 in NPY interneurons; this enables us to directly activate NPY cells using photostimulation to cause NPY release. To test the effects of endogenously released NPY on PST induced LTP, we used combined electrical stimulation of the TA pathway and optical stimulation of NPY cells applied simultaneously during the PST protocol. The combined stimulation also consistently induces TA LTP lasting over 1 hour. Blocking NPY receptors with the Y1 antagonist BIBP and the Y2 antagonist BIIE before PST stimulation caused a significant increase in the magnitude of LTP. This indicates that endogenous NPY release can attenuate LTP in the TA pathway. This study is the first demonstration of the impact of endogenously released NPY on long-term plasticity in the TA pathway, and provides a possible link between NPY's effects on circuit function and its role in regulating hippocampal-dependent behavior.

Poster #33

Phosphatidylinositol (4,5)-bisphosphate coordinates functional interactions in the dopamine transporter to promote amphetamine preference

S. J. MABRY, J. I. AGUILAR, A. SHEKAR, H. MATTHIES, A. GALLI.

The psychostimulant amphetamine (AMPH) mainly mediates its pharmacological and behavioral effects by increasing extracellular dopamine (DA) availability. DA homeostasis is maintained by the dopamine transporter (DAT), a presynaptic membrane protein that mediates the high-affinity reuptake of released DA from the synaptic cleft. We have previously demonstrated that AMPH induces N-term phosphorylation of the DAT, which leads to transport-mediated efflux of DA. Furthermore, we have shown that phosphatidylinositol (4, 5)-bisphosphate (PIP2) directly interacts with the DAT and facilitates AMPH-induced DA efflux, but is not required for DA uptake. Specially, PIP2 binds DAT through electrostatic interactions with positively charged DAT N-terminal residues. Disrupting the interactions between DAT and PIP2 or depleting PIP2 diminishes reverse transport (efflux) of DA. Previous studies on the human serotonin transporter show that non-N-terminal PIP2 binding sites (within the fourth intracellular loop) are essential for AMPH-induced reverse transport of serotonin, but not substrate uptake. Here, we show that residue R443, which resides in the fourth intracellular loop of DAT, also modulates AMPH-induced DA efflux despite normal DA uptake. Furthermore, we translate our molecular discoveries in vivo by using a coordinated genetic and pharmacological approach in Drosophila melanogaster. We demonstrate that disrupting the interaction between PIP2 and R443 disrupts various AMPH-induced behaviors and, in specific, AMPH preference.

Poster #34

Dopaminergic fibers from the locus coeruleus indirectly modulate cerebellar Purkinje cells through Bergmann glia activation

N. MCCARTHY, W.LI, L. POZZO-MILLER.

Some key features of Rett Syndrome (RTT), an autism spectrum disorder, are stereotypic hand movements, dystonia, and a dyspraxic gait. Since these symptoms all involve motor coordination, the abnormalities may stem from dysfunction in the cerebellum. Considering the role of dopamine in motor control, we hypothesize that dysfunction in dopaminergic signaling in the cerebellum is responsible for these motor deficits in RTT. Notably, there was limited data on dopaminergic pathway inputs to the cerebellum. Previous work in our lab shows clear dopamine expression in the cerebellum, and dopamine receptor type 1 (D1) distributed on Bergmann glial cells (BGCs) rather than Purkinje cells (PCs), the only neuronal output of the cerebellum. We aim to determine if dopaminergic fibers from the substantia nigra pars compacta (SNc) and locus coeruleus (LC) modulates PCs indirectly by regulating BGCs. We measured protein levels of glutamate AMPA receptor subunits and their phosphorylated versions by Western immunoblotting. Using immunohistochemistry (IHC) in brain sections from mice, we observed dopaminergic fibers originating in the SNc projecting to the cerebellum. By performing single-molecule fluorescence in situ hybridization (smFISH) in cerebellar sections, we located D1 receptors in BGCs, but not in PCs, implicating that PCs are indirectly modulated. Future studies include implementing the deletion of D1 receptors selectively in BGCs to determine the consequences on motor function.

Poster #35

Ventral hippocampal inputs to the mPFC regulate social memory

M. PHILLIPS, L. POZZO-MILLER.

Altered ventral hippocampal (vHIP) input to the medial prefrontal cortex (mPFC) has been implicated in many disorders including autism, schizophrenia, and PTSD. Here we use Mecp2 knockout (KO) mice as a model of the autism-associated disorder Rett syndrome to define the behavioral consequences of altered vHIP-mPFC projections. We first identified an increased influence of vHIP afferents on mPFC network activity in Mecp2 KO mice when compared to wildtype (WT) littermates, as determined by larger and wider spreading voltage sensitive dye (VSD) signals during subthreshold synaptic potentials evoked by stimulation of vHIP fibers in mPFC slices. To identify active neurons during specific behavioral tasks, we performed retrobead tracing to label pyramidal neurons in the vHIP that project to the mPFC, followed by c-Fos immunohistochemistry as a surrogate of neuronal activity. This approach revealed that mPFC-projecting vHIP neurons are selectively activated in WT and Mecp2 KO mice during social tasks, compared to non-social tasks and to other vHIP projection neurons. Using unbiased machine-learning classifiers to score behaviors in freely moving mice, we identified social memory deficits in Mecp2 KO mice. To test if stronger vHIP inputs to the mPFC are causal to social memory deficits in Mecp2 KO mice, we altered the activity of mPFC-projecting vHIP neurons by intersectional chemogenetics. Increasing the activity of mPFC-projecting vHIP neurons between P34-P45 with an excitatory DREADD impaired social memory in WT mice. In addition, this manipulation resulted in larger vHIP-evoked VSD signals in mPFC slices, resembling those in Mecp2 KO mice. On the other hand, reducing the activity of mPFC-projecting vHIP with an inhibitory DREADD was sufficient to restore social memory in Mecp2 KO mice, while reducing vHIP-evoked VSD signals in mPFC slices, resembling responses in WT mice. Further analyses revealed that the amplitude of vHIP fiber-evoked VSD signals in mPFC slices of inhibitory DREADD-expressing Mecp2 KO mice correlate with their performance in social memory tasks. These data demonstrate that the vHIP-mPFC projection is necessary for social memory.

Poster #36

Focused ultrasound blood brain barrier opening mediated delivery of MRI-visible nanoclusters for noninvasive neuromodulation with spatiotemporal precision

M. RICH, J. SHERWOOD, Y. BAO, F. D. LUBIN, M. BOLDING.

Systemic drug delivery produces off target effects which limits the ability to pharmacologically treat or investigate region specific brain function. Furthermore, side effects can often outweigh clinical treatment potential and confound preclinical results. Additionally, many potentially useful drugs cannot penetrate the blood brain barrier (BBB) requiring drug modifications that jeopardize or completely abolish its therapeutic action. Local drug delivery currently requires invasive methods such as injections, cannulae, and pumps that damage tissues confounding results and limiting translational efficacy. Agents that are not BBB permeable can now be delivered to specific brain regions via focused ultrasound (FUS) mediated BBB opening. FUS can be targeted anywhere in the brain with high spatial resolution to open the BBB, allowing location specific passage of systemic agents into target brain regions. However, FUS BBB opening by itself requires the use of BBB impermeable agents, lacks temporal control and circulating drugs can still cause systemic effects. Here we employ an MRI visible albumin based nanoclusters to encapsulate neuromodulators for delivery to target brain regions noninvasively via FUS facilitated BBB opening. We show that nanoclusters can encapsulate neuromodulators such as glutamate and NBQX with a very low baseline release rate. In addition, we show that IV injected nanoclusters can locally diffuse into the brain with FUS facilitated BBB opening (BBBO) and provide enhanced MRI contrast at the site of delivery. Drug release into brain tissue is triggered by a second FUS treatment (release-FUS) using different parameters from the FUS used to open the BBB. Furthermore, FUS-release causes a change in MRI contrast providing in-vivo confirmation of drug release. Importantly, we show that the drug loading capacity of the nanoclusters is sufficient for inducing localized changes in neural activity in response to glutamate release from nanoclusters in vivo. This new platform will provide noninvasive activation and silencing of spatially precise brain locations to test for effects on behavior while providing independent validation of the site of neuromodulation. This avoids the circularity of using the neuromodulatory effect to verify location of delivery.

Poster #37

Tau-SH3 interactions are critical for amyloid-β toxicity in primary neurons

J. R. ROTH, T. J. RUSH, S. J. THOMPSON, O. A. STATON, J. N. COCHRAN, E. D. ROBERSON.

The microtubule-associated protein tau has been extensively studied because it aggregates into neurofibrillary tangles within neurons, which are one of the hallmarks of Alzheimer's disease (AD). Genetic knockout of tau is protective in several models of AD, making it an exciting therapeutic target for treatment of the disease. Interestingly, tau reduction also reduces network hyperexcitability, which may contribute to neurodegeneration, in these models. Similarly, in a primary neuron culture system, tau reduction protects from amyloid-β (Aβ) toxicity and glutamate or NMDA-induced excitotoxicity. Since tau reduction is protective, it is important to determine the mechanism by which it prevents Aβ toxicity and network hyperexcitability. While the microtubule-binding domain of tau has been studied heavily, less is known about tau's proline-rich region, which is hyperphosphorylated in AD. This region of tau has several PxxP motifs that mediate binding with SH3 domain–containing proteins, including the nonreceptor tyrosine kinase Fyn. Fyn is also an important mediator of network hyperexcitability, as it phosphorylates AMPA and NMDA receptors to strengthen their signaling and regulates dendritic spine dynamics. Exogenous Aβ activates Fyn in the postsynaptic density, leading to NMDAR phosphorylation and excitotoxicity in neurons. In mouse models, expressing a truncated form of tau excludes Fyn from dendrites and protects against cognitive deficits and seizure susceptibility, showing that these deficits may be influenced by tau-SH3 interactions like that with Fyn. We developed a peptide inhibitor of tau-SH3 interactions that mimics Fyn's primary binding site on tau, the 5th and 6th PxxP motifs, to competitively inhibit its interaction with SH3-containing proteins that bind to these motifs, including Fyn. We first confirmed that it blocks the tau-Fyn interaction in cells using proximity ligation assay. The peptide inhibitor of tau-SH3 interactions protected rat primary hippocampal neurons against Aβ toxicity by multiple outcome measures, including neurite loss and metabolic dysfunction. Our results show that tau-SH3 interactions contribute to Aβ-induced toxicity and inhibiting them could be a therapeutic target for AD.

Poster #38

Increasing O-GlcNAc levels alters DNA methylation and reduces epileptiform activity

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Epigenetic mechanisms, such as 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) DNA methylation, have been implicated in the pathogenesis of temporal lobe epilepsy (TLE). However, the role of DNA methylation in the development of TLE is unclear. Post-translational modification of proteins by the O-linked N-acetylglucosamine (GlcNAc) transferase (OGT) and its antagonist O-GlcNase (OGA) plays a role in cellular survival. OGT co-localizes with the Ten-Eleven Translocation proteins that catalyze 5mC to 5hmC in eukaryotic cells, thus linking protein O-GlcNAcylation to chromatin structure. Here, we assessed protein O-GlcNAcylation, OGT, and DNA methylation levels in hippocampal tissue from TLE patients compared to aged-matched controls (Average age: 39.6yrs). We found a dramatic decrease in protein O-GlcNAcylation, OGT, and 5hmC levels in hippocampal TLE tissue compared to controls. Using the kainate-induced experimental TLE model, we found similar decreases in protein O-GlcNAcylation, OGT, and 5hmC levels in the rat epileptic hippocampus. To restore protein O-GlcNAcylation levels in the rat epileptic hippocampus, OGA was inhibited with Thiamet-G, which reduced epileptiform activity and frequency oscillations in our TLE rodent model, while 5hmC DNA methylation levels in epileptic hippocampus returned to baseline. Collectively, these findings demonstrate the therapeutic potential of Thiamet-G, and a novel epigenetic role for protein O-GlcNAcylation in TLE.

Poster #39

Impaired copper transport in schizophrenia results in a copper-deficient brain state: a new side to the dysbindin story

K.E. SCHOONOVER, S. L. QUEERN, S. E. LAPI, R. C. ROBERTS.

Dysbindin is downregulated in several brain regions in schizophrenia and modulates copper transport required for many crucial functions including myelination and monoamine metabolism. In dysbindin knockout mice, the copper transporters ATP7A and CTR1 are markedly reduced. These transporters, together with ATP7B, transport copper between the blood and the brain. Several reports have indicated an increase in copper levels in the blood of schizophrenia patients, while agents that decrease copper in the brain produce some behavioral and pathological abnormalities similar to that seen in schizophrenia. To resolve this conundrum, we sought to determine dysbindin and copper transporter protein expression, as well as copper content in schizophrenia patients.

We studied the substantia nigra (which exhibits one of the highest copper contents of the human brain) using Western blot and inductively-coupled plasma mass spectrometry. We characterized specific protein domains of copper transporters ATP7A, CTR1, ATP7B, and dysbindin isoforms 1A and 1B/C in postmortem substantia nigra in schizophrenia patients (n=15) and matched controls (n=11), as well as whole substantia nigra tissue copper content in patients (n=14) and matched controls (n=11). As a preliminary investigation, we examined medication status in medicated (n=11) versus unmedicated schizophrenia patients (n=4).

The combined schizophrenia group exhibited increased levels of C-terminus, but not N-terminus, ATP7A. Schizophrenia patients expressed less transmembrane CTR1 and dysbindin 1B/C than controls. When subdivided, the increased C-terminus ATP7A protein was present only in medicated patients versus controls. Unmedicated patients exhibited less N-terminus ATP7A protein than controls and medicated patients, suggesting medication-induced rescue of the ATP7A N-terminus. Schizophrenia patients exhibited less nigral copper content than controls.

These results provide the first evidence of disrupted copper transport in the substantia nigra in schizophrenia that appears to result in a copper-deficient state. Furthermore, copper homeostasis may be modulated by specific dysbindin isoforms and antipsychotic treatment.

Poster #40

Exercise effects on an experimental rodent model of temporal lobe epilepsy

S. C. SINT JAGO, F. D. LUBIN.

Epilepsy is a common neurological disorder affecting about 1% of the population. One of the most common forms of epilepsy is mesial temporal lobe epilepsy (mTLE), which is often characterized by seizures originating from the hippocampus resulting in neuronal death and hippocampal atrophy. Studies have indicated that seizures in the human and animal temporal lobe impairs cognition and damages hippocampal circuitry, leading to progressive memory loss present in about 50% of people with epilepsy. Physical activity and exercise have been described as a strategy for combatting cognitive deficits in epilepsy. However, our understanding of how exercise contributes to alleviating memory loss with increased seizures is lacking. The goal of this study is to investigate exercise-related effects on epileptic phenotype including memory function and hippocampal sclerosis in an experimental kainate (KA) rat model of TLE. Often, animal studies report brain-derived neurotrophic factor (BDNF) assayed from hippocampal tissue, this study will take advantage of measuring serum BDNF that can be translated and assayed in humans for clinical relevance. We will determine the impact of physical exercise on working memory performance in epilepsy and investigate if exercise induced changes in serum BDNF levels (ELISA) and hippocampal glutamate and GABA (MRS) modulate working memory performance. We hypothesize that an increase in serum BDNF levels, increase in hippocampal GABA, and a decrease in hippocampal glutamate will correspond with improved performance on working memory tasks following exercise. Our findings will help identify the underlying mechanisms that are disrupted with epilepsy that contribute to memory loss.

Poster #41
Rab27b modulates alpha-synuclein release and toxicity
R. UNDERWOOD, B. WANG, T. YACOUBIAN.

Alpha synuclein (αsyn) is the primary component of proteinaceous aggregates termed Lewy Bodies that pathologically define Parkinson's Disease (PD). αSyn is hypothesized to spread through the brain in a prion-like fashion by misfolded protein forming a template for aggregation of endogenous αsyn. The release and uptake of αsyn from cell to cell are essential processes for this prion-like spread. αSyn does not have a signal peptide for classical secretion and is thought to be released through non-classical secretion mechanisms regulated by a family of proteins called Rab GTPases. Rab27b is one of several GTPases essential to the endosomal-lysosomal pathway and is necessary for the proper localization of endosomal compartments. We have developed an in vitro doxycycline-inducible αsyn model in M17 neuroblastoma cells (termed ISYN cells). Induction of αsyn expression by doxycycline in ISYN cells causes a corresponding increase in the release of αsyn into the conditioned media (CM). When transferred to separately-cultured primary neurons, thisαsyn-enriched CM is toxic to these neurons. We found that upon αsyn induction Rab27b protein expression increased by ~2 fold in the ISYN cells. Similarly we observed a ~2 fold increase in Rab27b expression in the postmortem human brain lysates from PD patients compared to healthy controls. To examine the impact of Rab27b dependent pathways on αsyn release and toxicity, we knocked down Rab27b expression by lentiviral transfection of shRNA. shRNA knockdown of Rab27b decreased αsyn release into the CM by ~40%. Surprisingly, despite the reduction in αsyn release, CM from induced ISYN cells in which RAB27b was knocked down cells induced greater toxicity in separately cultured SH-SY5Y cells compared to control. These data indicate a potential role for Rab27b in the release and toxicity of αsyn and ultimately in PD pathogenesis.

Poster #42

The Alzheimer's disease risk gene BIN1 regulates network hyperexcitability.

Y. VOSKOBIYNYK, J. COCHRAN, T. RUSH, J. ROTH, M. WAQAS, E. D. ROBERSON.

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 have identified bridging integrator 1 (*BIN1*) as one of the leading genetic risk factors in AD. Neurons express unique BIN1 isoforms, and a growing body of evidence indicates loss of neuronal BIN1 in AD. However, the function of neuronal BIN1 remains unclear and its contribution to AD is critical to investigate. We generated brain-specific BIN1 knockout (KO) mice and discovered that the loss of BIN1 in the brain leads to network hyperexcitability, with increased seizure susceptibility. Network hyperexcitability is 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. To investigate the mechanisms by which brain-specific BIN1 loss induces network hyperexcitability, we generated mice lacking BIN1 in inhibitory or excitatory neurons. Assessing pharmacologically-induced seizures, behavior, and acute slice electrophysiology, we investigated the mechanisms by which BIN1 loss in inhibitory or excitatory neurons regulates network hyperexcitability. We found that loss of BIN1 in inhibitory neurons increased seizure susceptibility, phenocopying BIN1 loss in the whole brain, while BIN1 loss in excitatory neurons decreased seizure susceptibility. Mice lacking BIN1 in inhibitory neurons had age-dependent behavioral deficits and decreased survival. In addition, initial electrophysiological studies provide evidence that loss of neuronal BIN1 decreases neuronal activity. These data generate fundamental insights about the mechanistic role BIN1 plays in AD to provide promising therapeutic strategies for targeting inhibitory neuron dysfunction and network hyperexcitability in AD.

Poster #43

Dendritic spine pathology links tauopathy mouse models to Alzheimer's disease

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Alzheimer's disease (AD) is the most common cause of dementia and by 2050, approximately 14 million people will be living with AD in the United States. AD is classified as a tauopathy, a disease where the primary pathology is aggregation of the microtubule-associated protein tau. The Tau P301S (Line PS19) transgenic mouse model is commonly used to study tauopathies, including AD. Neuronal synapse or dendritic spine loss correlates more strongly with cognitive impairment than classical pathologic hallmarks of AD, and a recent study by our group indicated that detrimental changes in dendritic spine density and morphology among AD patients correlated strongly with neurofibrillary tangle pathology, but not Aβ plaques. Therefore, we sought to explore the contribution of tau pathology to dendritic spine changes in AD by determining whether the PS19 mouse line recapitulates the spine alterations that occur in dementia patients. Tau P301S and non-transgenic (NTG) littermates aged 6-9 months underwent behavioral testing, including elevated plus maze, Y maze, open field, and passive avoidance test. Individual pyramidal neurons in the prefrontal cortex, hippocampus, and entorhinal cortex were targeted for iontophoretic microinjection of Lucifer yellow fluorescent dye, followed by high-resolution confocal microscopy and neuronal three-dimensional reconstructions for morphometry analysis. Tau P301S mice exhibited memory deficits in the passive avoidance test as well as abnormalities in open field, including increased ambulatory distance, in comparison to age and sex-matched NTGs. Behavioral deficits in the Tau P301S mice correlated with alterations in dendritic spine density and morphology in the prefrontal cortex, hippocampus, and entorhinal cortex. Additional statistical analyses showed similarities and differences in dendritic spine morphologic profiles among Tau P301S mice and AD patients.

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Poster #44

Relation of white matter lesion load to cortical gray matter thickness in healthy aging

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Cerebral white matter hyperintensities (WMH) measured by magnetic resonance imaging (MRI) are associated with vascular risk factors and are thought to reflect small vessel disease. Recently, Kern et al. (2017), used a multivariate technique, the Scaled Subprofile Model (SSM; Alexander & Moeller, 1994) to identify a WMH-related covariance network of regional gray matter volume related to differences in blood pressure control. Here, we sought to extend this multimodal multivariate approach, by deriving a covariance network of WMH-related cortical thickness (WMH-CTh), and to evaluate its relation to age and vascular risk in a cohort of community-dwelling, healthy older adults, 50 to 89 years of age. Volumetric T1 and T2-FLAIR MRI scans were acquired in 182 older adults (mean Age = 69.8 ± 10.4, 90F/92M, hypertension = 122N/60Y). Systolic blood pressure (SBP) was computed from average ambulatory blood pressure over 24 hours. T1 scans were processed using FreeSurfer v5.3 (Fischl et al., 2002) to extract cortical thickness values from 64 regions. Global WMH maps were generated from T1 and T2-FLAIR scans using a multispectral algorithm (Schmidt et al., 2012). The SSM was applied to regional cortical thickness measures to derive the covariance pattern related to total WMH load. The WMH-CTh pattern accounted for 15.1% of the variance in WMH load and was characterized by cortical thickness reductions bilaterally in superior temporal and right precentral regions, with bilateral relative increases in rostral and caudal anterior cingulate regions. Greater expression of the WMH-CTh pattern was associated with increasing age (r^2=0.36, $p \leq 4.72E-19$) and hypertension (r^2=0.03, $p \leq 1.98E-2$), but was not related to SBP ($p = 0.15$). After we controlled for gender, hypertension, diabetes, smoking history, and SBP, the relation between WMH-CTh and age remained significant (R^2 change=0.31, $p \leq 2.49E-17$). These results suggest that, in healthy older adults, aging is associated with an increasing relation between WMH lesion load and regional cortical thickness that is distinct from common vascular risk factors. Together, these findings support the use of multimodal network covariance methods to advance understanding of the relation between gray and white matter differences in the context of brain aging.

Poster #45

Effect of sex and ApoE genotpye on regional brain volumes and white matter integrity in mice using high resolution MR imaging

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Sex differences in the progression of Alzheimer's disease (AD) in APOE4 carriers is eminent in the early stages. Early changes in white matter microstructure and alteration in regional brain volumes can be indicative of neurodegeneration during disease progression. APOE4 homozygotes have a higher accumulation of white matter hyperintensities, as seen on T2-FLAIR MRI, during normal aging, which is further increased after AD diagnosis. To establish translational validity of the humanized APOE mouse model for clinical findings, we conducted magnetic resonance imaging (MRI) on these mice. Male or female mice (n=11) with a targeted replacement of mouse APOE gene with either human APOE3 (ApoE3TR) or APOE4 (ApoE4TR) were used in the study. Fixed mouse brains were collected at their age of 16 months, and underwent high-resolution 3D T2-weighted RARE (75 micron isotropic voxels, 192x320x128 matrix) with TR/TE=1500/10ms. Multi-shell super-resolution diffusion-weighted MRI was also carried out on these brains with b=1000, 2000, 3000, 4000, 5000, 6000 s/mm2, (200 micron isotropic voxels, 96x96x26 matrix). MRI was carried out on a 7T Bruker Biospec, using a volume coil for excitation and a 4-channel phased-array surface coil for reception. Images were processed using ITKsnap and MRIcron for brain extraction and biased corrected using the N4 routine in the Advanced Normalization Tools (ANTs). A T2-weighted reference image and atlas with 356 regions of interest (ROIs) (Steadman et. al., Autism Res, 2014) was registered to each animal using the SyN in ANTs. 14 regions of the brain, inclusive of white matter and grey matter areas were compared across all 4 groups. Female ApoE4TR mice had significantly larger cortical regions than the male ApoE4TR mice. Female ApoE4TRs trended to have larger white matter areas inclusive of anterior commissure, posterior commissure and corpus callosum. Other grey matter areas such as the hippocampus, striatal area and thalamus also trended to be larger in the female ApoE4TR mice. The diffusion weighted MRI will be used for evaluation of brain microstructure including measures of white matter integrity and connectivity. The results from the study suggested sex differences in regional brain volumes in the ApoE4TR mice. The ongoing analysis of white matter integrity will provide further structural and functional information in understanding the tissue microstructure differences induced by sex or ApoE genotype in the aging brain, and its contribution to AD onset and progression.

Poster #46

RIPK1 regulatory activity in Alzheimer's disease

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Severe neuronal loss is a key characteristic of the Alzheimer's disease (AD) brain, and is a focal point for AD research. Necroptosis is a programmed form of necrosis, which involves the formation of the necrosome, a multiprotein complex containing receptor-interactive protein kinases (RIPK) 1 and 3, which activates the mixed lineage kinase domain-like (MLKL) protein. We found that necroptosis is activated in human AD brains. Specifically, we found that RIPK1 and MLKL positively correlated with Braak stages, and inversely correlated with cognitive scores. Furthermore, we generated a causal gene regulatory network modeling RIPK1 interaction in AD-relevant tissues. The network was inferred from DNA and transcriptomic data generated from post-mortem samples across two brain regions, which were used to build RIPK1 networks in the anterior prefrontal cortex and the entorhinal cortex. Across both regions, we identified 819 genes whose expression covariate with RIPK1 expression. These genes significantly overlapped with multiple, independent AD gene expression profiles, comprising non-demented AD (which are characterized by moderate neuropathology, without cognitive impairment) and clinical AD. There was uniform consistency between the signed relationship linking RIPK1expression with its downstream neighbors, and the direction of differential expression in the clinical AD profiles; specifically, genes negatively regulated by RIPK1 overlapped with genes down regulated in AD. This large, concordant overlap between genes regulated by RIPK1 and genes differentially expressed across multiple AD severity and regional contexts suggests that RIPK1 activity could explain a significant portion of transcriptomic changes in AD.

Poster #47

Age-dependent correlation between spatial and working memory does not extend to object recognition

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As average life expectancies continue to increase around the world, it is critical to understand the normative characteristics of brain and cognition during aging. While it is well-documented that certain changes in learning and memory are to be expected as we age, it is also well-appreciated that there is significant variability in the extent to which different domains of cognition are impacted in any given individual. To better understand the complexity of individual differences in cognition during aging across the lifespan, we designed a battery of behavioral tests that assess the functional integrity of distinct brain regions. This battery consists of the spatial and cued versions of the Morris watermaze, spontaneous object recognition (SOR), and a delayed matching-to-place working memory task. Male Fisher 344 rats were examined at three ages: young adult (6mo), middle-aged (15mo), and aged (23mo) at the beginning of testing. The first step in our analysis process is to assign cognitive category levels on the basis of performance on the hippocampus-dependent spatial version of the Morris watermaze: low, average, or high within a given age group. These spatial cognition categories were then compared to working memory performance within young animals: the high-performing animals on the spatial task were also high performing on the prefrontal cortex-dependent working memory task. The opposite was true for the aged group of rats, however, as the old animals that performed poorly on the spatial version of the water maze, performed well for their age group on the working memory version of the task. The middle-aged rats showed relationships between spatial and working memory that were intermediate between the young and aged groups. With respect to the perirhinal cortex-dependent object recognition memory task, there were significant differences across age, consistent with previous observations in aged rats, monkeys (Burke et al., 2012), and humans (Ryan et al., 2012). These changes in recognition memory were not related to the spatial cognitive category for any age group, even though both the perirhinal cortex and hippocampus are required for adequately using cue recognition for processing spatial input (Burke et al., 2018 in press). Additionally, there was no correlation between SOR performance and working memory performance across age, where comparable delays were used in both tasks. Taken together, these data emphasize the importance of understanding the relationship between the function of these brain regions across age, as it may provide insight into how these processes can be optimized for the highest quality of life as human life expectancy continues to rise.

Poster #48

Chronic exposure to the therapeutic progestin nestorone promotes neurogenesis: Implications for sustaining regeneration in female brain

S. CHEN, N. KUMAR, Z. MAO, T. WANG, R. SITRUK-WARE, R. D. BRINTON.

Neurogenesis is the principal regenerative mechanism to sustain the plasticity potential in adult brains. Decreased neurogenesis parallels the cognition decline with aging, and has been suggested as a common hallmark in the progression of many neurodegeneration diseases. We previously reported that acute exposure to Nestorone (NES, segesterone acetate), alone or in combination with 17β-estradiol (E2), increased rat neural progenitor/neural stem cell proliferation and survival in brain hippocampus both in vitro and in vivo. The present study expanded our previous findings to investigate the more clinical related chronic exposure NES alone or in combination with E2 on the regenerative capacity of adult brain. To mimic the chronic contraception exposure in women, 3 months old female mice (n = 110) were treated with NES, with or without co-administration of E2, for 4 weeks. Neural cell proliferation and survival and oligodendrocyte generation were assessed and the involvement of insulin-like growth factor 1 (IGF-1) signaling pathway was studied. Our results demonstrated that chronic NES and E2 alone or in combination increased neurogenesis by a comparable magnitude, with minimum to no antagonistic or additive effects between NES and E2. In addition, chronic exposure of NES or NES+E2 stimulated oligodendrocyte generation, indicating potential elevated myelination. IGF-1 and IGF-1 receptor (IGF-1R) were also upregulated after chronic NES and E2 exposure, suggesting the involvement of IGF-1 signaling as the potential underlined regulatory pathway transducing NES effect.These findings provide preclinical evidence and mechanistic insights for the development of NES as a neuroregenerative therapy to promote intrinsic regenerative capacity in female brains against aging and neurodegenerative disorders.

Poster #49

Lateral but not Medial Entorhinal Cortex population representations become more sparse with age

A. COMRIE, J. P. LISTER5, M. K. CHAWLA, C. A. BARNES.

The hippocampus undergoes biological changes with age that are associated with changes in memory function. Subregions of the hippocampus receive major inputs from and send back projections to superficial and deep layers of Entorhinal Cortex (EC), respectively. Yet, how behaviorally-relevant neural activity in EC may change with age remains poorly understood. In contrast to the well-studied Medial Entorhinal Cortex (MEC), Lateral Entorhinal Cortex (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, including odors. In this study, we examined whether LEC and MEC neuron populations are selectively activated in response to distinct odors during track running, and hypothesize that aging may alter EC activity patterns that contribute to memory dysfunction. To test this, adult and aged rats were trained to run on a 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 mins. A second group (AB) also ran two sessions, but the odor stimuli were distinct between the epochs. We used cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) to visualize the time-dependent subcellular distribution of Arc mRNA in EC principal cells. We identified neurons activated during the first, second, or both sessions in superficial and deep layers of EC. We found that AA and AB behaviors elevated LEC and MEC activity compared to a control condition. Population activity, however, failed to distinguish the distinct A and B odor experiences. This suggests that EC neural population activity stably represents higher order features of the behavioral experience regardless of altered odor input. Surprisingly, more cells reached Arc activation thresholds during the second epoch than the first in LEC, but not in MEC. This may indicate that LEC circuits are sensitive to priming by similar past experience. Furthermore, a lower proportion of LEC neurons participated during the behavior in aged rats than in adult rats, while activation in MEC was preserved in aged animals. This result is in line with data from humans that show that anterolateral, but not dorsomedial, EC becomes hypoactive with age and that this reduction is related to cognitive deficits (Reagh et al., 2018). Exactly how the sparser network representations in aged rat LEC contribute to altered behavioral function across the lifespan awaits further investigation.

Poster #50

Tract-specific white matter correlates of age-related reward devaluation deficits in macaque monkeys

N. M. DE LA PENA, D. T. GRAY, L. UMAPATHY, S. N. BURKE, T. P. TROUARD, C. A. BARNES.

The ability to revalue reinforced stimuli according to changing biological or psychological needs is critical for adaptive, reward-driven behaviors. Alteration in this cognitive function is known to occur during cognitive aging in both humans and macaque monkeys. Lesion and functional imaging studies suggest that interactions between the orbitofrontal cortex (OFC) and amygdala are critical for proper revaluation performance. Tracer-based anatomical studies in nonhuman primates suggest that the OFC and amygdala are monosynaptically connected via at least two separate white-matter tracts (e.g., Lehman et al., 2011): the uncinate fasciculus and the amygdalofugal pathway through the anterior segment of the internal capsule. Diffusion tensor imaging (DTI) approaches allow for quantitative estimates of white-matter integrity, and in humans these estimates have been shown to decrease across the lifespan in the uncinate fasciculus (Hasan et al., 2009), although no studies have examined the significance of this with respect to cognition. Our group has previously shown that, in macaques, the volume of the OFC is reduced with age, and that these alterations significantly correlate with reward devaluation performance (Burke et al., 2014). Given the data showing that OFC-amygdala disconnection lesions impact revaluation performance (Izquierdo and Murray, 2004), we hypothesize that communication between the OFC and amygdala should show age-related changes that relate to worsened revaluation performance. Here we apply DTI and probabilistic tractography to assess the uncinate fasciculus and amygdalofugal tracts. The data indicate a selective relationship between the integrity (fractional anisotropy: FA) of the UF of old animals and revaluation behavior. The amygdalofugal pathway did not show this relationship. These results suggest that, in nonhuman primates, age-related declines on revaluation abilities are not due to a general degradation of connectivity between the amygdala and OFC, but rather to changes specific to the fibers contained within the uncinate fasciculus pathway.

Poster #51

Allopregnanolone restores cognitive function in APOE4+ females and males and promotes metabolism of fuels required for ATP generation

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Sex differences in the effect of ApoE4 on risk and progression of AD have been reported, with greater adverse impact in women. To address sex and APOE genotype impact on therapeutic efficacy of the regenerative neurosteroid Allopregnanolone (Allo), we investigated behavioral and metabolomic outcomes following Allo treatment in aged APOE4-/+ female and male mice. Female and male ApoE3, E4, E3/4 mice were treated 1/week with intramuscular dose of 2 mg/kg Allo for 26 weeks or placebo from 10-16 months-of-age. Dose, formulation and duration of treatment were designed to reflect the human Phase 1b/2a clinical trial of Allo, (ClinicalTrials.gov ID: NCT02221622). Behavior was assessed using Novel Object Recognition. Plasma and cortex were queried for 185 metabolites using ultra-performance-LCMS. Behavioral analyses indicated significantly increased novel object recognition in ApoE4 females and males with greatest effect in ApoE4 females, higher Discrimination Index (DI) and significantly better novel object recognition. Allo had no effect in APOE3/3 mice. Metabolomic analyses indicated changes in lipid and Arg metabolism between females and males within and across the three genotypes. In ApoE3 and ApoE4 females, plasma glycerophospholipid metabolism was significantly downregulated ($p<0.05$). Glycerophospholipids were lowest in ApoE3/4 females. In cortex, biogenic amines (α-aminoadipic acid, putrescine) and amino acids (Arg and Phe) were lowest in ApoE3 and ApoE4 females suggesting increased Arg catabolism. Following Allo treatment, ApoE4 female plasma showed decreased glycerophospholipids and increased acylcarnitines, suggesting increased lipid catabolism. In ApoE4 male plasma, Allo increased ADMA, ornithine, and acylcarnitines, indicating increased Arg and lipid catabolism. Allo exerted an APOE genotype dependent effect to improve cognitive function in ApoE4+ female and male mice with ApoE4+females exhibiting greater response to Allo. Metabolomic data are suggestive of an effect of Allo to increase lipid metabolism to generate acetyl-CoA to feed into the TCA cycle ATP generation in the mitochondria. Further, Allo treatment increased indicators of protein metabolism. In summary, efficacy of Allo was evident in both females and males and modified by ApoE genotype. Further therapeutic development of Allo is underway. Research supported by Alzheimer's Association SAGA Award, National Institute on Aging U01-AG047222 and Arizona Alzheimer's Consortium.

Poster #52

Dynamic expression of RNA stress granule components in behaviorally characterized young, middle aged and old rats

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RNA Stress Granules (SGs) are dynamic cytoplasmic structures that assemble in response to various cellular insults. During this process, these non-membrane bound organelles sequester specific mRNAs causing inhibition of translation initiation, resulting in cell protection during times of stress. Upon stress removal, RNA SGs disassemble and translation is reinitiated. These changes in RNA SGs have been linked mechanistically to age-related neurodegenerative disease suggesting that they may play a key role in the aging process. In order to examine how SGs may be influenced by the aging process, we investigated the expression of RNA SG-associated proteins including PABP, FMRP, TIAR and EIF2alpha and found that there is a region-specific distribution across rat brains, and that there are dynamic changes in the transcript levels of SG components in both flies and rats. Similar dynamic changes in rat brains were found for translation initiation factors EIF4G2, EIF4E-BP, EIF4A1 and EIF4E during aging. These molecular analyses were performed on brain regions isolated from young adults (6-8 mo, middle-aged (15-17 mo) and old (23-25 mo) rats that were previously assessed for their spatial and working memory using the Morris watermaze. Reverse transcription (RT) qPCR analyses of rat cerebellum and hippocampus brain regions revealed that the PABPC1, EIF2alpha, EIF4G2, EIF4E-BP, EIF4A1 and EIF4E transcripts show no significant differences in young or old rats in the hippocampus, however middle aged rats show a significant increase in EIF4E transcript only. In the cerebellum, all tested transcripts show robust changes during aging and interestingly, EIF4E-BP transcript is significantly reduced in aged animals only. The Morris watermaze task revealed that aged rats were memory impaired compared to both middle aged and young animals, and middle aged rats were also memory impaired compared to young rats. A linear regression analysis between RT qPCR for each of the tested transcripts and spatial memory in the hippocampus revealed no significant correlation. The relatively small changes in transcript levels in the hippocampus may reflect a lack of involvement of RNA SGs in hippocampus-dependent learning under normal conditions in aging. Because the changes in SG-associated transcripts were larger in the cerebellum, we are currently investigating an association of RNA SGs in that structure with motor system assays. In addition, we are investigating RNA SG component expression in the prefrontal cortex in relation to the working memory behaviors we have obtained from these animals.

Poster #53

Relation between physical sport activity and white matter hyperintensity volume in older adults

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Cerebral white matter lesion load, as measured by white matter hyperintensities (WMHs) on MRI, have been associated with cardiovascular risk factors like hypertension as well as increasing age and poorer cognitive performance. Physical activity (PA) may play an important role in maintaining cerebral white matter (WM) in the context of healthy aging. We sought to determine whether high levels of self-reported physical sport activity are associated with lower WMH volume. Self-report ratings of physical sport activity were obtained from 196 healthy older adults (mean ± SD age = 69.8 ± 10.6 years). Participants reporting high sport activity (n=36) were compared to those with low sport activity (n=160). MRI scans were acquired at 3T, including volumetric T1 and T2 FLAIR scans. Total WMH volume was computed with a multispectral, automated lesion segmentation method to produce probability maps using Statistical Parametric Mapping (SPM12) and the lesion segmentation toolbox (LST; Schmidt et al., 2012). ANCOVA tested age group (young-old (YO) = 50-69 years; old-old (OO) = 70-89 years), PA group, and age by PA group interaction effects after controlling for gender and hypertension status. No main effect for PA group ($p > 0.05$) was observed. We found a main effect for age group ($p = 0.005$) and age by PA group interaction ($p = 0.005$). Simple effect analyses indicated that total WMH volume for the high PA group is comparable between the YO and OO. In addition, the OO with low PA had a significantly higher WMH volume than both the YO with low PA ($p = 2.72E-10$) and the OO with high PA ($p = 0.00038$). These findings remained significant after correcting for total intracranial volume (TIV). These results suggest that high levels of physical sport activity may be an important lifestyle factor that can help to diminish WMH lesion load in old age, potentially reducing the impact of brain aging.

Poster #54

Thalamocortical white-matter integrity and the relationship between auditory function and cognitive decline in aged macaque monkeys

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Hearing loss, or presbycusis, is a hallmark of normative brain aging, with an estimated eighty percent of individuals over age 50 experiencing reduced hearing capacity to some degree. It has been known for some time that auditory processing abilities correlate with cognitive function, even when cognition is assessed using non-auditory tasks (e.g., Humes et al., 2013). Despite these relationships, no direct brain measurements have been made in an attempt to link age-related cognitive decline with presbycusis. To this end, we assessed a colony of adult and aged macaque monkeys 1) on a battery of behavioral tasks meant to probe multiple cognitive functions, 2) with temporally precise physiological estimates of auditory function (auditory brainstem and mid latency responses), and 3) with structural and diffusion-weighted magnetic resonance images to extract quantitative estimates of volume and connectivity between distinct auditory and cognitive brain regions using probabilistic tractography. Our results suggest that aged macaques are impaired on several tasks thought to require both frontal and medial temporal lobe function, as well as show a reduction in temporal processing of auditory information, both findings that have been reported previously (e.g., Hara et al., 2012; Ng et al., 2015). Only performance from specific tasks significantly correlated with estimates of temporal auditory processing, whereas other tasks did not relate to these same measures. Estimates of the white-matter integrity along the thalamic auditory radiations correlated both with estimates of temporal auditory processing and with reversal learning memory, but not any other cognitive domain tested here. These correlations preliminarily suggest that the white-matter integrity of thalamocortical fibers may contribute to the observed relationships between specific aspects of cognitive decline and presbycusis. To expand upon this concept, these correlations will be presented alongside similar analyses using estimates from the thalamic radiations connecting anterior and midline thalamic nuclei with the prefrontal cortices and medial temporal lobes.

Poster #55

Hysterectomy with ovarian conservation uniquely impacts cognition and serum hormone profiles in a rat model

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Hysterectomy (surgical removal of the uterus) is the most common gynecological surgery following only cesarean section (CDC, 2010; Carlson et al., 1993). The majority of hysterectomies are performed in women prior to age51 (Wright et al., 2013), which is the average age for natural menopause onset, and prior observations suggest that surgical removal of the ovaries before natural menopause onset may be detrimental to cognition. Thus, ovaries are preserved in about half of hysterectomy procedures. In the last decade, these findings have been extended, such that hysterectomy itself prior to natural menopause onset has also been implicated in an increased relative risk of developing dementia compared to women who did not undergo gynecological surgery (Rocca et al., 2007, 2012; Phung et al., 2010). The factors underlying cognitive and brain changes with variations in surgical menopause remain unclear and warrant further evaluation. Here, we examined spatial memory in a novel rat model of hysterectomy with ovarian conservation. Adult Fischer-344-CDF female rats underwent hysterectomy or sham surgery. Following surgery, subjects were tested on the water radial-arm maze, a spatial working and reference memory task. Results indicate that hysterectomy impaired spatial working memory performance when working memory load was taxed. Serum ovarian hormone profiles were altered in rats with hysterectomy compared to sham-operated rats, while histological analyses of the ovarian tissue suggested that surgical intervention did not alter ovarian morphology itself, at least at the time point assessed. This is the first systematic pre-clinical evaluation of the cognitive effects of hysterectomy. Relationships among cognition, hormonal changes, and ovarian morphology will be discussed. Overall, these data provide important insight into how hysterectomy may alter cognition during aging.

Poster #56

Convolutional neural networks for fast and accurate 3D reconstruction of histological sections

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While in vivo imaging offers an excellent view of the brain's "macro" structure, it lacks the resolution and intensity markers required to identify details of interest to many neuroscientists. Histological sectioning offers the ability to identify chemical and cytoarchitectural markers, but does not maintain the structure of the intact brain. This necessitates methods of 3D histological reconstruction. A significant remaining challenge of this field is to balance the computation time with the accuracy of a reconstruction scheme. Previous work on histological reconstruction has used either intensity-based warping techniques, which are slow due to iterative image-wide multiplication, or landmark or feature-based registration which reduces computational complexity at the expense of accuracy (Pichat et al., 2018, Medical Image Analysis). We propose a new automated approach for histological leveraging recent advancements in machine learning to perform image registration using convolutional "spatial transformer networks", which accurately perform non-rigid registration without iteration. Our method involves a global search strategy. First the MRI is resampled for a given θ-yaw, θ-pitch, z-position, xy-plane resolution, and z-plane resolution. These terms account for position and for shrinkage or expansion that occurs during sectioning. Next, histological sections are registered to the MRI, estimating x-position, y-position, θ-roll, and non-rigid terms for each section. These terms account for deformations that occur during the tissue mounting process. Next, a cost function is computed that considers: 1) The intensity-based similarity between the histology and MRI, 2) regularization terms that quantify the deformation energy of the registration, and 3) an estimate of the probability of reconstruction derived from pre-computed intensity-based similarity distributions S(dx,dy,dθ) between neighboring histological sections. This process is used to search θ-yaw, θ-pitch, z-position, xy-plane resolution, and z-plane resolution for the optimal solution. With these parameters selected, we overtrain the spatial transformer networks to find the best x, y, θ-roll, and non-rigid terms for each section. We find this approach is extremely accurate and drastically reduces execution time allowing researchers to integrate histological data into 3D structural MRI images quickly, accurately, and automatically. Applications include quick integration of new histological data into existing brain atlases, creation of de novo brain atlases, and construction of MRI-based probabilistic atlases that provide information on histological markers.

Poster #57

Aged-related impairments in spatial reference frame updating

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Both the hippocampus and the medial portion of the entorhinal cortex (MEC) contain functionally distinct sub-networks of spatially modulated neurons which are believed to work cooperatively to support spatial navigation. The two broad categories of spatial feedback utilized to anchor and update the spatial firing of these cells are allocentric (i.e., external) and egocentric (i.e., self-motion). As with older adults, aged rats show robust impairments on a number of different spatial navigation tasks (Lester et al., 2017). There is some evidence that these navigation impairments are accompanied by a bias away from using an allocentric navigation strategy towards relying on an egocentric strategy. To test the degree and timing with which aged animals utilize these two forms of spatial information, a novel behavioral arena was developed in which rats are trained to traverse a circular track and to stop at a learned goal location that is fixed with respect to a panorama of visual cues projected onto the surrounding walls. By instantaneously rotating the cues we are able to put allocentric and egocentric reference frames in direct and immediate conflict and characterize how quickly and accurately aged animals utilize allocentric feedback to navigate to a new rotated goal location. Behavioral data collected from five young (9 – 15 mo) and four aged (23 - 30 mo) animals reveal that both age groups are able to update their behavior following cue rotation, although aged rats tend to perseverate to the original goal location more often. Young rats, by comparison, were more likely to stop at some intermediate location between the original and rotated goal location. These findings suggest that when spatial reference frames are put in conflict, young rats settle on a strategy that combines both sources of spatial information, while aged animals adhere more rigidly to only one spatial reference frame. We are currently collecting electrophysiology from both CA1 and MEC while animals perform the task. Based on our behavioral findings, we predict that when spatial reference frames are put into conflict, the CA1 place cells in young animals will show variability in terms of which reference frame they anchor to (as in Lee et. Al., 2004). We predict that aged CA1 place cells, by comparison, will have a greater tendency to remain anchored to the already established reference frame. If the age-related behavioral changes we observe are due to intrahippocampal network impairments, spatially-modulated cells of upstream MEC should show comparable realignment in both age groups.

Poster #58

Hormone loss and intervention initiated at different endocrine status differentially regulate brain bioenergetic function: Implications for Alzheimer's disease

Z. MAO, F. YIN, Y. SHANG, R. BRINTON.

The perimenopause is an aging transition unique to females and is associated with multiple neurological symptoms. Our previous study in a rodent model of human perimenopause revealed the perimenopausal transition as a critical transition period characterized by a significant decline in bioenergetic and synaptic functions, that is reminiscent of early stage of Alzheimer's disease (AD). Combinations of 17β-estradiol (E2) and progestogens (P4) in varying regimens are widely used as hormone therapy for menopause-related climacteric symptoms. The present study was aimed to determine the efficacy and optimal intervention window of E2 in combination of cyclic P4 therapy on female rat brain at different stages of the perimenopausal transition, against bioenergetic deficits and AD risks. Placebo or E2+CyP4 therapy was initiated on female rats at 9-10 months with either pre- or perimenopause stages at the same age, and for each stage, ovariectomy (OVX) or Sham OVX surgery was performed before the intervention. Hormone therapy consisted of two 30-day cycles of continuous E2 and cyclic P4 (10 days/cycle) delivered by silastic capsules. Upon completion of the regime, rats were subject to transcriptomic, biochemical, immunocytochemical and brain metabolic investigations. We previously reported that a two-month treatment of E2+CyP4 on (OVX) young rats induced a bioenergetic gene-expression profile comparable to the ovary intact females. Our data from this study indicate that the efficacy of E2+CyP4 therapy on brain bioenergetic functions in terms of glucose metabolism and mitochondrial respiratory capacity was differentially affected by the endocrine status of the rats when the intervention was initiated. In addition, our data also suggested that OVX initiated on pre- or perimenopausal stages elicited differentiated effects on bioenergetic-, inflammatory- and AD-related gene expressions. Immunocytochemistry study suggested that the E2+CyP4 therapy could effect through the PI3K-Akt pathway that was inhibited by OVX. Bioinformatic analysis of the hippocampal transcriptome identified interactions between the biological pathways being affected by hormone depletion, endocrine transition and E2+CyP4 therapy. Outcomes of this study will help determine the window of opportunity for preventing the at-AD-risk bioenergetic phenotype by hormone intervention in women and will provide mechanistic details for developing novel strategies to maintain neurological health and function throughout menopausal aging against AD vulnerability.

Poster #59

Sex differences in metabolic and inflammatory aging in humanized APOE-ε4 knock-in rat brain

A. MISHRA, F. YIN, Z. MAO, Y. SHANG, L. DO, T. P. TROUARD, R. D. BRINTON.

Women APOE-ε4 carriers are susceptible to accelerated aging and undergo faster rates of conversion from Mild Cognitive Impairment (MCI) to Alzheimer's disease (AD) (Lin et al, Alzheimer's & dementia, 2015). Using humanized APOE-ε4 gene knock-in rat model, we conducted a longitudinal study to characterize the individual and combined impact of sex and APOE-ε4 genotype on the brain aging process. APOE-ε4 and wildtype (WT), female and male rats, were assessed at four aging windows: 7-8 months (m), 9-10 m, 12-13 m and 15-16 m. Reproductive cyclicity in female rats was assessed by vaginal lavage. During the longitudinal follow-up, we conducted 18FDGmicroPET/CT(18-fludeoxyglucose micro Positron Emission Tomography/Computational Tomography) to determine brain glucose uptake, and established peripheral metabolic profiles. Hippocampal RNA-Seq and magnetic resonance imaging (MRI) were conducted at end-of-study. MRI was conducted in fixed rat brain using a 3-dimensional high-resolution (100 micron isotropic) T2-weighted sequence. Diffusion-weighted MRI was also conducted using a segmented EPI sequence with b-values up to 6000 s/mm2. Metabolically, female APOE-ε4 rats underwent an age-related decline in insulin with concomitant rise in plasma levels of ketone bodies. In comparison to WT-females, APOE-ε4 females exhibited significant decline in 18FDG uptake at 12-13m, following reproductive senescence. The decline in glucose uptake in APOE-ε4 females worsened with age. Female APOE-ε4 rats had lower 18FDG uptake than males across all time points. MRI-based quantitative volume assessment of brain regions revealed that white matter areas – anterior commissure and posterior commissure, in the APOE-ε4 female brain trended towards larger volume relative to APOE-ε4 males. Assessment of myelin integrity, via diffusion parameters, is currently underway. In the APOE-ε4 females, grey matter areas – neocortex ($p<0.05$) and hippocampus, were relatively smaller in comparison to APOE-ε4 males. RNA-seq analysis from the hippocampus revealed an upregulation of MHC-I, IL1R and IL6R in APOE-ε4 females. Upregulation of these genes may indicate activation of neuroinflammation in APOE-ε4 female brain. APOE-ε4 females also show an upregulation of PLA2G4 (cPLA2) indicating possible activation of the arachidonic acid pathway involved in breakdown of myelin (Klosniski et al, eLife, 2016). Thus far, the longitudinal data indicate that APOE-ε4, in combination with the aging endocrine transition state, worsens the metabolic trajectory which is associated with changes in regional brain volumes and neuroinflammation in the aging female brain.

Poster #60

Differential effects of healthy aging on directed and random exploration

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The explore-exploit tradeoff is a fundamental behavioral dilemma faced by all adaptive organisms. Should we explore new options in the hopes of finding a better meal, a better house or a better investment vehicle for our savings, or should we exploit the options we currently believe to be best? Recently, we have shown that young adults solve the explore-exploit dilemma using a mixture of two strategies: “directed exploration”, in which a competition between information seeking and ambiguity aversion drives exploration by choice, and “random exploration”, in which adaptive behavioral variability drives exploration by chance. In addition, work in adolescents has found that directed, but not random, exploration increases with age between the ages of 12 and 18. In this work we investigated whether explore-exploit behavior continues to change in old age.Our preliminary data from older adults (n = 29, ages 65-74) suggests that explore-exploit behavior continues to change throughout the lifespan. In particular, compared to 284 healthy younger adults (ages 18-22), these data suggest that healthy aging is associated with substantial changes in explore-exploit behavior. In particular, we found that older adults showed higher ambiguity aversion overall ($p < .0001$), suggesting that they were less likely to choose an unknown, exploratory, option in general. However, we also found that older adults could overcome this ambiguity aversion through increased directed exploration in situations where exploration had value ($p<.05$). In contrast to this increase in directed exploration, we found a trend towards reduced random exploration, ($p = 0.07$) in older adults. The finding that ambiguity aversion changes as a function of age is consistent with previous findings in the decision-making literature. However, it is surprising that directed exploration appears to continue increasing into old age. One reason for this could be a possible relationship between directed exploration and temporal discounting which, at least in theory, suggests a negative relationship between discounting and directed exploration. It is well known that older adults discount future rewards less than young people and such an relationship could explain our effect. The finding that directed exploration has a different age dependence to random exploration is consistent with a number of recent findings suggesting that directed and random exploration rely on dissociable systems in the brain.

Poster #61

Changes in whole transcriptome in hippocampus sub-regions of aged rats

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Background. Here we used next generation RNA sequencing to investigate differential changes in the rat whole transcriptome within each of three hippocampal subfields CA1, CA3 and Dentate Gyrus (DG). We investigated the genes associated with normal aging and the sub-regional specific transcriptome differences regardless of age, extending our previous study conducted on protein coding mRNAs (Ianov et al., Front Aging Neurosci. 2017;9:383).

Methods. The experiments (Morris Water Maze) were conducted on Male Fisher 344 rats of two different age classes: young (5-6 months; n = 10) and aged (17-22 months; n = 24). The whole transcriptome was sequenced using the Illumina HiSeq2500, and differentially expressed genes (DEGs) were detected using DESeq2. Cell specific expression of DEGs was estimated using the Brain RNAseq database. All the results were compared with human public datasets (i.e: GSE11882).

Results. We detected a total of 34 genes dysregulated (most upregulated) and associated with aging across the 3 subregions, with the highest number of DEGs in CA1. Most of them were detected in our previous studies, whereas five of them (Laptm5, Ctss, Trem2, Itgb2, and Gpr183) were also detected in the human hippocampus dataset. Most of the DEGs were expressed in microglia, and are responsible for the immune upregulation observed by enrichment analysis. The results were confirmed in the human dataset, where we also uncovered the role of endothelial genes and processes associated to platelets and hemostasis. We also reported the upregulation of the pseudogene AABR07006310.1 (CA1), and lncRNA AABR07001734.1 (DG), which expression levels are strongly correlated with other key DEGs in the corresponding subfields. The analysis of transcriptome of the hippocampus subfields (regardless aging) highlighted the presence of specific signatures for both protein coding and lncRNAs genes.

Conclusions. We confirmed and extended our previous study on aging conducted on rat hippocampus, highlighting the increased susceptibility of CA1 in aging. We detected a list of 18 genes strongly validated in our previous study, with 5 of them associated with aging in an human hippocampus dataset including individuals with both sexes. We also detected specific genes expressed in microglia and involved in the neuroinflammation processes occurring in the aging brain. The role of endothelial genes we observed in the human hippocampus could be related to the increased incidence of thrombotic disease related with aging. Moreover, the dysregulation of Anxa3 (Annexin A3, involved in agiogenensis) could be potentially linked to a compensative mechanism acting to improve the defective Blood Brain Barrier as consequence of the aging process. We reported the upregulation of AABR07006310.1 and AABR07001734.1 in association with aging, although the clarification of their function requires further experimental evidences. Finally, we demonstrated a relationship between lncRNA profiling and cytoarchitectural boundaries in the rat hippocampus subfields, confirming the pattern observed for protein-coding genes.

Poster #62

Behavior and brain: uncovering relationships between 17-beta-estradiol dose, spatial memory performance, and protein expression in the brain of middle aged ovariectomized rats

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The endogenous estrogen 17-beta-estradiol (E2) is involved in cognitive function, as evidenced in human work and in rodent studies. During the perimenopausal period and at menopause, there are alterations in E2 levels, with an eventual decrease in circulating E2 levels, along with other ovarian-derived hormones. E2-containing hormone therapy is commonly used to alleviate many physiological symptoms associated with menopause. Thus, it is critical to understand how E2 impacts not only cognitive performance, but also the putative underlying neuromechanisms involved in cognitive function. Studies indicate that E2 can increase the expression of insulin-like growth factor-1 receptor (IGF1-R) and activated extracellular regulated kinase (Erk) 2 in the dorsal hippocampus, and there is evidence that IGF1-R and activated Erk 2 are required for E2-induced cognitive effects. Here, we examined how two doses of E2 - 0.3 µg/rat for the low dose and 3.0 µg/rat for the high dose - impact IGF1-R expression and activated Erk 1/2 expression in the dorsal hippocampus, ventral CA1/2 hippocampus, perirhinal cortex, and entorhinal cortex in middle-aged, ovariectomized rats. All animals underwent testing on a behavioral battery evaluating spatial working and reference memory simultaneously (water radial-arm maze) and spatial reference memory alone (Morris water maze) prior to brain analyses, allowing us to evaluate how IGF1-R and activated Erk 1/2 expression relate to learning and memory performance. On the water radial arm maze, the low E2 dose improved spatial working memory performance compared to the vehicle and high E2 dose groups. Interestingly, a linear relationship was found between IGF1-R expression in the perirhinal cortex and E2 dose, whereby as E2 dose increased, IGF1-R expression increased linearly. Additional analyses are underway to determine how IGF1-R expression, and how activated Erk1 and Erk2 expression, in each of the brain regions analyzed relate to learning and memory performance. Determining how behavioral and brain outcomes change as a function of E2 dose, and how these measures relate to each other, is a crucial piece of the puzzle that will help elucidate the role E2 plays in cognitive function concurrent with other factors known to impact efficacy, such as variations in menopause status. A more complete understanding of how E2 impacts the brain, and how this relates to behavior, may lead to the design of hormone therapies that capitalize on E2-induced molecular changes in the brain to obtain optimized cognitive outcomes.

Poster #63

A direct comparison of dye- and imaging-based removal of lipofuscin-induced autofluorescence from primate brain tissue

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Brain tissue contains autofluorescing elements that are potentially detrimental to accurate identification of neurons in brain tissue. In fluorescence imaging studies this autofluorescence can be visually indistinguishable from immunolabeled cells and can significantly impact the ability to detect the desired signal from noise. Because some autofluorescent bodies such as lipofuscin tend to accumulate with age, this can create a serious problem for studies examining multiple age groups. Lipofuscin is an intracellular collection of various lipids and trace metals within lysosomes that evades degradation and can amass to surround the entirety of a neuron's cell body (Brizzee et al., 1974). This particular autofluor has been shown to possess a spectral profile which spans the emission ranges of commonly used fluorophores utilized in fluorescent microscopy (Edwin and Jackman, 1981; Feldman et al., 2015). The most widely used method to combat this autofluorescence involves sequestering the fluorescent emission with lipophilic dyes such as Sudan Black B (Romijn et al, 1999). While effective, this treatment seems to come at the cost of potentially reducing and sometimes completely obscuring the emission of fluorescent probes used in immunohistochemical experiments (Schnell et al., 1999). Fortunately, with the advent of more sophisticated fluorescence detection systems, it is possible to record spectral data on a pixel-by-pixel basis. These methods can be used for a non-chemical, imaging-based approach for autofluorescence removal. The present study compares the spectral imaging and linear unmixing technique with the Sudan Black B (SBB) treatment method. Images of tyrosine hydroxylase- (TH) and calbindin-immunolabeled (Cb) cells from the midbrains of aged rhesus macaques are acquired on a Zeiss LSM880 inverted confocal microscope, and then undergo image segmentation analysis and cell counting. Results suggest improved preservation of fluorescence signal in Cb-Unmixed over Cb-SBB treated images based on an automated thresholding algorithm (on average 52 ± 3% fewer signal pixels after SBB-treatment). Furthermore, on average, more cells were counted in Unmixed images compared to SBB images (TH: 9.83 ± 2.48% and Cb: 33.56 ± 5.49%). Together these data suggest that the spectral imaging and unmixing method improves the visibility of individual immunolabeled cells for analysis and that this method is a viable alternative to Sudan Black B-treatment.

Poster #64

Perimenopausal aging brain is characterized by a bioenergetic-inflammatory transition state that indicates Alzheimer's vulnerability

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Perimenopause is a female aging transition that proceeds- and leads to reproductive senescence and is associated with multiple neurological symptoms, including those associated with increased Alzheimer's risk. We previously demonstrated declined bioenergetic and synaptic functions in perimenopausal brains that are reminiscent of early stage AD phenotypes. Using pathway-centric bioinformatic approaches, the present study is aimed to determine the underlying biological processes that drive the transformation of perimenopausal brain and their contribution to AD vulnerability. Hippocampal and hypothalamic RNAs from six groups of female rats at different age and endocrine status were sequenced and analyzed through Principal Component Analysis (PCA), Differentially Expressed Gene (DEG) analysis and Gene Set Enrichment Analysis (GSEA). We developed a new ranking system for enriched pathways among biological groups by summarizing all pairwise GSEA results. Hierarchical clustering was applied to identify significant interactions between emerged pathways. PCA revealed that rats during perimenopause exhibited substantially higher variance in overall hippocampal gene expression, supporting the perimenopausal brain being at an unstable transition state. While PCA and DEG analyses of hippocampal RNA suggested significant differences among age-matched pre-/peri-/menopause brains, the difference in the hypothalamus was minor, suggesting hippocampus being more affected by endocrine aging than hypothalamus. GSEA further revealed alterations in bioenergetic-, inflammatory-, and cell proliferation pathways during the transition featured by declining bioenergetic genes and low-grade activation of immune pathways. Moreover, nuclear- (nDNA) or mitochondrial DNA (mtDNA)-encoded bioenergetic genes are differentially regulated by chronological- and endocrine aging: mtDNA genes correlated closely with chronological aging whereas nDNA-encoded counterparts were largely endocrine dependent. Our findings suggest that hippocampal transcriptome during perimenopause is at a transition state characterized by perturbations to primarily bioenergetic- and inflammatory pathways, which could contribute to increased AD risk in women. This study provides novel mechanistic insights into the impact of perimenopausal transition on brain function, which could have implications for identifying phenotypes of AD risk for earliest detection in aging females.

Poster #65

First degree family history of Alzheimer's disease influences paired associates performance and is modified by apolipoprotein e genotype, heart disease, and smoking

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Background A first-degree family history Alzheimer's disease (FH) can be a proxy for heritable and non-heritable risk factors of dementia. However, the exact influence of FH on cognition across the lifespan is poorly understood. Further, the presence of FH specific interactions with lifestyle choices, medical conditions, and genetics on cognition remains largely unexplored. We examined the influence of FH on paired associate learning (PAL) task performance and the interaction with modifiable and non-modifiable factors. Methods We developed a web-based PAL task (at www.mindcrowd.org) and tested over 75,000 individuals between the ages of 18-85. Next, we developed a follow-up health and lifestyle factor survey that was completed by over 7,000 individuals from the cohort. Lastly, we examined the well-known Alzheimer's disease genetic risk factor, the apolipoprotein E (APOE) epsilon 4 allele, in over 500 FH positive individuals via dried blood spot collection from the cohort. Results FH was associated with significantly decreased performance on PAL. This difference was larger in participants under the age of 60. Propensity score matching analysis revealed an effect size of approximately half a word pair deficit in FH individuals. Next, we identified factors modifying the FH effect. We found that a history of heart disease or smoking significantly interacted with FH and elevated an individual's risk of lowered PAL performance. Of note, the smoking interaction was only significant in females. Lastly, FH positive carriers of the APOE E4 allele also demonstrated a higher risk for decreased PAL performance. Conclusions This study suggests that FH, APOE genotype, heart disease, and smoking are important factors that modify the trajectory of an individual's cognitive performance across their lifespan.

Poster #66

NPTX2 knockout rats: a novel model for protection of synaptic function in aging and disease

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Neuronal Pentraxin 2 (NPTX2) is an immediate early gene involved in binding and clustering of AMPA receptors at synapses and mediates homeostatic scaling of circuits. In the hippocampus, this involves the synapses of excitatory pyramidal cells onto inhibitory parvalbumin-containing basket cells. Thus, low NPTX2 levels may tilt the excitatory-inhibitory balance of hippocampal circuits toward excitation. NPTX2 has been proposed to play a role in protection of synaptic function in aging and the progression of Alzheimer's disease (AD; Xiao et al., 2017), and levels of NPTX2 in brain are predictive of whether individuals with pathologically defined brain levels of amyloid plaques and tangles are cognitively symptomatic (demented) or asymptomatic (cognitively normal). That is, if levels of NPTX2 are high in brain, as in the case of normal controls and asymptomatic AD, then cognition is intact – if NPTX2 is low in brain, as in symptomatic AD, the individuals are demented. In fact, NPTX2 levels in CSF are a more sensitive predictor of cognitive status than are markers for amyloid or tau (Xiao et al., 2017). To investigate this role of NPTX2, we have begun to examine behavior, brain structural integrity by high resolution MRI, and function with single unit and EEG recordings from area CA1 of the hippocampus in NPTX2 knockout (NPTX2 KO) rats compared to wild-type (WT) controls. The larger study will examine these variables across the lifespan at 6, 12, 18 and 24mo. We report here preliminary data from the young group. So far, we do not detect overall performance differences between the young NPTX2 KO rats in spatial or working memory versions of the Morris watermaze, in motor behavior on a rotarod, or in anxiety tests using the elevated zero maze. Interestingly, the NPTX2 KO rats exhibited twice as many interruptions of on-going behavior during the spatial and working memory tasks. In the spontaneous object recognition task, the WT animals spent more time than did NPTX2 KO animals with the novel object (mean ratio novel/familiar, KO= 1.26 +/- 0.11, WT = 2.10 +/- 0.05), suggesting poorer overall recognition memory. Additionally, the NPTX2 KO rats explored the objects considerably less than did WT rats (mean number object alternations, KO = 4.1 +/ -3.3; WT = 10.0 +/- 3.0). Hippocampal volume in this young age group of NPTX2 KO rats was not different compared to WT controls (mean normalized hippocampal volume KO = 0.041 +/- 0.0, WT = 0.040 +/- 0.0). Electrophysiological studies are on-going. The results of these experiments should lead to a better understanding of NPTX2's potential role in the protection of synaptic function during aging and in neurodegenerative disease.

Poster #67

Hippocampal mediation of subjective memory complaints differs by hypertension status in healthy older adults

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Subjective memory complaints may be an important early indicator of cognitive aging. We previously found that in healthy older adults with hypertension, having mild memory complaints was associated with poorer objective memory performance than in those without memory complaints, but this difference was not observed in those without hypertension (Nguyen et al., 2016). In the present study, we sought to investigate whether differences in hippocampal volume underlie subjective memory complaints, if this relationship differs by hypertension status, and how the association is related to objective memory performance in healthy older adults.
A cohort of 208 older adults [104F/104M, mean±sd age = 69.9±10.4, mean±sd Mini-Mental State Exam = 29±1.2, hypertension (yes/no) = 69/139], 50 to 89 years of age, completed a scale of subjective memory complaints and a battery of neuropsychological tests. T1-weighted 3T volumetric MRIs were processed using Freesurfer (v6.0) software to obtain right and left hippocampal volumes. Total intracranial volume (TIV) was computed using T1 scans with SPM12 and white matter hyperintensities (WMH) were computed using T1 and T2 FLAIR scans and a lesion segmentation toolbox. Mediation analyses were performed using PROCESS macro software in SPSS (Hayes, 2012). Analyses revealed that the mediation of the relation between age and mild subjective memory complaints by right hippocampal volume was moderated by hypertension status (-.03 (SE= .01), 95% CI, [-.06, -.01]). These findings remained significant after including gender, education, hypertension duration, WMH volume, and total recall on word list learning test as covariates. There were no significant mediation effects of the relation between age and memory complaints for left hippocampal volume with or without covariates. Additionally, a sequential mediation model in individuals with hypertension revealed that age predicted right hippocampal volume, which then predicted subjective memory complaints, and in turn predicted objective memory performance (-.16 (SE= .08), 95% CI, [-.38, -.05]). There were no significant sequential mediation models for left hippocampal volume or in individuals without hypertension. These results indicate that, in healthy older adults, the combination of mild subjective memory complaints and hypertension has an anatomical substrate, reflected by reduced right hippocampal volume, which in turn leads to differences in objective memory performance. Together, these findings suggest that mild memory complaints may provide an early marker of cognitive aging, when observed in the context of hypertension, a common age-related vascular risk factor.

Poster #68

Allopregnanolone rescues mitochondrial dysfunction in ovariectomized triple-transgenic Alzheimer's mouse brain and familial Alzheimer's neural stem cells

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We previously reported that reproductive senescence or ovarian hormone depletion by ovariectomy (OVX) significantly exacerbates glucose hypometabolism, mitochondrial deficits and AD pathology that features the female triple-transgenic Alzheimer's mouse brain (3xTgAD). We also demonstrated that the neurosteroid allopregnanolone (Allo) promotes neural stem cell regeneration, restores cognitive function and reduces AD pathology in female AD mouse brains. The present study was aimed to further investigate the potential therapeutic effect of Allo on the bioenergetic system of the female Alzheimer's brains and its underlying mechanism. Our results demonstrated that Allo reversed OVX-induced deficits in mitochondrial respiration and elevation in proton leak in 3xTgAD mice, which was supported by the increased expression and activity of key mitochondrial bioenergetic enzymes, pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (αKGDH). In vitro primary cultures suggested that Allo manifested a similar mitochondrial potentiating effect across multiple cell types including hippocampal neurons, mixed glia and neural stem cells (NSC). Consistent with the restored mitochondrial efficiency, Allo reversed OVX-induced increase in lipid peroxidation, an indicator of redox dysregulation and oxidative stress. Mechanistically, Allo enhanced brain metabolic activity, restored redox homeostasis and reduced amyloidogenesis via up-regulating genes involved in glucose metabolism, mitochondrial bioenergetics and the removal of reactive oxygen species (ROS) while simultaneously down-regulating genes involved in AD pathology, fatty acid metabolism and mitochondrial uncoupling and dynamics. Upstream regulator analysis predicted that Allo could effect through activating PPARGC1a and PPARG pathways while inhibiting the PSEN1, PTEN and TNF pathways. Further, the potential therapeutic effect of Allo on AD via promoting mitochondrial energy transduction was supported by assays performed with NSCs derived from induced pluripotent stem cells (iPSCs) of a familial AD patient with PSEN1 A431E mutation. Collectively, our findings suggest that Allo functions as a systems-biology regulator of bioenergetics, redox homeostasis, and β-amyloid metabolism in the female AD brains, thus providing a plausible rationale for Allo as a therapeutic strategy to promote female brain bioenergetic function that is compromised upon depletion of ovarian hormones, at natural menopause or after premenopausal oophorectomy.

Poster #69

Combining mitochondrial haplogroup, APOE genotype, and sex as a predictive responder identifier to regenerative therapeutic allopregnanolone for Alzheimer's disease

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Late onset Alzheimer's disease (LOAD) is a systemic disease with multiple etiologies, and is associated with compromised brain metabolism and regenerative capacity. Allopregnanolone has been shown to promote brain mitochondrial function, neurogenesis, and memory in mouse models, and is currently being investigated as a regenerative therapeutic for AD (NCT02221622). While genetic markers such as APOE genotype may predict risk of AD, there is currently no genetic markers to predict therapeutic outcomes for AD. Because mitochondrial genetic variances and APOE genotype are known to be differentially associated with respiratory capacity and cell proliferation, in this study, we evaluate whether they can be used as potential genetic markers to predict responders for Alzheimer's disease therapeutics. T-cells from allopregnanolone clinical trial participants were reprogrammed to iPSCs via a non-integrating, non-viral method, and then differentiated into NSCs using dual inhibition of SMAD signaling. Mitochondrial respiration and regenerative capacity were determined by metabolic analyzer and FACS. To determine mitochondrial haplogroups of the participants, DNA was extracted from whole blood of the participants, and Hypervariable region 1 and 2 of mitochondrial DNA were amplified, sequenced, and aligned to the Revised Cambridge Reference Sequence. Mitochondrial haplogroup was assigned using HaploGrep2 based on identified variants. Analysis revealed that allopregnanolone treatment preferentially increased maximum respiration in NSCs derived from participants of mitochondrial haplogroups A, L, M, and N compared to those from haplogroups H, HV, and J. Further, NSCs derived from male APOE4 carriers exhibited significantly different proliferation pattern relative to male non-APOE4 carriers following allopregnanolone treatment. Ongoing analyses will determine whether mitochondrial haplotype in combination with APOE genotype and sex can serve as predictive biomarkers of response to allopregnanolone on clinical level. Mitochondrial haplotype, APOE genotype, and sex in combination is a promising predictive biomarker to identify potential allopregnanolone responders. Predictive biomarkers will significantly contribute to a precision medicine strategy to identify responders to therapeutic agents for Alzheimer's disease.

Poster #70

An evaluation of short-term and long-term ovarian hormone deprivation in the APP/PS1 mouse model of Alzheimer's disease

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With no known cure, Alzheimer's disease (AD) is the most common form of dementia, affecting more than 5.7 million Americans. The aged population is not affected by AD equally; women are at a greater risk for developing AD than age-matched men. This disproportionate risk may be associated with changes in the female hormone profile that occur during reproductive senescence. Further, there is evidence that women who undergo surgical menopause (i.e. oophorectomy, or removal of the ovaries) before the onset of natural menopause are at a greater risk for dementia. We used a double transgenic AD mouse model (APP/PS1), with transgenic mice expressing APP and PS1 gene mutations resulting in beta-amyloid pathology development, to evaluate a short-term period (Study 1) and a long-term period (Study 2) of complete ovarian hormone deprivation. The long-term deprivation timepoint was based on prior work using a triple transgenic AD mouse model (Carroll et al., 2007). At three months of age, wildtype (Wt) mice and APP/PS1 mice underwent either Sham surgery or Ovariectomy (Ovx) surgery, the surgical removal of the ovary in rodents. Study 1 consisted of a short-term cohort that was tested on a battery of behavioral tasks assessing spatial reference memory and spatial working memory one month following surgery and subsequent hormone deprivation. These tasks included the Morris water maze, the delayed match to- sample (DMS) water maze, and the visible platform control task. Study 2 consisted of a long-term cohort tested three months following surgery and subsequent hormone deprivation on the same behavior battery. DMS results from Study 1 revealed that, in the learning phase of the task, genotype interacted with surgical menopause status, such that after a short-term deprivation, no genotype effect was present after Sham surgery, while Ovx induced a genotype effect, with APP/PS1 mice showing poorer cognitive scores relative to their Wt counterparts. DMS results from Study 2 showed a similar pattern of effects, with a comparable interaction between genotype and surgical menopause status. However, this effect persisted across all testing days, suggesting a global, more persistent effect with a long-term ovarian hormone deprivation. These preliminary behavioral findings indicate that ovarian hormone deprivation exacerbates cognitive deficits in APP/PS1 mice. Additional behavioral and neuropathological analyses currently underway will allow us to determine relationships between temporal parameters of surgical menopause, cognitive status within varied domains, and AD-like pathology.

Poster #71

L-DOPA-induced striatal gamma oscillations split into low- and high-frequency components following ketamine exposure in an animal model of L-DOPA-induced dyskinesia

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Preclinical evidence from our group indicates that a single extended 10 hour exposure to sub-anesthetic ketamine leads to a weeks-to-month long reduction in L-DOPA-induced dyskinesias (LID) associated with the treatment of Parkinson's disease (PD) (Bartlett et al., 2016). Considerable evidence also indicates that ketamine exposure provides lasting relief of treatment-resistant depression and chronic pain. Despite advances in its therapeutic application, the systems-level mechanisms underlying ketamine's effectiveness are not understood. A common component of disorders treated with ketamine is the presence of hypersynchronous oscillatory activity. Our general hypothesis is that ketamine disrupts oscillatory activity associated with these disorders. In the present study, we investigated whether ketamine reduces hypersynchrony associated with LID. To answer this question, local-field recordings were acquired from rodent models of PD and LID (unilateral 6-OHDA-lesioned male rats; for the LID model PD animals were primed for 21 days daily with L-DOPA; 7 mg/kg, i.p.). Dyskinetic rats with abnormal involuntary movements (AIMs) scores of 33.6 ± 6.6 (mean ± SD) were implanted with electrode arrays in motor cortex (M1), dorsolateral striatum (DLS), dorsomedial striatum (DMS), and the nucleus accumbens (NAc). Neural recordings were acquired over 11 hours during which LID (n=7) and PD rats (n=7) were administered five ketamine (20 mg/kg i.p.) or saline injections every 2 hrs. As previously reported, we determined that L-DOPA administration (7 mg/kg, i.p.) was associated with wideband gamma oscillations (40-90 Hz) in M1 and DLS, and that, contrary to our hypothesis, the power of these oscillations was not affected by ketamine administration. In the present investigation, we performed a more detailed analysis of the effects of ketamine on frequencies within the wideband gamma range (40-90 Hz). Analysis of this signal during LID revealed that ketamine administration resulted in this wideband signal splitting into a clearly discernable low-gamma (30-50 Hz) and high-gamma (70-90 Hz) component ($p=0.005$). This effect was not observed when ketamine or L-DOPA were administered separately. These observations suggest that an influx of dopamine produced by L-DOPA paired with NMDA receptor blockade by ketamine engages distinct gamma-generating networks in the striatum. This also suggests ketamine's therapeutic could be due to ketamine engaging distinct striatal networks.

Poster #72

Impact of APOE genotype on the sex differences in bioenergetics and Alzheimer's risks in aging mouse brain

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Age, APOE4 genotype, and female sex are among the top risk factors for Alzheimer's disease (AD). Our previous studies demonstrated substantial sex disparities in brain bioenergetic trajectories in normal aging- and familial AD transgenic mice, and the bioenergetic deficits occurring in the perimenopausal brain could contribute to an increased AD risk in females. The goal of the present study is to determine the impact of APOE genotype on the sex-differentiated AD at-risk phenotypes during brain aging. With age-matched female and male humanized APOE4 (hAPOE4) and hAPOE3 mice, we characterized their peripheral metabolic profile at 6- and 16 month-of-age, as well as their brain hippocampal transcriptome at 16 month-of-age. Our results indicated that at 6 month-of-age, APOE4 genotype elicited significantly lower plasma levels of glucose (in both females and males) but higher levels of ketone bodies (only in females) compared to age- and sex-matched hAPOE3 mice, and this pattern persisted to 16 month-of-age. At 16 month-of-age, the females had higher total triglyceride levels relative to genotype-matched males while APOE genotype did not elicit a difference. Moreover, hippocampal RNA-seq analysis of these mice suggested distinctive effects of APOE genotype and sex on regulating hippocampal gene expression: in terms of differentiated expressed genes (DEGs), variation in APOE genotype alone led to a more significant change than that of sex alone, and when these two factors combined, the most DEGs were identified between male hAPOE3 and female hAPOE4 mice. Furthermore, our pathway-centric bioinformatic analysis indicated that APOE4 genotype elicited a significant impact on the expression of bioenergetic- and inflammatory genes: Gene Set Enrichment Analysis (GSEA) suggested bioenergetic pathway being substantially suppressed while inflammatory pathway being activated, in both male- and female hAPOE4 mice relative to sex-matched hAPOE3 mice. These findings suggest that APOE4 genotype regulates the age-related decline in brain bioenergetic function and increased AD risk differentially in females and males. Outcomes of this study will provide mechanistic details of the APOE4 genetic burden on the sex-differentiated bioenergetic fluctuation during aging and its contribution to the onset of the prodromal AD endophenotype and higher AD risks in women.

Inter-Institution

Poster #73

Relation of physical activity to regional maps of cortical gray matter volume in the healthy oldest old: findings from the McKnight Brain Aging Registry

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Physical activity (PA) may play an important role in maintaining cognitive and brain health during aging. Wrist-worn accelerometers provide a way to objectively measure engagement in moderate to vigorous physical activity (MVPA). How this PA measure relates to brain health in oldest old adults has yet to be investigated. We sought to determine whether having high levels of MVPA are associated with greater cortical regional volumes in a cohort of oldest-old adults from the McKnight Brain Aging Registry. For this initial analysis, 40 community-dwelling, cognitively unimpaired older adults, ages 85 to 95 were included [mean±sd age = 88.6±3.2; M/F = 17/23; mean±sd Mini-Mental State Exam = 28.4±1.5]. Volumetric T1-weighted 3T MRI scans were acquired across the McKnight Brain Institutes at the University of Arizona, University of Alabama at Birmingham, University of Miami, and University of Florida – Gainesville. The MRI scans were processed using Freesurfer software (v6.0) and total intracranial volume (TIV) was computed using SPM12 to adjust the vertex-wise maps of cortical gray matter volume for head-size differences. Measures of MVPA were acquired with Actigraph accelerometers worn on the non-dominant wrist for up to seven consecutive days. MVPA was defined as time spent above an accelerometer vector magnitude of 100mg using the GGIR package (v1.6.0) in R (v3.4.4). Analyses tested the relation of MVPA to cortical gray matter volume maps using CFT and Monte Carlo extent thresholds to maintain an overall $p<0.05$ false positive rate (Greve and Fischl, 2018). Results showed that, after adjusting for TIV, higher levels of MVPA were significantly associated with increased volumes in the vicinity of left and right precentral cortical regions. These findings suggest that, among oldest old adults, engaging in more moderate to vigorous activity is associated with greater brain volume in regions of frontal cortex. Together these results provide further support for the role of PA in maintaining brain health in the context of successful cognitive aging. Future work will evaluate how different aspects of PA influence individual differences in cognitive aging within our growing cohort of oldest old adults from the McKnight Brain Aging Registry.

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