

1) Recovery Narratives: Traumatic Brain Injury in Young Adult Literature

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Background: Since Dr. Rudine Sims Bishop's essay "Windows, Mirrors, and Sliding Glass Doors," the field of YA literature has been asking: to what extent does literature accurately represent, reflect, and provide opportunities for the diverse young adults who consume it? In an attempt to further answer this question, I've added a question of my own: what are the literary narratives of recovery for young adults who have, or whose family members or friends have a brain injury?

Method: First, materials were selected specifically looking at YA fiction cataloged with a subtopic of "brain injury, concussion, post-concussion syndrome" under both the Dewey Decimal and Library of Congress cataloging system (this cataloging indicating the book answers "yes" the question: If you could have one book on the subject would this be your book?). (loc.gov, FAQ CYAC) Second, materials were gathered and reviewed for injury mechanism, recovery factors and influences, time for recovery, and character injured. Subheadings were cross referenced for overlap with other subjects.

Results: Ultimate findings in the literature are that the injuries are caused by real world factors: war, sports, self-harm, drunk driving, etc. and that recoveries are not necessarily unique to just the person, but to their environment. Long term injury impacts are not uncommon in the narratives, but healthcare intervention, parental influence, and support networks play major roles in the recovery of injured characters. More often than symptom reduction, increase of familial, peer, and self-understanding often leads to character "recovery." The indications of the findings are of a broad definition of injury recovery, as well as an intricate conception of brain injury by YA authors. Narratives of brain injury recovery most frequently overlap with narratives of romance, family, sports, high school, and the Iraq War.

Discussion: Despite discoveries, several questions remain: how do these stories impact young adults (injured and not)? What is the importance and role of recovery narratives in both young adult literature, and brain injury research? Considering these narratives, how can other narratives of recovery change our understanding of what it means to tell the story of brain injury? Most importantly, where do narratives of real young adult brain injury recovery intersect with the narratives of imagined young adult recovery; is there a separation?

(Citations: "Frequently Asked Questions: Children's and Young Adults' Cataloging Program (CYAC)" The Library of Congress. www.loc.gov. Updated 7/10/2014 Violet, Harris J. "In Praise of a Scholarly Force: Rudine Sims Bishop" National Council of Teachers of English. www.Library.ncte.org)

2) Home Stimulation for Learning in Very Preterm and Control Preschoolers

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Mentor: H. Gerry Taylor, PhD

Introduction: School readiness is a concern for very preterm (VPT) children due to challenges in areas of cognitive functioning and pre-academic skills. An important factor contributing to school readiness is the home learning environment, with previous studies showing that greater home stimulation for learning facilitates the development of pre-academic skills. However, we know little about the level of home stimulation for learning in VPT children compared to the term-born peers or characteristics of the home environment associated with stimulation for learning. The aims of this study were to examine 1) differences between 4-year-old VPT children and Term controls in home stimulation for learning and other characteristics of the family environment; and 2) associations between stimulation for learning and other aspects of the family environment.

Methods: Parents of 52 VPT children and 39 Term controls completed the StimQ2 – Preschool questionnaire to assess parental engagement in the child's learning. Measures of other family characteristics included the Parent-Child Relationship Inventory, Parenting Stress Index, and Depression Anxiety Stress Scale. Group comparisons were conducted using t tests and correlations used to examine associations of the StimQ2 – Preschool questionnaire with other family measures.

Results: On the StimQ2, parents of VPT children reported lower general engagement ($t(90) = -2.27, p = .03$) and lower involvement in child development ($t(90) = -2.75, p < .01$) and reading ($t(90) = -2.69, p < .01$) than parents of Term controls. On other family measures, VPT parents reported less child autonomy ($t(90) = -2.75, p = .04$), more traditional parent gender roles ($t(63) = -2.24, p = .03$), lower levels of communication with their child ($t(89) = -4.1, p = .001$), and less satisfaction in interacting ($t(89) = 2.92, p < .01$). Parents who reported higher stimulation for learning had lower social risk scores and endorsed less depression and less traditional parent gender roles (all p 's $< .05$). Similar associations were observed in both groups.

Discussion: Parents of VPT children scored lower on most measures of home stimulation for learning. Lower levels of stimulation, in turn, were associated with more parenting stress and a lower quality of the parent-child relationship. The findings suggest that more parent stress and poorer family functioning may contribute to lower home stimulation for learning in VPT children. To be effective, interventions to improve parent stimulation for learning may need to address other aspects of family functioning.

3) Exploring Interactions Between Physical Activity, Fitness, Sleep, and Cognitive Performance in Young and Older Adults

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Extant studies have indicated a positive relationship between physical activity and cognition in older adults. To date, there is minimal evidence linking physical activity and cognition in young adults. Our previous research (Hayes et al., 2015) has shown age-dependent associations with cardiorespiratory fitness and cognition. Whether similar age-dependent associations for physical activity metrics and cognition exist remain unclear. Moreover, sleep metrics have also been linked to cognition in young adults, yet the relationship between physical activity, sleep, and cognition in younger and older adults remains to be elucidated. The goal of this study is to explore the relationships between physical activity, sleep behaviors, fitness measures, and cognition, via subjective and objective measurements in a sample of 100 young and 100 older adults. Body composition, grip strength, mobility, walking speed, balance, and resting heart rate assessments will measure physical fitness. For seven days, participants will wear an Actigraph, which utilizes an accelerometer to objectively measure daily intensities of physical activity and sleep metrics, such as total sleep time, sleep efficiency and waking after sleep onset. These results will be compared to daily logs of activity and sleep. Participants will complete a battery of cognitive tasks to measure aspects of executive function, cognitive flexibility, processing speed, language and learning, as well as episodic, associative and working memory. This includes the NIH Cognitive Toolbox, a sustained attention task, the mnemonic discrimination task, the delayed discounting task, and a face-name memory task. To subjectively measure physical and mental health, participants will complete a series of self-report questionnaires assessing physical function, global health, social interactions, alcohol use, anxiety, depression, fatigue, and daily life satisfaction. To determine which physical activity, fitness, and sleep attributes are most closely correlated with cognitive performance, we will implement univariate and multivariate approaches. Understanding the interactions between these variables is the primary goal and will allow us to determine which interventional health-related behaviors are most important for optimizing cognitive performance throughout adulthood.

4) Gestational age, birth weight, income, and race are associated with severity of cerebral palsy

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Purpose: The cause and severity of cerebral palsy (CP) is multifactorial and not well understood. Previous literature has identified many risk factors for severity of CP including gestational age, birth weight, mechanism/time of injury, genetics, and socioeconomic status (SES) of the family. The purpose of this study was to (1) describe severity of CP using the Gross Motor Classification System (GMFCS) by gestational age and birth weight, and (2) investigate the associations between severity, type, and distribution of CP, gestational age, birth weight, annual income, and race.

Methods: N= 100 children with CP of all severity levels, ages 4.9 ± 2.1 years old (cohort of larger RCT: ACHIEVE 2015C2-1507-31899). Parents completed a medical history form and Hollingshead scale, used to assess SES, at baseline. Percentages were used to describe gestational age, birth weight, and severity. Pearson Chi-square analyses were used to investigate associations between all variables.

Results: 43.8% of children were born full-term (>37 weeks), 9.9% were born premature (32-36 weeks), 7.4% were born very premature (28-31 weeks), and 29.8% were born extremely premature (<28 weeks). Of children born full-term, 55% had moderate-to-severe CP (GMFCS III-V) and 45% had mild CP (GMFCS I-II). Of children born extremely premature, 48% had moderate-to-severe CP and 52% had mild CP. 47.5% of children were born at full birth weight (>2500 g), 4.1% were low birth weight (1500-2499 g), 9.8% were very low birth weight (1000-1499 g), and 28.7% were extremely low birth weight (<1000 g). Of the children born at full birth weight, 53.6% had moderate-to-severe CP and 46.4% had mild CP. Of the children born at extremely low birth weight, 48.6% had moderate-to-severe CP and 51.4% had mild CP. There were significant associations between CP distribution and gestational age ($p < .001$), income and gestational age ($p = .049$), CP distribution and birth weight, and CP type and race ($p = .01$).

Conclusion: The results from this study show (1) children with CP born at full term/full birth weight demonstrated higher percentages of moderate-to-severe CP, (2) children with CP who were born extremely premature/extremely low birth weight demonstrated higher percentages of mild CP, (3) children born extremely premature/extremely low birth weight had more instances of left hemiplegia, (4) children born at full-term/full birth weight had more instances of right hemiplegia and quadriplegia, (5) children of parents making \$100,000-150,000/year had children born extremely premature at higher rates than expected, and (6) black/mixed race children had higher instances of spastic CP.

5) TBI Induced Functional Deficits are Ameliorated by Forced Turnover of Microglia

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The Ohio State University Traumatic brain injury (TBI) induces progressive microglia mediated neuroinflammation that leads to acute symptoms and chronic dysfunction. Though acute complications often resolve, cognitive and psychiatric impairments may develop or persist years after injury. Despite the commonality of TBI, therapeutic targets and thus treatment options are limited. We have characterized unique transcriptional patterns of microglia following subacute (1dpi), acute (7dpi) and chronic (30dpi) injury by utilizing PLX5622-mediated microglia depletion. However, the functional and inflammatory effects of allowing microglia to repopulate following TBI is relatively unexplored. Therefore, we eliminated microglia 7d after midline fluid percussion injury and allowed for subsequent repopulation to examine functional recovery. Cortical gene expression was quantified using Nano String's Neuropathology gene expression assay (760 genes). TBI induced inflammatory gene expression (Clec7a, C1qc, Tlr2) was reversed following microglia turnover. Notably, microglia repopulation attenuated TBI associated astrocyte gene expression (Aqp4, Gfap, S100b), but did not reverse morphological astrogliosis. This suggests TBI-induced chronic pro-inflammatory microenvironments are influenced by microglia turnover. TBI associated N1 and N2 compound action potential deficits in the corpus callosum were rescued through microglia repopulation. TBI resulted in hyper-intensity of white matter fluorescent labeling in the somatosensory cortex. This phenomenon, associated with neurodegeneration, was not affected by microglia repopulation. Novel object location and recognition behavioral tasks were used to assess hippocampal and cortical learning and memory function. Analysis of these behaviors indicate cognitive dysfunction following chronic TBI is reversed by microglia turnover. Additionally, repopulation of microglia eliminated TBI-induced depressive-like behavior. Together these data suggest microglia are a potential therapeutic target to treat persistent neuroinflammation and improve Executive Functioning Predicts Academic Readiness in Very Preterm Children prove cognitive impairments sustained by TBI.

6) Executive Functioning Predicts Academic Readiness in Very Preterm Children

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Very preterm (VPT) children (GA of <30 weeks) are at high risk for deficits in executive function (EF). These deficits include problems in self-regulatory abilities, such as selective attention and inhibition of inappropriate behaviors, that can adversely affect children's everyday functioning. EF skills are also an important basis for successful school entry, and VPT children who lack these abilities can have difficulties in acquiring academic skills. Academic readiness is typically defined by meeting five major milestones: motor, play, motivation and self-control, communication, and cognition, including knowledge of letters and math concepts. However, we know little about how deficits in EF in VPT children contribute to academic readiness. This study tested two hypotheses: 1) Preschool-aged VPT children would perform more poorly than an age-matched group of full-term (FT) children on an EF task measuring inhibition and attention, as well as on measures of academic readiness; and 2) EF scores in the VPT group would be associated with more difficulties on formal assessments of academic readiness and parent report of these skills.

52 preschool-aged VPT children were compared to 39 FT peers on a measure of inhibition and attention, as measured by the mean accuracy score on a Go/No-Go task called the Zoo Game. Children's academic readiness was assessed by tests of global cognitive ability, knowledge of letters, and math concepts, as well as by parents' ratings of children's progress in meeting behavior and academic milestones.

Compared to FT group, VPT children exhibited deficits in EF skills as measured by Go/No-Go mean accuracy ($t(75) = 3.32, p = .001$), as well as lower scores in areas of academic readiness, such as global cognitive ability ($t(87) = 6.41, p = .001$), knowledge of letters ($ps < .001$), and math concepts ($t(81) = 5.53, p = .001$). VPT children's lower scores on the Go/No-Go task were associated with lower scores on most measures of academic readiness ($rs = .32 - .45, ps < .04$), and with parent report of how well children are meeting behavior and academic milestones ($rs = .33 - .43, ps < .03$). Findings suggest that VPT children's lack of self-regulatory skills is associated with poor performance in critical areas of academic readiness such as literacy, numeracy, and cognition. EF skills, such as inhibition and attention, may be critical skills to target in designing interventions to help VPT children prepare for the transition to school.

7) The saturated fatty acid palmitate activates hippocampal and amygdalar microglia from young and aged rats

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Chronic consumption of a high fat diet (HFD) is associated with a neuroinflammatory response and subsequent cognitive impairment in both rodents and humans. This phenomenon is exaggerated in aged animals such that short-term consumption (3-day) is sufficient to induce a proinflammatory response in the hippocampus and amygdala and impairment in both hippocampal and amygdalar-dependent memories. This could be due to the “primed” microglial phenotype observed in the normal aging process in rodents in which aged microglia display a potentiated response to immune challenge. HFD is associated with an increase in saturated fatty acid (SFA) accumulation in the brain which is also known to produce a pro-inflammatory response. However, little is known about how SFAs affect microglia in the hippocampus or amygdala, specifically. Here, we investigated whether SFAs would evoke a potentiated pro-inflammatory response in aged hippocampal and amygdalar microglia, thus providing a mechanism for the potentiated pro-inflammatory response in aged HFD-fed rats. Rapidly isolated microglia from the hippocampus and amygdala of young and aged male rats were treated with increasing concentrations of palmitate, the most abundant SFA found in HFD, for 2 h. Following treatment, microglia were processed for RT-PCR analysis for pro-inflammatory markers. Palmitate increased gene expression of markers of microglial activation, cd11b and MHCII, and the pro-inflammatory markers IL-1b, NLRP3, and CX3CR1 in both hippocampus and amygdala-derived cells. Aged microglia did not show any statistical difference from young microglia in response to palmitate, suggesting that SFA sensitivity of microglia, under these experimental conditions, is not responsible for the exaggerated inflammatory response in aged HFD-fed rats.

8) Sensory sensitivity for upright stance sub-acutely following concussion

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Background: Postural control impairments are common following concussion, but it is unknown if sensory processing contributes to these postural control impairments.

Objective: To examine sensory reweighting for upright stance sub-acutely following concussion. Design:

Case-control. Setting: Virtual environment in a research laboratory. Participants: 13 student-athletes (8

women, 21 ± 3 years) between 2 weeks and 6 months following concussion who reported being asymptomatic at the time of testing and 26 controls (8 women, 22 ± 3 years) with no concussion history.

Independent variable: Group (i.e., concussion versus control). Outcome measures: Sensory reweighting for upright stance was assessed by simultaneously perturbing visual, vestibular, and proprioceptive systems. The visual stimulus was a sinusoidal translation of the visual scene at 0.2Hz, the vestibular stimulus was ± 1 mA binaural monopolar galvanic vestibular stimulation (GVS) at 0.36Hz, and the proprioceptive stimulus was Achilles tendon vibration at 0.28Hz. The visual stimulus was presented at different amplitudes (0.2m, 0.8m). Center of mass gains to each modality were computed. Main Results:

Gain to vision was higher among the concussion ($M=0.977$ cm/m, 95% confidence interval= $0.788-1.166$) than the control cohort ($M=0.623$ cm/m, 95% confidence interval= $0.489-0.757$, $F_{1,37}=9.541$, $p=0.004$, $\eta^2=0.205$). Gain to GVS was higher among the concussion ($M=0.097$ cm/mA, 95% confidence interval= $0.078-0.115$) than the control cohort ($M=0.053$ cm/mA, 95% confidence interval, $F_{1,37}=15.429$, $p<0.001$, $\eta^2=0.294$). Gain to vibration was not different between groups ($F_{1,37}=0.145$, $p=0.705$, $\eta^2=0.004$). Conclusions: Despite being asymptomatic, participants in the concussion cohort had higher gains to visual and vestibular stimuli for standing balance than participants in the control cohort. These findings suggest that individuals are more perturbed by sensory stimuli following concussion and may indicate an area for future targeted rehabilitation interventions.

9) Post-operative cognitive dysfunction is made persistent with morphine treatment in aged rats

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Post-operative cognitive dysfunction (POCD) is the collection of impaired cognitive symptoms, lasting days to months, experienced by individuals following a surgery. Persistent POCD is most commonly experienced by older individuals and is associated with a greater vulnerability to developing Alzheimer's disease, but the underlying mechanisms are not known. It is known that laparotomy (exploratory abdominal surgery) in aged rats produces memory impairments for four days. Here we report that post-surgical treatment with morphine extends this deficit to at least two months while having no effects of its own. Indeed, hippocampal-dependent long-term memory was impaired two, four, and eight weeks post-surgery only in aged, morphine-treated rats. Short-term memory remained intact. Morphine is known to have analgesic effects via μ -opioid receptor activation and neuroinflammatory effects through Toll-like receptor 4 activation. Here we demonstrate that persistent memory deficits were mediated independently of the μ -opioid receptor, suggesting that they were evoked through a neuroinflammatory mechanism and unrelated to pain modulation. In support of this, aging, laparotomized, and morphine-treated rats exhibited increased gene expression of various proinflammatory markers (IL-1, IL-6, TNF, NLRP3, HMGB1, TLR2, and TLR4) in the hippocampus at the two-week timepoint. Furthermore, central blockade of IL-1 signaling with the specific IL-1 receptor antagonist (IL-1RA), at the time of surgery, completely prevented the memory impairment. Finally, synaptophysin and PSD95 gene expression were significantly dysregulated in the hippocampus in these rats, suggesting that impaired synaptic structure and/or function may play a key role in this persistent deficit. This instance of long-term memory impairment following surgery closely mirrors the timeline of persistent POCD in humans and may be useful for future treatment discoveries.

10) Behavioral changes associated with loss of NSPC derived VEGF in vivo after KA induced excitotoxic injury

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Seizures are sudden abnormal electrical activity in the brain that lead to excitotoxic tissue damage, changes in mood and behavior, and even death. Vascular endothelial growth factor (VEGF) has been shown to protect against seizure and excitotoxic injury in rats. We have recently shown that neural stem and progenitor cells (NSPCs), despite being a relatively small population of cells in the dentate gyrus (DG) of the hippocampus, produce almost one third of the vascular endothelial growth factor (VEGF) in this critical brain region that mediates memory and emotions. In order to study the contribution of NSPC produced VEGF in modulating seizures and their sequelae, we used VEGF^{fl/fl}NestinCreERT2 mice, which allows for tamoxifen (TAM)-inducible knock down (KD) of VEGF in NSPCs, in a kainic acid (KA) induced excitotoxicity model. Mice were given IP injections of TAM (180 mg/kg/d) for 5 days and had a two-day break before vehicle or KA injection (15mg/kg). Mice were then given 2 weeks of rest before undergoing hippocampus-dependent behavioral tests consisting of a novel arm test, object location test (OLT), and elevated plus maze (EPM). Analysis of the OLT and novel arm tasks confirm that the KA model impairs memory in KA treated mice compared to vehicle treated controls. Surprisingly, NSPC-specific VEGF KD seem to result in decreased memory at baseline compared to control mice and may or may not be further impacted by excitotoxic injury. Analysis of EPM indicates a decrease in anxiety in VEGF KD mice following excitotoxic injury. Elucidating the functional effects of NSPC-derived factors such as VEGF in the context of injury is a critical step to understanding how stem cells modulate brain function and will aid in the successful implementation of NSPCs as therapeutic agents.

11) RF imaging for detection and evaluation of hemorrhagic stroke

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Stroke is a leading cause of morbidity and mortality worldwide. It is largely classified as hemorrhagic and ischemic in nature. Rapid identification of stroke type and worsening are crucial for the successful implementation of therapeutic interventions. These aims are currently achieved by radiographic brain imaging techniques including computed tomography (CT scan) or magnetic resonance imaging (MRI). However, both of these modalities have limited applicability as a bedside monitoring tool for hemorrhagic transformation or edema worsening. Earlier studies with simulations have shown that both modalities individually have the potential to identify areas with hemorrhage or fluid accumulation. The goal of this pilot study is to develop a bedside non-invasive imaging technology for the detection and evaluation of ischemic and hemorrhagic stroke.

For the in vitro experiment, we constructed a six-layer brain phantom with a blood clot on one hemisphere to simulate a hemorrhagic event. Data collection was performed using a Vector Network Analyzer (VNA) and an array (16x2) of dipole antennas were used for both monostatic and bistatic data collection. The antenna elements were fabricated on a 32mil flexible dielectric making them conformal to the head. Our preliminary results indicate that presence of the blood clot modifies the backscatter signals in a repeatable pattern.

12) Buckeye Concussions: The Beginnings of a Cross-Platform OSU Student Concussion Information and Monitoring System

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Challenge: Despite present resources offered by the university, there is a significant lack of coordination between care teams and patients upon initial diagnosis of Traumatic Brain Injury (TBI). Additionally, access to resources as well as communication is limited, and many students often leave the process without significant understanding of their prognosis. Furthermore, typical medical tests for concussion patients are subjective in nature. To help resolve these problems, our team was tasked with designing an app that monitors and tracks a patient's concussion recovery journey, helps facilitate communication with their providers and standardize the tests.

Solution: We designed a mobile app that serves as a virtual 'patient care coordinator' for OSU students diagnosed with, or recovering from a concussion, as well as their care team. This app presents a consolidated system for patient-physician communication and connection. It tracks concussion specific patient information, provides screening and educational tools for emotional health, including biofeedback, meditations and a Patient Health Questionnaire (PHQ). Educational information on concussion is also consolidated with integrated outside resources for education and social support. Balance assessment, and heart rate variability is calculable with connection to dual sensors, to better analyze emotional health, as well as assist with standardized balance testing viz. BESS. This helps alleviate the subjectivizes of these tests. The information is stored in a secure database from which both doctors and patients can access information, make conclusions, and communicate with each other as necessary. We expect this system to ultimately provide the opportunity for Big Data collection and the consequent development of an AI algorithm to predict and analyze student recovery. This algorithm will act as a virtual assistant to doctors and help further reduce the subjectivizes of the tests.

Future prospects: This app consolidates all of the OSU resources for concussion in one place, is accessible, affordable, and user friendly for both the patient and healthcare provider. The goal is to help patients be more knowledgeable about their concussion health needs and standardize corresponding medical tests. Having an understanding of this process will likely speed up patient's recovery as well as help them feel more connected and supported. In addition, the prospect of having a Big Data system from the app would facilitate further concussion research to better predict concussion recovery outcomes.

13) Toward Non-Invasive Brain Temperature Sensing

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Various studies have shown potential links between an increase in brain temperature following traumatic brain injury and worsened histopathological outcomes, as well as the efficacy of maintaining hypothermic conditions in the brain to decrease such negative effects [1-3]. As such, monitoring brain temperature over the course of an injury could detect inflammation that could otherwise go undetected. Unfortunately, current standards of care to determine brain or core temperature (defined as the temperature of blood at the hypothalamus [4]) are either inaccurate or highly invasive. In terms of core temperature measurement, esophageal [5], nasopharynx [6], and pulmonary artery [4] thermometers are considered the most accurate but are not feasible outside of specific surgeries, whereas rectal, tympanic, and other near core measurements do not always reflect the core temperature [7]. Furthermore, such measurements may not detect an increase in brain temperature caused by localized inflammation. Zero-heat-flux thermometers worn on the forehead have been proposed as an accurate, non-invasive solution; however, the efficacy and validity of their measurements have been called into question, especially at the lower hypothermic temperatures shown to preserve brain function during injury [8-10]. Non-invasive microwave radiometers have likewise been proposed as a solution, but the technological limitations inherent to previous systems (e.g. narrowband antennas and unrealistic models) reduce measurement accuracy and efficacy below what is considered clinically acceptable [11-15]. To address shortcomings in the state of the art, we build on prior work performed by our team on: (a) bio-matched antennas to enable broadband, into-body measurements [16], (b) radiative transfer models [17], and (c) microwave radiometers [18] that have non-invasively and accurately retrieved the temperature profiles of layered ice sheets (similar to how human body tissues are layered). Combining these capabilities, we propose a wideband microwave radiometry system to non-invasively and accurately determine a temperature versus depth profile of the human brain. In pursuit of this goal, to date we have designed and characterized human-body phantoms matching the electrical and thermal properties of the human brain and combined the bio-matched antennas and radiometer to perform repeatable preliminary measurements with these single-layer phantoms. Additionally, in preparation for in vivo temperature retrieval, we have begun exploring transient thermal simulations of a layered human head for varying core temperature changes and environmental conditions.

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14) Repopulation of Microglia Produces Differential Age Effects in Mice

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As resident macrophages of the central nervous system, microglia are primary mediators of innate immune function in the brain. Microglia are long-lived and thus experience limited turnover, which can result in age-associated dysfunction including deficits in phagocytosis. Furthermore, microglial phagocytic activity has been shown to influence learning and memory, aspects of cognition that decline with age. Indicators of phagocytic impairment including increased intracellular lipofuscin and CD68+ lysosome size have been observed in aged microglia, and such impairment could result in dysregulated production of reactive oxygen species (ROS), which may damage surrounding cells via oxidative stress. We have previously shown that drug-induced repopulation of aged microglia reduces indicators of impairment. Therefore, we hypothesized that repopulation of microglia in aged mice would mitigate both phagocytic and cognitive dysfunction. To test this hypothesis, adult and aged BALB/c mice were administered CSF1R antagonist rodent chow to induce microglial depletion. This diet was then discontinued, allowing microglia to repopulate the brain. To examine the effects of repopulation on cognitive function, we assessed mouse performance in the Barnes Maze and Object Learning behavioral tasks. The phagocytic capacity and ROS content of microglia from repopulated versus untreated adult and aged mice were then examined *ex vivo*. We found that repopulation failed to increase phagocytic capacity or reduce ROS content in aged microglia. However, repopulation rescued deficits in strategic spatial learning and restored expression of learning-associated genes *Arc*, *Fos*, and *Npas4* in aged mice. Surprisingly, adult mice with repopulated microglia showed decreased expression of *Arc* and *Npas4* as well as the memory-associated and neuroprotective gene *BDNF*. Taken together, these data suggest that repopulation of aged microglia ameliorates certain aspects of age-associated cognitive dysfunction independent of phagocytic capacity and ROS content. Furthermore, microglial repopulation may in fact disrupt cognitive function in the adult brain. As such, these findings may lead to further clarification of the mechanisms of age-related cognitive decline.

15) Longitudinal Assessment of Cognition and Eye-related Symptoms in Youth Hockey Players

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Purpose:

Compared to many other youth sports, hockey has a long season. We performed longitudinal (early-, mid- and late-season) assessments of cognitive function and symptoms in Bantam-aged hockey players and determined repeatability across season for results collected with these concussion screening tools.

Methods and Study Design:

Repeated measures cohort study. 18 males, 13 years old, were enrolled at start of 2018-19 hockey season. Symptoms were quantified with Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ). Cognitive function was measured using CogState Computerized Concussion Assessment. Data was collected in 3 sessions, each session separated by approximately 2 months.

Results:

There was a significant ($P < 0.01$, 1-way RM ANOVA) increase in standardized scores for the CogState Learning task at visit 2 (105.811.2 SD) and visit 3 (111.111.4), compared to visit 1 (97.911.6). There was a small, but significant ($P = 0.03$) decrease in score for Processing Speed task at visit 2 (99.38.2), but not visit 3 (101.65.8), relative to first visit (104.88.6). In contrast, there were no significant ($p > 0.05$) score differences at subsequent visits from baseline for the Attention and Working Memory Speed tasks. Using Bland-Altman analysis of test repeatability, the bias score for the Learning task was 7.91 for the visits 1 and 2 comparison, and 13.14 for the visits 1 and 3 comparison, illustrating the increased within-individual scoring on this task across the season. Although CISS uses questions that are vision-specific, compared to queries about overall well-being on RPCSQ, the scores for the two surveys were highly correlated ($R^2 = 0.70$, $p < 0.001$).

Conclusions:

There was significant improvement across the hockey season on the Learning task (one card learning accuracy) of the CogState assessment in Bantam-aged players. Processing Speed (detection speed), Attention (identification speed), and Working Memory Speed (one back speed) task scores were more repeatable across the season. Individuals with greater visual symptom severity, as assessed with CISS, will also report higher symptom severity on RPCSQ.

16) Fitness and Cortical Thickness in Cognitively Healthy Young Adults

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Research Staff

Psychology

Mentor: Scott Hayes, PhD

The Ohio State University Numerous studies have demonstrated cortical thinning in aging. Recent work has demonstrated that modifiable physical attributes such as cardiorespiratory fitness are positively associated with cortical thickness among older adults. To date, few studies have explored the relationship between measures of physical fitness and cortical thickness in young adults, with some work indicating null effects or a negative relationship with fitness brain structure, suggesting there may be age-dependence in the fitness-brain relationships. However, extant studies may be underpowered to detect a relationship among young adults. To address this issue, we examined several measures of physical fitness (gait speed, grip strength, cardiorespiratory fitness, and body mass index; BMI) and their relationship to cortical thickness in young adults (N=968, ages-22to 37; mean age 28.8 years) using data from the Human Connectome Project. High-resolution T1-weighted MRI scans were processed using FreeSurfer v6.0. Surface data were smoothed using a 20-mm Gaussian kernel. General linear models were constructed on a vertex-wise basis using built-in tools, and clustering and significance testing of the resulting significant vertices was done using the software Permutation Analysis of Linear Models (PALM, v alpha 117). Among young adults, a negative association between age and cortical thickness was observed in the lateral frontal and temporal lobes, the insula, and precuneus ($p < 0.05$). No significant associations between cortical thickness and grip strength, cardiorespiratory fitness, or gait speed were observed. BMI showed a positive association with cortical thickness in the temporo-parieto-occipital region of both hemispheres, as well as in the left frontal lobe ($p < 0.05$). Our results indicate that cortical thinning may begin in young adulthood. However, with the exception of BMI, modifiable physical attributes that often show relationships among older adults may not show associations with brain metrics in young adulthood. This suggests there may be a nonlinear relationship between physical fitness and cortical thickness across the lifespan.

17) Examining the feasibility of aerobic exercise during brain functional MRI

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Psychology
Mentor: Scott Hayes, PhD

Age-related neural and cognitive decline are accelerated by poor cardiometabolic health (e.g., hypercholesterolemia, hypertension, diabetes). It is well known that exercise improves cardiometabolic health, and over the last decade multiple studies have demonstrated positive associations between cardiorespiratory(heart, vascular, and lung) fitness, the brain, and cognition .To date, functional Magnetic Resonance Imaging (fMRI) studies have examined brain function during rest, while the participant lies still on the scanner bed. Thus, the acute effects of exercise on regional blood-oxygenation-level-dependent (BOLD) signal are unknown. FMRI during exercise might uncover abnormalities in cerebral blood flow in much the same way that a cardiac stress test identifies abnormalities that were not observable at rest, and that this could potentially identify those individuals most at risk for cognitive decline. The purpose of this study was to demonstrate the feasibility of collecting fMRI data during exercise. Our goals were to implement an exercise stimulus while acquiring BOLD data and track real-time changes in cardio respiratory function (heart rate and respiration). An exercise challenge consisting of alternating 90 sec work (Power max = 80-100Watts, stepping to metronome)and 60 sec rest(Power=0 Watts, no stepping)blocks was implemented using a cardio stepper, an MRI-compatible device (similar to a Stairmaster) capable of generating an aerobic exercise stimulus. Images were collected using a Siemens Prisma 3 Tesla MRI scanner. Data were collected from 3 young adult subjects (age 23-24 years). FMRI scans were preprocessed using FMRIB Software Library (FSL) using standard processing procedures. ICA-AROMA was used to calculate, classify, and remove orthogonal motion components. As expected, HR (beats per minute) was significantly greater during exercise blocks ($X_{work}= 91.1$)compared to rest($X_{rest}= 76.2$, $t=7.7$, $p<0.001$), as was respiration (breathes per minute, $X_{work}= 21.8$, $X_{rest}= 17.3$, $t=3.3$, $p<0.01$). Although there was significantly greater head motion($X_{work}= 4.08$ mm)during exercise compared to rest($X_{rest}= 0.202$ mm, $t= 3.40$, $p<0.01$) blocks, the amount of motion varied considerably by subject(1.5%-18.0% volumes identified with excessive motion using Artifact Detection Toolbox intermediate thresholds).Based on this small sample, motion was acceptable. Preliminary analyses showed strong correlations between BOLD signal changes in the insular cortex and HR across subjects ($r=0.67$) and strong correlations between motor cortex and stepping power across subjects ($r=0.80$). This small pilot study indicates valid data can be collected during an aerobic exercise challenge during fMRI, although there was variability across subjects.

18) Cognition and Quality of Social Relationships in EPT Adolescents

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Mentor: H. Gerry Taylor, PhD

Introduction:

Extremely preterm adolescents (EPT; gestational age <28 weeks) are at greater risk for deficits in cognition and social competence when compared to full-term (FT) children. Little is known, however, about the cognitive correlates of these deficits. The two aims of this study were to 1) examine the differences in cognition and quality of social relationships in EPT and FT adolescents and 2) explore associations between cognitive and social outcomes.

Methods:

Data from this study were obtained from 41 adolescents (23 EPT and 18 FT) between 11 and 16 years of age (Mage = 13.59; S.D. = 1.70). Quality of relationships with family and friends was assessed using the Network Relationships Inventory-Relationship Qualities Version (NRI-RQV). Tests of working memory, processing speed, and executive function from the WISC-V and NIH Toolbox Cognition Battery were administered to examine cognitive correlates of relationship quality. Group comparison were conducted using t-tests and associations between cognition and relationship quality using partial correlations that controlled for group and SES.

Results:

On the NRI-RQV, the EPT group reported being closer to their siblings ($t(36) = -2.42, p < .03$) than the FT group, with a trend for EPT youth to also report a closer relationship with their parents ($t(39) = -2.01, p = .052$). The EPT group also obtained significantly lower scores on the Processing Speed and Working Memory composites of the WISC-V ($p < .01$) and on both the Fluid and Crystallized cognitive composites of the NIH Toolbox (p 's $< .001$). Lower Processing Speed scores was associated with reports of closer relationships with siblings ($r = -.40, p = .02$), mothers ($r = -.34, p = .05$), and fathers ($r = -.42, p < .02$). Higher scores on the NIH Toolbox Dimensional Change Card Sort were related to closer relationships to peers relative to parents ($r = .35, p < .05$).

Discussion:

EPT adolescents scored less well than FT youth on cognitive measures and higher on quality of social relationships with siblings and parents. A measure of processing speed was negatively associated with level of closeness with immediate family members. Results suggest that EPT adolescents and less cognitively able youth may be less prone to seek relationships outside of their family. Future research is need to examine preterm adolescents' social networks more comprehensively and further explore the effects of gender and age.

19) Traumatic brain injury disrupts acute sleep-wake function

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Neuroscience

Mentor: Olga Kokiko-Cochran, PhD

Multiple aspects of sleep function are disrupted following traumatic brain injury (TBI). While some sleep disruption effects of TBI have been previously described, the associated pathophysiology is still not fully understood. We hypothesize that neuroinflammation and apoptosis may play discernible roles in the dysregulation of sleep following TBI, particularly in the ability to achieve and maintain sleep. To observe these effects, 10 week-old, male and female mice received either a lateral fluid percussion TBI or a control sham injury. Following recovery mice were introduced into a noninvasive piezoelectric cage to define acute sleep patterns for 3 days post-injury (DPI). In addition, at 3 DPI blood and brain tissue were collected to further define pathophysiology that may contribute to TBI-induced sleep/wake disturbances. To accomplish this flow cytometry was performed on blood and Immunohistochemistry was performed on the collected brains. At 3 DPI, animals that received TBI sleep less than sham mice and have shorter sleep bouts than sham control when they are able to achieve sleep. Intriguingly, differences between TBI and sham groups are clustered in the hours preceding and immediately after light-dark transition. Shorter sleep bouts were most evident in TBI mice during the light (sleep) phase of the day, suggesting that the ability to maintain sleep may be compromised after brain injury. Together these data indicate that TBI disrupts acute sleep/wake behavior and may inhibit the ability to anticipate light/dark transitions. Ongoing studies aim to identify inflammatory changes within the brain and blood that may contribute to these sleep/wake deficits. In summary, this study provides evidence that the pathophysiology of TBI is affecting sleep function in multiple ways. Moreover, TBI-induced sleep deficits are not uniform but instead change over time. Neural mechanisms related to light entrainment and circadian rhythm may be particularly vulnerable to the effects of TBI.

20) Immediate Effects of Treadmill Walking in Individuals with Huntington's disease and Lewy Body Dementia

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Background: Treadmill training may improve gait disorders associated with neurodegenerative diseases. In Parkinson's disease, treadmill training alters gait patterns after one session, and long-term training improves gait parameters, fall risk, and quality of life. This study examined the feasibility of using this intervention for people with Huntington's disease (HD) or Lewy body dementia (LBD).

Methods: Ten individuals with HD, 8 individuals with LBD, and 10 control individuals walked for 20 minutes on a treadmill starting at a slow comfortable speed and increasing incrementally toward their normal over ground speed. Gait measures, Timed Up and Go (TUG) scores and quantitative measures of motor function (Q-motor; precision grasp force variability, finger and foot tapping frequency) were assessed.

Results. Treadmill training is feasible in HD and LBD; although, participants could not initiate treadmill walking at their comfortable over ground speeds, and only 3 participants with HD were able to achieve their over ground walking speed within the 20-minute session. No changes in gait measures, TUG times, and Q-motor measures were found among HD and LBD participants following the treadmill walking. Control participants demonstrated significant increases in several gait measures, and foot tap speed frequency after one session.

Conclusions. A 20-minute treadmill training session proved safe and feasible for individuals with HD and LBD, but no significant motor effects were found. Longer and more frequent sessions may be needed to see an effect in these disorders. Motor and cognitive impairments associated with these diseases may make them less amenable to the short-term effects of treadmill training.

21) Sleep Disruption Exacerbates and Prolongs the Inflammatory Response to Traumatic Brain Injury

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Traumatic brain injury (TBI) alters stress responses, which may influence neuroinflammation and behavioral outcome. Sleep disruption (SD) is an understudied post-injury environmental stressor that directly engages stress-immune pathways. Thus, we predicted that maladaptive changes in the hypothalamic-pituitary-adrenal (HPA) axis after TBI compromise the neuroendocrine response to SD and exacerbate neuroinflammation. To test this, we induced lateral fluid percussion TBI or sham injury in female and male C57BL/6 mice aged 8-10 weeks that were then left undisturbed or exposed to 3 days of transient SD. At 3 days post-injury (DPI) plasma corticosterone (CORT) was reduced in TBI compared to Sham mice, indicating altered HPA-mediated stress response to SD. This response was associated with approach-avoid conflict behavior and exaggerated cortical neuroinflammation. Post-injury SD specifically enhanced neutrophil trafficking to the injured brain in conjunction with dysregulated AQP4 polarization. Delayed and persistent effects of post-injury SD were determined 4 days after SD concluded at 7 DPI. SD prolonged anxiety-like behavior regardless of injury and was associated with increased cortical Iba1 labeling in both Sham and TBI mice. Strikingly, TBI SD mice displayed increased number of CD45+ cells near the site of injury, enhanced cortical GFAP immunolabeling and persistent expression of Trem2 and Tlr4 7 DPI compared TBI mice. These results support the hypothesis that post-injury SD alters stress-immune pathways and alters inflammatory outcomes after TBI. These data provide new insight to the dynamic interplay between TBI, stress, and inflammation.

22) Injectable Glucose Sensors as Potential Monitors of TBI Extent/Recovery

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Materials Science & Engineering

Mentor: John Lannutti

Innovative glucose monitoring technologies are critically needed to effectively assess, manage and treat traumatic brain injury (TBI). It has recently been shown that small differences in arterial glucose – ~25 mg/dl or less – distinguish patients exhibiting 'good' versus 'poor' recovery following TBI. A large binational study found that mortality in association with dysglycemia was stronger for patients with TBI than in those with having subarachnoid hemorrhage [2]. While the connection between blood glucose and TBI extent is clear, these studies often measure only a single time point [2] or one point/24h period [1]. Blood draws to provide more refined glucose profiles are impractical, expensive and typically lack the temporal resolution needed to manage glucose metabolism related to changes in the injured brain and the creation of more effective treatments [3]. Based on recent research at OSU funded by AFRL and DARPA, a method producing easily injectable, electrospun glucose sensors has been developed. These sensors could create the ability to optically measure glucose levels within the body's interstitial fluids through the skin in real time using a commercialized reader system. We report on our efforts to fabricate and monitor new sensor options utilizing a commercially available reader head.

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23) Brain Tissue and Functional Recovery in Ischemic Stroke Model via Nanotechnology-Based Cell Reprogramming

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Mentor: Daniel Gallego-Perez, PhD

The second leading cause of death world-wide, stroke (85% of which are ischemic-derived) results in an estimated 42% death-rate¹ and is correspondingly responsible for a >70-billion USD financial burden². Stroke survivors are often subject to other complications as well such as paralysis, visual and speech impairment, etc. due to significant cellular (e.g. neuronal, vascular) deficiencies in the infarct region. Thus, there is a clear need for alternative therapies for stroke recovery as traditional therapies, focused on boosting endogenous repair mechanisms, are often insufficient¹. A multitude of cell-based therapies for stroke recovery have previously shown promising results^{3,4}. Angiogenic cell therapies promote nerve repair and neurological recovery by providing growth factors and scaffolding to support nerve regeneration. Current approaches rely on the use of progenitor stem-like cells or induced pluripotent stem cells, which pose significant risks due to uncontrolled/undesirable differentiation, tumorigenesis, genetic abnormalities, etc⁵. Although induced-endothelial cells (iECs) derived through direct cell reprogramming could present a safer alternative, there is currently no example of directly reprogrammed iECs for brain injury therapies. Moreover, reprogramming methodologies are heavily dependent on viral vectors, which pose additional safety concerns⁶. The present work describes the development and implementation of a novel and more efficient non-viral approach to generate iECs through nanochannel-mediated direct cell reprogramming for treatment of brain injury. C57BL/6 mice were exposed to a middle cerebral artery occlusion (MCAO) ischemic stroke. Brain injury was confirmed at 48HRs post MCAO via magnetic resonance imaging (MRI). Primary mouse embryonic fibroblasts (PMEFs) were reprogrammed into iECs via nanoelectroporation (NEP) using a novel transcription factor cocktail of Etv2, Foxc2, and Flt1 (EFF) and were subsequently intrathecally injected into the subarachnoid space, directly placing the iECs in contact with the infarct region. iEC-treatment demonstrated a significant increase in topical brain perfusion, 67% reduction in infarct area and up to 90% recovery in behavioral parameters. Moreover, IHC results displayed a significant increase in vascular and neuronal markers present in the infarct area as well as a significant decrease in glial scar formation for iEC-treated mice compared to control. We report that EFF-nanoelectroporated cells have the ability to induce a remarkable increase in blood flow in injured brains, thus suggesting that these cells can modulate the formation of blood-conducting vasculature in the injured brain in vivo. Moreover, our results show the feasibility of using iEC-based cell therapies to aid tissue repair and functional recovery after ischemic brain injury.

24) The Effect of Tau Aggregates on Endoplasmic Reticulum Calcium Homeostasis

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Neuroscience
Mentor: Hongjun Fu, PhD

Alzheimer's Disease (AD) is the most common form of dementia amongst the elderly and is increasing at an alarming rate. It has been pathologically characterized by extracellular amyloid β ($A\beta$) plaques, intraneuronal neurofibrillary tangles (NFTs) composed of the hyperphosphorylated microtubule-associated protein tau, gliosis, and progressive neuronal loss. However, the mechanisms of the disease are unclear. Endoplasmic Reticulum (ER) stress and its associated calcium dyshomeostasis have been implicated in the pathogenesis of AD, but it has been much debated as to whether and which tau species cause the ER stress. In this study, we aimed to investigate whether tau pathology causes ER stress, and whether tau aggregates induce ER- Ca^{2+} dyshomeostasis using two ER- Ca^{2+} cell reporter lines.

Methods

PS19 transgenic mouse and B6C3 mouse brains were sectioned and treated with antibodies corresponding to the PERK ER-Stress pathway. ER- Ca^{2+} cell reporter lines SH-SY5Y GCaMPer (10.19) line and SH-SY5Y GLuc-SERCaMP) and control cell lines (SH-SY5Y GCaMPer (WT) and SH-SY5Y Gluc- Stop) were treated with thapsigargin (positive control), Tau aggregate cell line lysate (DS9), control cell lysate (DS1), Tau monomer and Tau Fibrils. The ER calcium over time was monitored by live-cell imaging and bioluminescence, respectively.

Results

There is a significant increase in the levels of pPERK, a downstream protein in the PERK pathway, for PS19 transgenic mice which overexpress tau. For both cell lines, there was a significant decrease in terms of ER- Ca^{2+} levels when treated with thapsigargin. However, there was no significant difference in the ER- Ca^{2+} level between reporter cells treated with DS9 and DS1 cell lysate (10 g). This result indicates that unknown materials in the control DS1 cell lysate can also induce the ER- Ca^{2+} flux and affect the monitoring system. The reporter cells treated with Tau monomer (3.2 M) and fibrils (3.2 M) showed no significant changes over 48h.

Conclusions

There is evidence of ER stress caused by tau pathology, but further experiments have to be done to investigate the other two ER stress pathways. The ER- Ca^{2+} cell reporter lines are a good system to monitor ER- Ca^{2+} levels and can be used to screen chemicals or targets against ER- Ca^{2+} homeostasis. However, tau seeds isolated from DS9 tau aggregate cell line might not be ideal for studying the ER- Ca^{2+} dyshomeostasis using our system due to the lack of ideal negative control. Purified tau preparations of different tau species, greater concentrations of those species, and longer time periods warrant further investigation.

25) Quantitative EEG of stroke patients in relation to motor performance: pilot results

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Stroke is a worldwide leading cause of arm motor impairment and disability. An early prediction of arm recovery may help to define a tailored rehabilitation approach and promote higher functional recovery after stroke. Recently, the PREP2 algorithm, which combines clinical and neurophysiological biomarkers, has been validated and implemented into clinical practice. The aim of this preliminary study is to detect specific EEG patterns according with arm prognostic class of recovery. In this study we analyze the EEG of 6 patients (2female) with subacute stroke (four weeks after injury). We investigate if quantifiers of brain rhythmic activity relate to motor performance. In particular, we are interested in comparing affected and unaffected hemispheres within patients, and stroke survivors to a control population of volunteers. We collected EEG in three main conditions: Eyes Open (EO), Eyes Closed (EC) and Movement Execution (ME), where the last one included attempting a reaching movement with the affected arm for 20 times. In the EO and EC condition, we detect power in the theta (5-8 Hz), alpha (8.5-15 Hz) and beta (16-30 Hz) range at each electrode and use values at F3-F4, C3-C4 and P3-P4 electrodes to compare affected and unaffected hemispheres. In the ME condition, we compute the event-related synchronization/desynchronization (ERS/D) in the alpha and beta range. We consider again C3-C4 representative of activity in Primary Motor Cortex (M1), F3-F4 in Premotor Area and P3-P4 for sensorimotor integration. We compare alpha and beta ERS/D to motor performance measured with the Fugl-Meyer Assessment (FMA) and the PREP2 arm prognosis (excellent, good or poor). We also compare our ERS/D results in patients to alpha ERS/D of 4 volunteers who showed no motor issue. Our pilot results suggest an inverse relation between FMA and alpha ERS/D in the affected hemisphere, which is less clear for patients that score highly in the FMA scale. During reaching movement, the activation of the unaffected hemisphere and the pre-motor areas was strictly related with motor impairment and prognosis severity. Our analysis also suggests a potential role of topographical analysis of brain rhythms in addressing the high variability in brain dynamics among stroke patients. In conclusion, quantitative EEG analysis can contribute to understand how brain activity after stroke relates to motor performance, and hence can be leveraged to explore meaningful rehabilitative strategies across the lifespan of motor recovery.

26) Bayesian Framework for Simultaneous Registration and Estimation of Noisy, Sparse and Fragmented Functional Data

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Statistics

Mentors: Oksana Chkrebtii, PhD, and Sebastian Kurtek, PhD

In applications like neuroimaging, smooth functions generate data that are recorded under a variety of observation regimes, e.g. dense, sparse, or fragmented sampling, often contaminated with noise. Analysis of functional data is usually approached sequentially through estimation, registration, and inference. This approach lacks formal uncertainty propagation and the ability to accommodate general observation regimes. We propose a unified Bayesian framework for simultaneous registration and estimation, that is flexible enough to accommodate inference on individual functions under these observation regimes. Our ability to do this relies on the specification of strongly informative prior models on the amplitude component of a function, which tracts vertical variability in a functional dataset. We provide two strategies for this choice: a data-driven approach that defines an empirical basis for the amplitude subspace based on available training data, or a shape-restricted approach when the relative location and number of local extrema is well-understood. The proposed methods build on the elastic functional data analysis framework to accommodate amplitude and phase variability inherent in functional data. We will present applications of these proposed methods for two different fractional anisotropy functional datasets obtained from diffusion tensor imaging.

27) Do Body Mass Index and Genetic Risk for Alzheimer's Disease Influence Conversion to Alzheimer's Disease?

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Psychology

Mentor: Jasmeet Hayes, PhD

Body mass index (BMI) is a risk factor for Alzheimer's disease (AD) although the relationship is complex. Obesity in midlife is associated with increased risk for AD, whereas evidence supports both higher and lower BMI increasing risk for AD in late life. This study examined the influence of individual differences in genetic risk for AD to further clarify the relationship between late-life BMI and conversion to AD. Participants included 54 individuals categorized as cognitively normal or mild cognitive impairment at baseline who converted to AD within 24 months and 54 matched controls from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. BMI was measured at baseline. Genetic risk for AD was assessed via genome-wide polygenic risk scores. Conditional logistic regressions were run to determine if BMI and polygenic risk predicted conversion to AD. Results showed an interaction between BMI and genetic risk, such that individuals with lower BMI and higher polygenic risk were more likely to convert to AD relative to individuals with higher BMI. These results remained significant after adjusting for apolipoprotein E 4 and cerebrospinal fluid biomarkers of AD. Sex-stratified analyses revealed this relationship only remained significantly in males. These results show that higher genetic risk in the context of lower BMI predicts conversion to AD in the next two years, particularly among males. AD-related brain changes associated with lower BMI and high genetic risk for AD may affect the same neural pathways and consequently increase the likelihood of clinical manifestation of AD.

28) Tissue nano-transfection drives localized delivery of therapeutics to the peripheral or central nervous system in a minimally invasive manner

Jordan Moore

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Biomedical Engineering
Mentor: Daniel Gallego-Perez, PhD

Current methodologies for therapeutic delivery to nerve tissues and the brain are fraught with caveats, which include heavy reliance on viral vectors, stochasticity, lack of specificity, and cellular damage, and severe immune/inflammatory responses. Gene and oligonucleotide therapies have emerged as a promising strategy for the treatment of neurological conditions, including neurodegenerative diseases and brain injury. Although adeno-associated viruses (AAV) are less pathogenic, AAV-host interactions and immunity are still a major concern, and while iPSCs target the problem of limited cell availability, tumorigenicity and off target effect potential remains. Unique nerve anatomy presents challenges for targeted delivery to axons of motor and sensory neurons which can span both the central (CNS) and peripheral nervous system (PNS). Our novel non-viral tissue nano-transfection (TNT) chip platform can be used to deliver therapeutic cargo to nerve tissue at both levels (i.e., peripherally and centrally) via the use of solid state nanochannels, coupled with nano-electroporation and nano-electrophoresis. Such nanochannels were fabricated via a combination of cleanroom-based manufacturing techniques. This novel platform was then used to controllably deliver a variety of cargos to the CNS and PNS of mice, including plasmid DNA and CRISPR/Cas9 components. Nano-electroporation conditions were optimized by delivering labeled plasmids at different voltages and pulse lengths. Delivery efficacy and retrograde transport from PNS to CNS was evaluated via immunofluorescence microscopy and qRT-PCR at different levels, including peripheral nerve bundles, dorsal root ganglion (DRG), and spinal cord (SC). Laser speckle imaging and electrophysiology measurements were used to evaluate potential alterations in perfusion and functionality post-TNT. Tissue sections collected shortly after transfection revealed successful cargo delivery following a short-lived (<100 ms) pulsed electric field across the nanostructured platform. Fluorescence intensity demonstrated up to ~50,000 fold change with respect to controls when varying voltage alone, and differences across groups of up to 20x when varying the duration of nano-electrophoresis. Immunofluorescence analysis and qRT-PCR confirmed tissue transfection and strong plasmid DNA and CRISPR/Cas9 activity at the peripheral nerve level, with varying degrees of expression/activity at the DRG and SC levels depending on the nano-electroporation conditions. No significant behavioral changes (e.g., paw clenching, gait perturbations) were noted in treated mice. Our nanostructured platform, with the use of non-viral cargo, showed the ability to efficiently transfect peripheral and central nerve tissue in a targeted and controlled manner. Ongoing studies focus on modulating tissue repair via induced tissue plasticity following TNT-based delivery of reprogramming factors.

29) Cognitive, Behavioral, and Overall School Readiness in Very Preterm Preschoolers

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Mentor: H. Gerry Taylor, PhD

Introduction: Very Preterm (VPT) children exhibit deficits in cognition, behavior, and pre-academic skills, thus compromising their overall school readiness. Little is known, however, about the relationship between these deficits, parental engagement in the child's learning, and child access to learning resources. School readiness requires children to be prepared cognitively and behaviorally. Previous studies suggest increased parental involvement, both through intentional engagement and readily available learning materials, such as educational books and toys, contribute to learning skills. The aims of this study were to 1) examine the differences in parental engagement and access to learning resources between a group of VPT and FT control 4-year-olds as assessed by the StimQ2 –Preschool parent questionnaire, and 2) explore associations between these factors and measures of preschool cognition, behavior, and pre-academic skills. **Methods:** Parents of 92 four-year-old children (53 VPT and 39 FT) completed the StimQ2 –Preschool parent questionnaire to evaluate parental engagement in the child's learning and child access to learning resources. Parents also completed measures of atypical behavior, mood, and affect through the Conners Early Childhood parent questionnaire. The Differential Abilities Scales (DAS II) and Test of Preschool Early Literacy (TOPEL) were also administered to assess the children's cognitive and pre-academic abilities. Analyses controlled for sociodemographic risk. **Results:** The VPT group obtained significantly lower scores on both the Parental Involvement in Developmental Advance (PIDA) ($p < .007$) and Reading ($p < .009$) sub scales than the FT children. Parents of VPT children reported having higher concerns about their children's mood and affect ($p < .01$) and atypical behaviors compared to parents of FT controls ($p < .01$). Decreased parental engagement in learning was associated with lower cognitive ability ($p < .03$), and child access to learning resources was marginally associated with pre-academic skills ($p < .06$). **Discussion:** Despite poorer school readiness in VPT children compared to FT controls, VPT children received less environmental support for learning. VPT children may therefore benefit from increased parental support and access to learning materials, to enhance their overall school readiness.

30) Invariance of Edit-Distance to Tempo in Rhythm Similarity

Matt Moritz

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Mentor: Yune Lee, PhD

Title: Invariance of Edit-Distance to Tempo in Rhythm Similarity

Abstract: Despite the long history of music psychology, rhythm similarity perception remains largely unexplored. Several studies suggest that edit-distance—the minimum number of notational changes required to transform one rhythm into another—predicts similarity judgements. However, the ecological validity of edit-distance remains elusive. We investigated if the edit-distance model can predict perceptual similarity between rhythms that also differed in a fundamental characteristic of music—tempo. Eighteen participants rated the similarity between a series of rhythms presented in a pair-wise fashion. The edit-distance of these rhythms varied from 1 to 4, and tempo was set at either 90 or 150 beats per minute. A test of congruence among distance matrices (CADM) indicated significant inter-participant reliability of ratings, and non-metric multidimensional scaling (nMDS) visualized that the ratings were clustered based upon both tempo and whether rhythms shared an identical onset pattern, a novel effect we termed rhythm primacy. Lastly, Mantel tests revealed significant correlations of edit-distance with similarity ratings on both within-tempo and between-tempo rhythms. Our findings corroborated that the edit-distance predicts rhythm similarity and demonstrated that the edit-distance accounts for similarity of rhythms that are markedly different in tempo. This suggests that rhythmic gestalt is invariant to differences in tempo.

31) Role of TLR-4 in Post-Operative Cognitive Decline and its Potential Use as a Novel Therapeutic Target

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Mentor: Ruth Barrientos, PhD

Post-operative cognitive decline (POCD) is a complication experienced by many surgical patients and is characterized by cognitive impairment ranging from mild confusion to difficulty with executive functions to inability to form long-term memories to dementia. These symptoms can last days to months following surgery. Persistent POCD, lasting weeks to months, is most commonly experienced by older individuals and is associated with an increased vulnerability to developing Alzheimer's Disease, although the underlying mechanisms remain unknown. It is well-regarded that the traumatic event of surgery initiates a deleterious neuroinflammatory response leading to long-term damage, the details of which have yet to be elucidated. Our recent work has implicated morphine, which is often administered post-operatively for pain management, in exaggerating this inflammatory response, leading to persistent POCD. Here, we explored the role of toll-like receptor 4 (TLR-4) in this process. TLR-4 is a pattern recognition receptor expressed by microglia. As we age, microglia naturally become sensitized and are more likely to mount an exaggerated neuroimmune response. Interestingly, morphine has recently been shown to have an inflammatory role via TLR-4 activation. We hypothesized that surgery, aging, and morphine synergize via TLR-4 activation to cause persistent POCD. We subjected 24 month old male rats to laparotomy as a model of POCD and administered analgesic morphine for 1 week. Following morphine treatment, the specific TLR-4 antagonist lipopolysaccharide from the bacterium *Rhodobacter sphaeroides* (LPS-RS) was administered via icm injection to explore the role of TLR-4 in mediating POCD and its potential use as a therapeutic agent for POCD. Using a contextual fear conditioning paradigm, performed 4 weeks after surgery (2 weeks after LPS-RS treatment), we have shown that administration of the TLR-4 antagonist LPS-RS ameliorates the long-term memory impairments associated with POCD in a dose-dependent manner. Our results indicate that TLR-4 does indeed mediate the development of persistent POCD and suggests that blocking its activation in the brain may be a promising therapeutic to treat POCD.

32) Impaired Glial IL-10 / TGF β Signaling Underlies the Prolonged Sickness Response in Aged Mice

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Mentor: Jonathan Godbout, PhD

Microglia and astrocytes, cells with major immune functions in the central nervous system, exhibit a robust pro-inflammatory phenotype as a function of normal aging. Microglia develop a pro-inflammatory, or “primed,” profile with age characterized by increased expression of inflammatory mediators. With aging, this altered neuro-immune communication results in heightened risk of mortality and co-morbidity of depression or dementia. For instance, acute bacterial infection in elderly patients often presents as acute cognitive impairment and altered mood. Moreover, these individuals are at an increased risk for progressive dementia and cognitive impairment even after the infection resolves. Moreover, this age-associated phenotype persists in mice when microglia are renewed with young cells, implicating a microglia-extrinsic mechanism for priming. Therefore, we used single-cell RNA-sequencing (scRNA-Seq) to identify cell- and time-specific responses to a peripheral immune challenge in both adult and aged mice. After immune activation, microglia produce interleukin (IL)-10, an anti-inflammatory cytokine. In response to IL-10, astrocytes produce transforming growth factor beta (TGF β), which completes a negative feedback loop and attenuates microglial activation. Using data gathered from our scRNA-Seq approach, we hypothesized impaired glial interleukin IL-10 / TGF β signaling underlies the prolonged sickness response in aged mice.

We found astrocytes in the aged brain express decreased levels of IL-10R and, as a result, produce decreased levels of TGF β in response to IL-10 signaling. This impaired negative feedback results in prolonged neuroinflammation after peripheral immune activation in aged mice compared to adults. Moreover, we found genetic knock-out of IL-10R on astrocytes recapitulates these effects in adult mice, as shown by increased social avoidance for an extended period of time and increased pro-inflammatory cytokine expression in the brain after peripheral LPS administration. Finally, we show augmentation of hippocampal astrocytic TGF β expression in aged mice is not sufficient to attenuate the exaggerated and prolonged sickness response to a peripheral immune challenge in aged mice.

These data indicate impaired IL-10 / TGF β signaling between microglia and astrocytes is both sufficient for the prolonged neuroinflammatory sickness response to a peripheral immune challenge, but there may be more underlying complications to address. Our data implicates a novel therapeutic target for treating the cognitive dysfunction affecting the elderly population after a peripheral infection, such as a respiratory or urinary tract infection. Furthermore, our novel scRNA-Seq data elucidates the temporal and cell-specific sickness response to peripheral infection in adult and aged mice, giving us further insight into the molecular mechanisms underlying the age-associated neuroinflammatory response to peripheral infection

33) Factors Associated with Symptom Improvement among Adolescents receiving Multidisciplinary Care for Pediatric Post-Concussive Symptoms

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Objective: To evaluate the effectiveness of a multidisciplinary treatment for adolescents experiencing prolonged recovery from concussion and to identify predictors of treatment outcomes.

Methods: Participants included 44 adolescents (80% female, 82% Caucasian) referred to the Nationwide Children's Hospital Complex Concussion Clinic (CCC). All patients included had persistent (≥ 30 days post-injury) post-concussion symptoms (SCAT-5 symptom score ≥ 10). Participants were aged 10-20 years (mean=14.9, SD=2.0). Patients with multiple previous concussions tended to be referred to this higher level of care sooner (M = 49.7 vs. M = 72.7 days post-injury). 55% of participants had a history of anxiety/depression and 25% had a history of ADHD or learning disorder. Multidisciplinary treatment included sessions with Neurology, Neuropsychology, Physical Therapy, and Athletic Training involving graded physical exercise, with an average treatment duration of 58.2 days. Participants completed neuropsychological screening (Digit Span and Trail Making Test) at their initial visit and SCAT-5 symptom scores were obtained at each visit.

Results: Symptoms significantly decreased between their initial (mean=46.2, SD=20.8) and final visits (mean=11.3, SD=14.3); $p < .001$. The effect of gender on symptom improvement after controlling for initial symptom severity approached significance; males experienced a greater percent improvement (mean=89%) as compared to females (mean=71%), $F(1, 41) = 3.17$, $p = .08$. Demographic factors, premorbid psychological history, and neuropsychological test performance did not predict rate of symptom improvement; though at the initial visit there was a significant negative association between number of previous concussions and performance on Trail Making Test, part B ($p < .05$).

Conclusions: Multidisciplinary care involving graded aerobic exercise and psychological intervention shows promise, particularly for boys with persistent post-concussive symptoms. Adolescents with a history of multiple concussions showed slightly greater deficits in executive functioning, though this may be because, in this sample, these patients were referred for evaluation earlier in recovery.

34) Wireless and Batteryless Brain Implants: Misalignment Considerations

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Mentor: Asimina Kiourti, PhD

Deep brain neuropotential monitoring offers unprecedented opportunities for patients with epilepsy, Alzheimer's, Parkinson's, etc., in addition to the advancement of neural modeling [1]–[4]. Traditional neurosensing technologies employ intracranial wires, but these devices inhibit the activities of daily life (thus limiting the testing environment) and are prone to infection [2], [4]. To overcome these issues, wireless implants have been reported but utilize batteries or energy harvesters for operation [5]. These battery-powered devices require replacement/recharging and can damage the surrounding neurons due to heat generation [6]. As an alternative, we proposed a new class of wireless, fully passive brain implants. In [7], we introduced a wireless, batteryless brain implant with a footprint of only $8.7 \text{ mm} \times 10 \text{ mm}$ and sensitivity up to $20 \text{ } \mu\text{Vpp}$ in vitro settings. This sensitivity was an improvement of up to 25 times compared to previous works and achieves the goal of detecting low voltage neural signals, viz. local field potentials (LFPs).

However, our recent studies indicate that the implant's sensitivity is highly prone to even slight misalignment between the implant antenna and the wearable interrogator antenna that is used to: (a) turn on the implant, and (b) receive its backscattered neural signals. Simulations show that misalignment of the interrogator antenna by $\pm 4 \text{ mm}$ in the 3D space implies an additional loss of 2.9 to 15.0 dB into the neurosensing system. That is, in real-world settings where perfect misalignment is not always feasible, system sensitivity may be degraded to the extent that local field potentials are no longer detectable. Thus, new antenna designs are currently being explored that are more tolerant to misalignment. For example, large spiral antennas used on the interrogator side (such as the one reported in [8]) show promise in reducing the misalignment loss as attributed to their symmetric design and wide footprint that always ensures line-of-sight. Our ultimate aim entails miniaturized antenna designs that are concurrently robust to misalignment and are strongly coupled to ensure minimum loss at all times.

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35) PTSD Symptom Severity is Associated with Accelerated Cognitive Decline among Vietnam Veterans

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Objective: To examine cross-sectional and longitudinal associations between posttraumatic stress disorder (PTSD) symptom severity, number of stressors experienced, and cognitive outcomes in Vietnam War veterans. **Methods:** 187 adults between 60-84 years old completed a Vietnam Veterans Alzheimer's Disease Neuroimaging Initiative Project (ADNI-DoD) baseline and 12-month visit. Number of stressful experiences was measured with the Life Stressor Checklist-Revised (LSC-R). Severity scores were assessed via the current Clinician-Administered PTSD Scale (CAPS). Hierarchical linear regressions were conducted to examine the effect of CAPS and LSC-R on baseline cognitive scores and cognitive changes over 12 months. Correlations were conducted between selected measures of stress and age, years of education, sex, ethnicity, and race. Demographic variables with significant associations with stress were included as covariates in the hierarchical regressions. Cognition was assessed via the Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive 13 (ADAS-13), Category Fluency Test (CFT), and Trail Making Test (TMT) parts A and B. **Results:** Higher CAPS scores (indicating higher PTSD severity) were associated with worse baseline cognitive outcomes on TMT B [$\Delta F(1,178)=4.501$, $p=0.035$, $R^2=0.08$], ADAS-13 [$\Delta F(1,182)=7.717$, $p=0.006$, $R^2=0.054$], and CFT [$\Delta F(1,182)=5.265$, $p=0.023$, $R^2=0.053$], although only the ADAS-13 survived multiple comparisons correction. Longitudinal analyses controlling for frequency of stressors showed that higher PTSD symptom severity was associated with greater decline on MMSE performance [$\Delta F(1,178)=9.06$, $p=0.003$, $R^2=0.203$], which survived multiple comparisons correction. Neither cross-sectional nor longitudinal analyses survived multiple comparisons correction when looking at the LSC-R. **Conclusions:** In a sample of older veterans, PTSD symptom severity was associated with worse performance on the ADAS-13 which maps onto domains including memory, reasoning, and language. Additionally, baseline PTSD symptom severity was associated with a steeper decline in MMSE performance over 12 months. The MMSE evaluates multiple domains of cognitive functioning including orientation, memory, and attention. Results suggest that the relationship between stressful experiences and cognitive outcomes may be explained by symptom severity above and beyond experiencing stress. Moreover, results indicate that PTSD symptom severity may accelerate cognitive decline. As such, treating PTSD symptoms should be considered instrumental in maintaining cognitive function as adults age.

36) Brain Injuries Caused By Domestic Violence: Partner-Inflicted Brain Injury

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When most people think of brain injury, they think of falls, car accidents, soldiers in combat, or football players or other athletes. Yet one group of people with extremely high exposure to head trauma—domestic violence victims—has been conspicuously absent in brain injury services and research. The Ohio Domestic Violence Network (ODVN)—in collaboration with research partner the Ohio State University—is on the cutting edge of paradigm shifting work to address an unrecognized public health crisis—partner inflicted brain injury (PIBI) --encompassing brain injuries caused by blows to the head, neck and face (traumatic brain injury) and strangulation (hypoxic-anoxic brain injury) in the context of domestic violence. Groundbreaking research conducted in Ohio by ODVN and OSU from 2016-2019 uncovered over 8 in 10 survivors in DV advocacy services were targeted for head trauma and strangulation by abusers, often repeatedly and concurrently. Partner-inflicted brain injury, rarely identified and almost never immediately treated, results in short and long term physical, emotional, and cognitive consequences that can impact every area of a person's life, including acting as a contributor to the health disparities domestic violence survivors currently experience and the behavioral drivers of these disparities, including substance use and suicidal ideation. ODVN built an enhanced advocacy approach called CARE. Because partner-inflicted brain injury is distinct and separate from other types of brain injuries for a myriad of reasons, it requires unique identification methods, responses, approaches, treatment, rehabilitation, and research frameworks. ODVN created the Center on Partner-Inflicted Brain Injury to raise awareness and provide support to practitioners and researchers working at the intersection of brain injury and domestic violence. The Center will work to facilitate increased collaboration across disciplines, service fields, among systems, between research and practice spheres, and in the traumatic brain injury and strangulation areas to better understand and respond to those impacted. ODVN is now poised to disseminate our knowledge to research social service, health care, and criminal justice systems, using a public health approach. We also are here to support and assist you in your work to help us develop an effective, trauma-informed responses that promotes healing and recovery from the terrible experiences of abuse. Come to learn more about partner-inflicted brain injury, future directions in both research and in-service provision, and ways to work together more closely on this issue.

37) Modifiable Physical/Health Variables and Cognition in ADNI1: a cross-sectional analysis using Partial Least Squares

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Mentor: Scott Hayes, PhD

Objective: To identify novel associations between modifiable physical and health variables, Alzheimer's disease (AD) biomarkers, and cognitive function in a cohort of older adults with Mild Cognitive Impairment (MCI).

Method: Metrics of cardiometabolic risk, stress, inflammation, neurotrophic/growth factors, AD, and cognition were assessed in 155 MCI participants (mean age = 74.2 years) from the Alzheimer's Disease Neuroimaging Initiative. Partial Least Squares analysis was employed to examine associations among these physiological variables and cognition.

Results: A unique combination of AD biomarkers, neurotrophic/growth factors, including brain-derived neurotrophic factor, and education were significantly associated with specific domains of cognitive function, including episodic memory, executive function, and processing speed and accounted for 47.9% of the covariance in the data. Age, BMI, and metrics tapping working memory, language or premorbid IQ were not significant.

Conclusions: Our data-driven analysis highlights the significant relationships between metrics associated with AD-pathology, neuroprotection, and neuroplasticity with tasks requiring fluid (episodic memory and executive function) rather than crystallized (premorbid IQ and language) ability. These data also indicate that biological metrics are more strongly associated with episodic memory, executive function, and processing speed than chronological age in older adults with MCI.

38) Sub-acute and chronic sleep fragmentation after traumatic brain injury differentially affects inflammation and stress responses

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Traumatic brain injury (TBI) impairs the body's ability to restore homeostasis in response to a stressor, reflecting dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis. As a result, everyday stressors may substantially compromise post-injury recovery and quality of life. Many common post-TBI stressors result in sleep disturbances, thus providing a common biological pathway to study the effects of stress and the dysfunctional HPA axis after injury. We hypothesize that sleep fragmentation (SF) is a physiologically relevant stressor that engages the HPA-axis after TBI and upon a dysregulated stress response promotes increased neuroinflammation. Mice were given lateral fluid percussion TBI or control sham-surgery and then either left undisturbed or exposed to daily, transient SF from 7-11 AM for either 7 (sub-acute) or 30 (chronic) days. At 7 days post-injury (DPI), TBI caused significant gliosis in the ipsilateral brain and thalamus, but sub-acute SF did not alter or exacerbate this response. Notably, nanoString analysis of the ipsilateral cortex after 7 days of SF showed increased expression of stress-responsive pro-inflammatory genes such as Fos, Ptgs2, and Il6. Further, preliminary data suggests that exposure to sub-acute SF after TBI results in altered stress circuitry activation, as indicated by FosB+ cells. These data indicate that 7 days of SF increases stress-induced inflammation, which may then contribute to post-TBI immune and HPA-axis responses. We next sought to define the inflammatory and stress consequences of chronic SF at 30 DPI. Notably, there was exacerbated microglial reactivity in the ipsilateral thalamus of animals exposed to post-TBI SF at 30 DPI. NanoString analysis of the ipsilateral cortex with chronic post-TBI SF at 30 DPI also altered inflammation-associated transcription factors such as Nr3c1, Stat3, and Relb indicating a more pro-inflammatory environment. We additionally saw altered stress circuitry activation, as indicated by preliminary analysis of FosB+ cells, indicating suppressed HPA-axis activity with 30 days of SF after TBI. This suggests that chronic post-injury SF can cause long-lasting transcriptional changes that could increase long-term, maladaptive inflammation either as a result of or contributor to TBI-induced HPA-axis dysfunction. Altogether, these data indicate that SF acts as a stressor after TBI and differentially influences inflammation and stress responses dependent upon length of exposure.

39) Counteracting maladaptive plasticity and chronic neurodegeneration following CNS trauma using a 'smart' drug delivery system (SDDS)

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Mentor: John Lannutti, PhD

Traumatic brain and spinal cord injury cause devastating neurological deficits and long-term disability due to detrimental structural and functional alteration in neuronal circuits. Currently, the cellular and molecular mechanisms that cause or contribute to pathophysiological changes in central nervous system (CNS) structure and function are not well understood. A number of studies, including ours, have demonstrated a remarkable convergence between structural and functional organization of neuronal circuits and expression of $\alpha 2\delta$ subunits of voltage gated calcium channels (VGCC). $\alpha 2\delta$ subunits positively regulate synaptic transmission by increasing plasma membrane expression of VGCC. However, these subunits may also play a pathological role following axonal injury. Expression of $\alpha 2\delta 1/2$ increases following axonal injury, resulting in aberrant neuron activities associated with chronic pain and posttraumatic epilepsy. Based on our new and published data, we hypothesize that increased $\alpha 2\delta 1/2$ expression hijacks the self-repair mechanisms of the CNS by forcing aberrant plasticity after trauma. Our proposed research seeks to examine whether it is possible to counteract these maladaptive changes by pharmacologically blocking $\alpha 2\delta 1/2$ in the brain and spinal cord using a 'smart' drug delivery system (SDDS). The SDDS we have demonstrated is made up of polymer-based injectable microspheres that fully degrade after drug delivery is complete.

40) Using a Random Forest Machine Learning Approach to Understand Predictors of Functional Decline in an Aging Population

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Independent activities of daily living (IADLs) encompass routine activities, such as paying bills and remembering appointments. The ability to carry out IADLs decreases throughout the aging process and is related to negative health outcomes and lower quality of life. It is also a cardinal symptom of Alzheimer's disease (AD). As the population ages, it will be critical to understand predictors of functional decline. However, little is known about the predictors of functional decline across different modalities.

In the current study, we looked at several modalities that could serve as predictors of functional decline. Data for these analyses were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database and were divided into one of five modalities: demographic, MRI, neurocognitive measures, FDG-PET, and fluid-based biological samples. Specifically, this included general demographic information, medical history, current medications, neurocognitive measures, T1-weighted 3T, non-accelerated magnetic resonance images (cortical volume, hippocampal subfield volume, subcortical volume, surface area, and thickness), fluorodeoxyglucose positron emission tomography (FDG-PET), polygenic hazard scores for AD, cerebrospinal fluid, blood plasma, and urine serum. Each single modality and each possible combination of modalities was independently tested to determine the most clinically appropriate approach to understanding functional decline. Thirty-one different combinations of modalities were included in total. A random forest machine learning algorithm was trained and tuned. Backwards recursive feature elimination was used for feature selection and repeated 10-fold cross validation with 50 repeats was used for cross validation. All models were run on The Ohio SuperComputer.

The highest accuracy for any single modality was achieved with neurocognitive measures (accuracy=82.1%; sensitivity=74.4%; specificity=91.1%; AUC=0.83). This model selected 18 out of 71 variables. The highest accuracy for any combination of modalities was achieved with neurocognitive measures and MRI variables (accuracy=84.0%; sensitivity=76.92%; specificity=91.14%; AUC=0.84). This model selected 211 of 408 variables.

In these models, cognitive performance and judgements of cognition best predicted functional decline with little to no improvement in accuracy when other modalities were considered. These results may be helpful clinically as they suggest that low-cost, low-burden neurocognitive measures alone provide critical information about future functional decline.

41) A Comparison of Histo-Chemical and Histo-Magnetic Detection of Iron

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Iron distribution in tissues at the sub-cellular level has become an important biomarker for identifying many neurological diseases. Iron content is typically analyzed via histo-chemical stains. However, the magnetic characteristics of iron has been key in recent years for developing safe, non-invasive techniques that aid in diagnosis, such as magnetic resonance imaging (MRI). In our recent studies, we elucidated that magnetic properties of iron can also be exploited to characterize differences in physiological and pathological iron distribution. To further develop this histo-magnetic approach, we need to extend it to sample protocols routinely prepared in histology. Histo-chemical staining protocols commonly use paraformaldehyde and formalin (for light microscopy) and glutaraldehyde (for electron microscopy) as fixing agents. However, the effect that various fixatives have on the chemical and magnetic properties has not been adequately confirmed. In this study, we have taken a systematic approach to determine the qualitative differences that fixatives cause on histo-chemical and histo-magnetic characterization of iron. Murine spleens were fixed using three common fixatives for ~24 hours, washed with PBS and immediately embedded in optimal cutting temperature (OCT) media. Histo-chemical characterization using Perl's and Turnbull's stains was used to qualitatively resolve the distribution of ferrous (Fe^{2+}) and ferric (Fe^{3+}) iron. Histo-magnetic characterization was performed using magnetic force microscopy (MFM) and superconducting quantum interference device (SQUID) magnetometry. Histo-chemical results show a substantial difference in the dispersion of the stain across fixatives. Histo-magnetic characterization on the other hand was not dependent of fixative treatment. The results from this study bring forth a novel method of tissue iron characterization based on biophysical magnetic properties of iron.

42) Utility of Post-Concussion Clinical Measures at Predicting Same-Season Re-injury in NCAA Athletes

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Mentor: Jaclyn Caccese

Background: Athletes are at 2-3 times increased risk of re-injury following recovery from concussion. By examining current post-concussion clinical measures, we may be able to identify athletes with persistent deficits, perhaps indicating premature return to play and increased risk of re-injury.

Objective: To identify clinical predictors of same-season sport-related concussion re-injury in NCAA athletes.

Design: Case-control.

Setting: Multi-site laboratory study.

Participants: 30 NCAA student-athletes who sustained more than one sport-related concussions in a single season, and 90 NCAA student-athletes who sustained only one sport-related concussion (i.e., control group). Control participants were matched 3:1 based on sex, prior history of concussion, sport, position, and month of injury.

Predictors: Change scores (i.e., return to play – baseline and 24-48h – baseline) were calculated for selected clinical measures, which included 1) Balance Error Scoring System (BESS) total score, 2) Brief Symptom Inventory (BSI)-18 somatic sub-score, 3) BSI-18 anxiety sub-score, 4) BSI-18 depression sub-score, 5) Standardized Assessment of Concussion (SAC) total score, 6) Sports Concussion Assessment Total (SCAT) total symptom score, 7) SCAT symptom severity score 8) Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) reaction time composite score (RT), 9) ImPACT verbal memory composite score (VERM), 10) ImPACT visual memory composite score (VISM), and 11) ImPACT visual motor speed composite score (VMS).

Outcome measures: Group (i.e., sport-related concussion re-injury versus control)

Main Results: The clinical measure change scores did not predict sport-related concussion re-injury (return to play, $X^2=10.776$, $p=0.462$, $AUC=0.728$; 24-48h, $X^2=9.724$, $p=0.555$, $AUC=0.754$). The odds ratio per unit change in selected clinical measures are presented for the return to play change scores (95% confidence intervals: BESS total score=0.94-1.21, $p=0.365$; BSI-18 somatic sub-score=0.21-1.07, $p=0.036$; BSI-18 anxiety sub-score=0.65-4.68, $p=0.265$; BSI-18 depression sub-score=0.56-2.10, $p=0.964$; SAC total score=0.52-1.19, $p=0.277$; SCAT symptom severity score=0.63-1.31, $p=0.605$; SCAT total symptom score=0.72-3.60, $p=0.225$; ImPACT RT=0.00-91.69, $p=0.471$; ImPACT VERM=0.94-1.07, $p=0.897$; ImPACT VISM=0.95-1.07, $p=0.750$; ImPACT VMS=0.84-1.17, $p=0.944$). Results were similar for the 24-48 change scores.

Conclusions: Current post-concussion clinical measurements are unable to predict sport-related concussion re-injury in NCAA athletes. Future work should examine more sensitive outcomes (e.g., advance postural control measures) to determine if these assessments can predict same-season re-injury. Alternatively, considering the improvements in concussion management over the past two decades, it is possible that sport-related concussion re-injury occurs as a result of unpredictable sufficiently hard impacts and are not a result of premature return to play. For now, extra caution and injury prevention methods should be considered for NCAA athletes who previously have been cleared to return to play following a concussion.

43) Alzheimer's disease prevalence may differ by Appalachian county designation

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Background: Areas designated as Appalachian may have a greater burden of underdiagnosed Alzheimer's disease and related disorders (ADRD).

Objective: To estimate the prevalence of ADRD in the Appalachian counties of Ohio, and to determine if differences exist by geographic location (Appalachian/non-Appalachian and rural/urban) and across time among Medicare beneficiaries.

Methods: Centers for Medicare and Medicaid Services Public Use Files from 2007-2017 were used to estimate county-level ADRD prevalence among all fee-for-service beneficiaries in Ohio. Negative binomial regression was used to estimate overall prevalence, by Appalachian Regional Commission's Appalachian/non-Appalachian designation, and by rural/urban (Rural-Urban Continuum Codes) classification. Models were repeated adjusting for county-level demographics and comorbidities. **Results:** Beneficiaries residing in Appalachian Ohio counties had 2% lower ADRD prevalence compared to non-Appalachian Ohio counties (9.9% vs. 10.1%; PR 95%CI: 0.96, 1.00). This association was modified by rural/urban county designation across the study period ($P=0.009$). Among urban counties, ADRD prevalence was 2% lower in Appalachian counties (95%CI: 0.96, 1.00), and 2% higher in rural Appalachian counties (95%CI: 1.00, 1.05). When adjusting for county-level demographics and comorbidities, ADRD prevalence for rural vs. urban counties was similar regardless of Appalachian/non-Appalachian designation.

Conclusion: There may be a disparate burden of ADRD in Ohio, and where one resides could be an important characteristic. This potential difference by Appalachian region is important to consider for availability of services and subsequent delivery of care. In order to further.

44) Promoting structural and functional reorganization of neuronal circuits after photothrombotic stroke

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Mentor: Andrea Tedeschi, PhD

Ischemic stroke causes devastating neurological deficits and long-term disability due to detrimental structural and functional changes in brain structure. Currently, the cellular and molecular mechanisms that cause or contribute to pathophysiological changes in structure and function of brain circuits are not understood. We and others have demonstrated a remarkable convergence between structural and functional organization of neuronal circuits and expression of Alpha2delta2 subunits of voltage gated calcium channels (VGCC). These subunits positively regulate synaptic transmission by increasing plasma membrane expression of VGCC. However, these subunits may also play a pathological role following brain injury. Based on our new and published data, we hypothesize that increased expression of Alpha2delta2 subunits hijacks the self-repair mechanisms of the brain by forcing aberrant plasticity after trauma. Here, we subjected adult mice to photothrombotic stroke, a minimally invasive procedure that allows targeting a specific area in the brain. We used transgenic mice expressing green fluorescent protein in a subset of neurons to study anatomical and functional changes in layer V motor neurons, a group of excitatory neurons that originate the corticospinal tract (CST). Among the descending motor pathways important for brain repair, the CST exerts the sensory and motor control that is necessary for accurate limb placement and voluntary movements. Finally, we tested whether Alpha2delta2 pharmacological blockade through Gabapentin (GBP) administration was sufficient to promote CST sprouting and functional reorganization after stroke in mice. If successful, our study may be considered for repurposing GBP as a novel treatment strategy for brain repair after stroke.