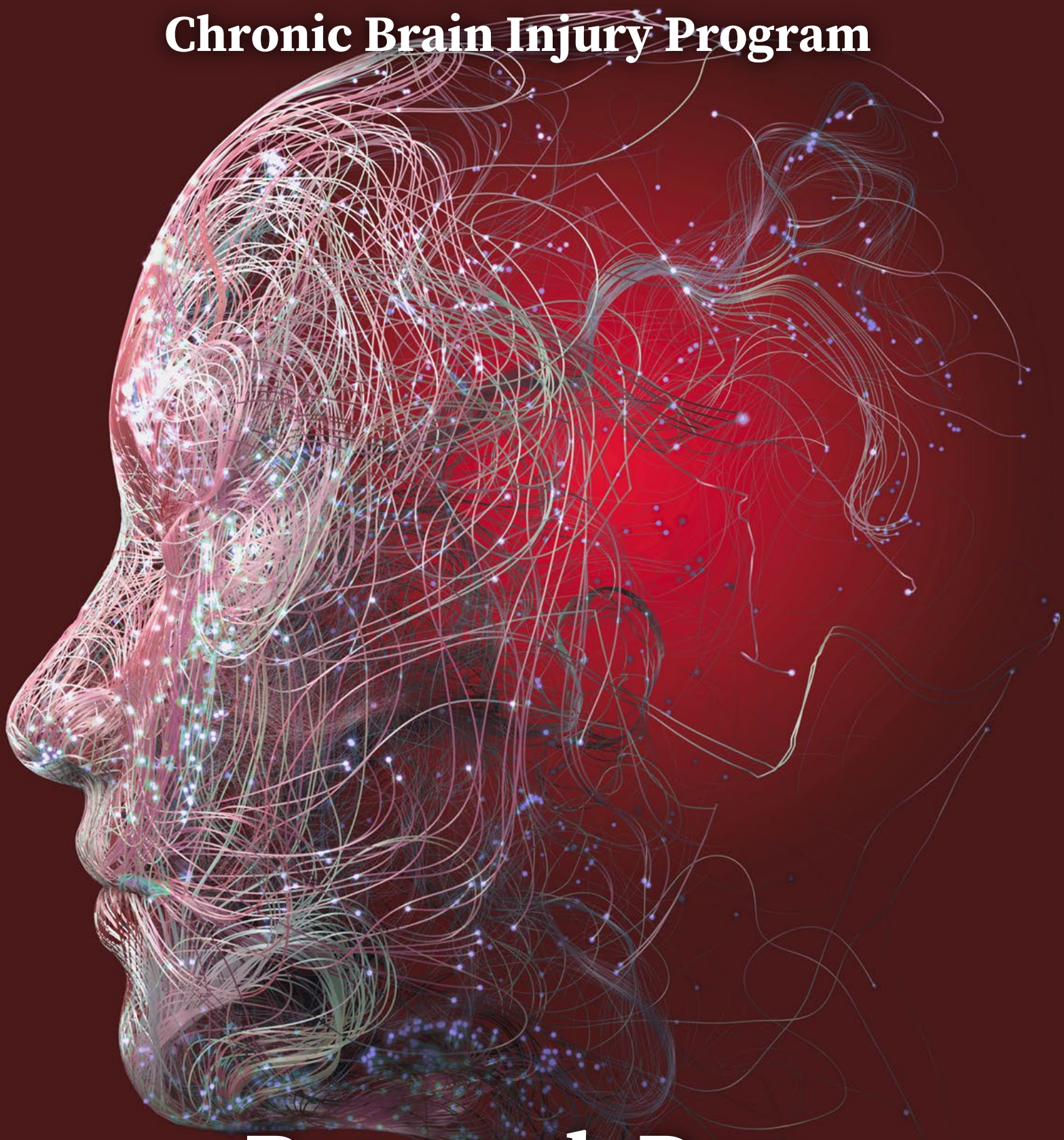
Chronic Brain Injury Program



Research Day

March 7 & 8, 2024 | Heminger Hall

Contents

Schedule

MARCH 7 | Heminger Hall Atrium, 130, 168

1577 Neil Ave, Columbus, OH 43210

POSTER SESSION
2:00PM-5:00PM

SESSION A: 2:30PM-3:30PM
SESSION B: 4:00PM-5:00PM

TRAINEE SOCIAL
6:00PM @ BOTTLE SHOP

237 King Avenue

Postdocs and graduate students are encouraged to attend and connect with one another at this informal event.

Hosted by
Enora Le Flao, PhD | Mentor: Jaclyn Caccese, PhD
Morgan Taylor, PhD | Mentor: Olga Kokiko-Cochran, PhD

MARCH 8 | Heminger Hall 100

1577 Neil Ave, Columbus, OH 43210

CHECK-IN & BREAKFAST

8:30AM

WELCOME REMARKS

9:00AM

Jonathan Godbout, PhD
Professor, Dept. of Neuroscience
CBI Faculty Director

Karla Zadnik, OD, PhD
Interim Executive Vice President & Provost
Dean, College of Optometry
Interim Dean, College of Public Health
CBI Lead Dean

SPOTLIGHT TALKS

9:15AM

Dementia epidemiology in the era of blood biomarkers and big data: the enduring importance of brain autopsy

Erin Abner, PhD
Professor, Epidemiology
Sanders-Brown Center on Aging
University of Kentucky

10:00AM

Flexible, Miniaturized Sensing Probes Inspired by Biofuel Cells for Monitoring Synaptically Released Glutamate in the Mouse Brain

Jinghua Li, PhD
Assistant Professor, Materials Science & Engineering
CBI Paper of the Year Winner
The Ohio State University

10:55AM

TBI, get with the (cellular response) program

Bogdan Stoica, MD
Associate Professor, Anesthesiology
Center for Shock, Trauma and Anesthesiology Research (STAR)
University of Maryland

LUNCH
11:40AM

KEYNOTE TALK
12:15PM

Mechanisms underlying traumatic brain injury-induced pain and opioid seeking

Alana Conti, PhD
Associate Professor, Neurosurgery
Wayne State University

SURVIVOR STORY
1:45PM

Kelli Trinosky

TRAINEE TALKS
2:00PM

Printed Circuit Board to Control Remote Food Dispenser for Assessing Pig Cognition

Eric Schwegler (Undergraduate)
Mentor: Saeedeh Ziaeefard, PhD
Electrical & Computer Engineering

Neuronal BAG3 attenuates AD-like pathology and cognitive deficits induced by traumatic brain injury via the regulation of autophagy-lysosome pathway

Nick Sweeney (Undergraduate)
Mentor: Harry Fu, PhD
Neuroscience

Examining the relationship between gait, balance, processing speed, and executive function across the lifespan

Grace Amadon (Graduate)
Mentor: Scott Hayes, PhD
Psychology

Youth Football Head Impact Exposure Differences Based on Four Data Cleaning Methods

Samantha DeAngelo (Graduate)
Mentor: Jaclyn Caccese
Health & Rehabilitation Sciences

Estimating Heart Rate Variability (HRV) Using a Wearable Magnetocardiography (MCG) Sensor

Ali Kaiss (Graduate)
Mentor: Asimina Kiourti
Electrical & Computer Engineering

The E3 Ubiquitin Ligase IDOL Regulates Microglial Phagocytosis in Alzheimer's Disease

Sarah Kaye (Graduate)
Mentor: Jie Gao, Phd
Neuroscience

The Neuroinflammatory Impact of High Fat Diet on Memory and Synaptic Degradation in an AD Model

Sabrina Mackey-Alfonso (Graduate)
Mentor: Ruth Barrientos
Psychiatry &Behavioral Health

Promoting CNS axon regeneration by manipulating cholesterol

Debasish Roy, PhD (Postdoc)
Mentor: Andrea Tedeschi, PhD
Neuroscience

Association of Elevated Concussive Symptoms on Driving Performance: A Comparison between Adolescent Drivers with Mild Traumatic Brain Injury and Matched Healthy Controls

Christopher Rundus (Postdoc)
Mentor: Ginger Yang, PhD
Nationwide Children’s Hospital Center for Injury Research & Policy

AWARDS & CONCLUDING REMARKS

3:00PM

Poster Listings

#	TIME	NAME	LEVEL	ABSTRACT TITLE	MENTOR
1	A	Kris Martens	Assistant Professor	Metagenomic sequencing to better understand gut microbiome contributions to TBI	
2	B	Ilaria Palmisano	Assistant Professor	Cohesin-dependent three-dimensional chromatin looping is required for axonal regeneration after injury	
3	A	Marjean Kulp	Professor	Quality of Life in concussed and non-concussed children with Symptomatic Eye Teaming, Focusing, and Tracking Problems	
4	B	Giles Plant	Professor	Combined Transplantation of Mesenchymal Progenitor and Neural Stem Cells to Repair Cervical Spinal Cord Injury.	
5	A	Giles Plant	Professor	Human Corticospinal Neurons Dreived from iPSC Transplanted to Repair Chronic Cervical Spinal Cord Injury	
6	B	Sarah Anderson	Postdoctoral Researcher	Using virtual technology to address home safety concerns for adolescents with brain injury: results from an exploratory mixed-methods pilot study	Lauren Wengerd
7	A	Nii-Ayi Aryeetey	Research Staff	Examining the role of the arcuate fasciculus on reading development by studying repetitive head impact	Zeynep Saygin
8	B	Maria Balch	Postdoctoral Researcher	Sample Procurement in the Operating Room: Advancing Clinical Research in a Learning Health System	Dana McTigue
9	A	Noor Chaudhry	Research Staff	Dynamic balance and gait, but not static balance, are positively associated with episodic memory performance across the adult lifespan	Scott Hayes
10	B	Matthew Farrow	Postdoctoral Researcher	The effect of low-glycemic index diet on postprandial hypotension in spinal cord injury: a case-series	Ceren Yarar-Fisher
11	A	Jillian Graham	Research Staff	Individual differences impact the relationship between cardiorespiratory fitness, visual episodic memory, and parahippocampal cortex thickness.	Scott Hayes
12	B	Yasufumi Hayano	Postdoctoral Researcher	Peripheral cancer remotely induces bilateral pain through excitation of the anterior cingulate cortex	Hiroki Taniguchi
13	A	M Shifatul Islam	Research Scientist	Stroke Diagnosis and Monitoring Using Microwave Imaging	Asimina Kiourti

#	TIME	NAME	LEVEL	ABSTRACT TITLE	MENTOR
14	B	Enora Le Flao	Postdoctoral Researcher	Concussion Symptoms in Law Enforcement Cadets Undergoing Defensive Tactics Training	Jaclyn Caccese
15	A	Da Lin	Research Staff	Arachidonic acid mobilization and peroxidation promote microglial dysfunction in Ab pathology	Jie Gao
16	B	Jenna McCloskey	Research Staff	Traumatic brain injury increases risk aversion in a probability discounting task and risky decision-making on a gambling task	Cole Vonder Haar
17	A	Raquel Minarsch	Research Staff	Assessing non-invasive spinal Stimulation and PT/OT for motor Improvement Response with ExaStim (ASPIRE)	Ceren Yarar-Fisher
18	B	Sinae Park	Research Staff	Developmental Stages of First Concussion and Psychological Outcomes in Young Adulthood	Jasmeet Hayes
19	A	Peipei Qi	Research Staff	Transcriptional regulations underlying the terminal differentiation of murine cortical chandelier cells	Hiroki Taniguchi
20	B	Debasish Roy	Postdoctoral Researcher	Promoting CNS axon regeneration by manipulating cholesterol	Andrea Tedeschi
21	A	Christopher Rundus	Postdoctoral Researcher	Association of Elevated Concussive Symptoms on Driving Performance: A Comparison between Adolescent Drivers with Mild Traumatic Brain Injury and Matched Healthy Controls	Ginger Yang
22	B	Tyler Shannon	Research Staff	Genetic diversity drives extreme responses to traumatic brain injury and post-traumatic epilepsy	Bin Gu
23	A	Marissa Smail	Postdoctoral Researcher	Profiling acute immune and chronic behavioral effects of pediatric traumatic brain injury in rats	Kathryn Lenz
24	B	Morgan Taylor	Postdoctoral Researcher	Tissue-specific bulk RNA sequencing reveals effects of traumatic brain injury and post-injury sleep fragmentation on the microglial transcriptome	Olga Kokiko-Cochran
25	A	Jingyun Zhang	Postdoctoral Researcher	Chandelier cells in the anterior cingulate cortex play a critical role in determining the pain threshold in physiological and pathological states	Hiroki Taniguchi
26	B	Fangda Zhang	Research Scientist	A simulator study assessing the association between symptom severity and driving performance post mild traumatic brain injury in young drivers	Ginger Yang

#	TIME	NAME	LEVEL	ABSTRACT TITLE	MENTOR
27	A	Zachary Zimomra	Research Staff	The Effects of Sleep Fragmentation on Plasma Corticosterone in Mice with Traumatic Brain Injury.	Olga Kokiko-Cochran
28	B	Adam Culiver	Postdoctoral Researcher	Does Neck Strength Predict Head Impacts in Youth Football Players?	Jaclyn Caccese
29	A	Anna Quatrale	Research Staff	Examining Variability of High-Level Visual Categories Across Development	Zeynep Saygin
30	B	Grace Amadon	Graduate Student	Examining the relationship between gait, balance, processing speed, and executive function across the lifespan	Scott Hayes
31	A	Aashi Anne	Graduate Student	Investigating the Role of NG2+ Glial Cells in Chronic Spinal Cord Injury Recovery using Transgenic mice	Dana McTigue
32	B	Rebecca Boland	Graduate Student	Investigating the Role of the Peripheral Immune System in post-TBI SF	Olga Kokiko-Cochran
33	A	Christopher Cotter	Graduate Student	Sleep Fragmentation compromises Sleep Recovery Patterns Following Traumatic Brain Injury	Olga Kokiko-Cochran
34	B	Amara Davis	Graduate Student	Interleukin-1 Receptor-1 Signaling mediates Neuroinflammation, Neuronal Dysfunction, and Cognitive Decline after Diffuse Traumatic Brain Injury	Jonathan Godbout
35	A	Samantha DeAngelo	Graduate Student	Youth Football Head Impact Exposure Differences Based on Four Data Cleaning Methods	Jaclyn Caccese
36	B	Olivia Horn	Graduate Student	Examining self-reported moderate-to-vigorous physical activity, actigraphy metrics, and subjective cognitive complaints across the lifespan	Scott Hayes
37	A	Sam Houle	Graduate Student	Stress Exposure Following Traumatic Brain Injury Dampens Acute Inflammatory Gene Transcription	Olga Kokiko-Cochran
38	B	Ali Kaiss	Graduate Student	Estimating Heart Rate Variability (HRV) Using a Wearable Magnetocardiography (MCG) Sensor	Asimina Kiourti
39	A	Sarah Kaye	Graduate Student	The E3 Ubiquitin Ligase IDOL Regulates Microglial Phagocytosis in Alzheimer's Disease	Jie Gao
40	B	Tae Yeon Kim	Graduate Student	Excitatory neuronal PLCG2 correlates with tau pathology in Alzheimer's disease	Hongjun Fu

#	TIME	NAME	LEVEL	ABSTRACT TITLE	MENTOR
41	A	Ana Leon-Rodriguez	Graduate Student	Primed microglia and increased hypothalamic neuroinflammation after acute stress in traumatic brain injured-mice	Jonathan Godbout
42	B	Sabrina Mackey-Alfonso	Graduate Student	The Neuroinflammatory Impact of High Fat Diet on Memory and Synaptic Degradation in an AD Model	Ruth Barrientos
43	A	Emika Miller	Graduate Student	Expert Interprofessional Community Advisory Board to Inform Dementia Caregiving Research	Kathy Wright
44	B	Jenna Rajczyk	Graduate Student	Broadband access may influence variation in Alzheimer's disease and related dementias prevalence in Central Appalachia	Jeffrey Wing
45	A	Jenna Rajczyk	Graduate Student	State-level effect of Medicaid expansion on Alzheimer's disease and related dementias mortality	Jeffrey Wing
46	B	Nicole Saltiel	Graduate Student	Health Outcomes in Contact Sport Athletes: The BUCKS Study	Jasmeet Hayes
47	A	Carly Smith	Graduate Student	Examining Sex and Neck Strength as Risk and Protective Factors for Repetitive Head Impact Exposure in Law Enforcement Cadets	Jaclyn Caccese
48	B	Jessica Stark	Graduate Student	Exploring the association between sedentary behavior, cardiorespiratory fitness, and episodic memory in aging.	Scott Hayes
49	A	Matthew Stauder	Graduate Student	Physical fitness mediates the relationship between physical activity and executive functions in aging.	Scott Hayes
50	B	Julie Strominger	Graduate Student	Density of Physical Activity Resources is Associated with Post-Stroke Physical Activity	Jeffrey Wing
51	A	Chao Sun	Graduate Student	Axon-Glial Mechanotransduction Induced by a Concussive Head Impact	Chen Gu
52	B	Alejandra Zaleta Lastra	Graduate Student	Effects of Early Life Stress + Adult TBI model development: Microglia as mediators of brain and behavioral outcomes	Kathryn Lenz
53	A	Gregory Edwards	Graduate Student	Comparing Horizontal Smooth Pursuit Outcomes after Concussion	Jaclyn Caccese
54	B	Jonathan Packer	Graduate Student	Impaired Cortical Neuronal Homeostasis and Cognition after Diffuse Traumatic Brain Injury Are Dependent on Phosphatase and Tensin Homolog and the PI3k-AKT Pathway	Jonathan Godbout
55	B	Habib Akouri	Undergraduate Student	The Impact of Pediatric Traumatic Brain Injury on Mast Cell and Oxytocin Content in Social Brain Regions in Rats	Kathryn Lenz

#	TIME	NAME	LEVEL	ABSTRACT TITLE	MENTOR
56	B	Alex Bruggeman	Undergraduate Student	Test-Retest Reliability using the Neurolign Dx-100TM for Oculomotor Testing in Healthy Adults	Jaclyn Caccese
57	A	Shannon Dobres	Undergraduate Student	Sleep Fragmentation Influences Sleep Behavior following Traumatic Brain Injury 3 Days Post Injury	Olga Kokiko-Cochran
58	B	Durshil Doshi	Undergraduate Student	Inter-rater Reliability Between Two Raters For Repetitive Head Impact Counts In Youth Tackle Football	Jaclyn Caccese
59	A	Lucas Ecker	Undergraduate Student	Examining the interaction of age and objective sleep quality on episodic memory performance	Scott Hayes
60	B	Hayes Johnson	Undergraduate Student	Deciphering the microstructure of the central nervous system white matter extracellular space	Wenjing Sun
62	B	Ethan Ma	Undergraduate Student	Deferoxamine Mesylate in Serum Containing and Serum-Free Environments alters Adult Schwann Cell Survivability under Hydrogen Peroxide Induced Cell Death	Giles Plant
63	A	Carly McPherson	Undergraduate Student	Effect of Baseline Neck Strength on HAE Magnitude in Adolescent Female Soccer Players	Jaclyn Caccese
64	B	Florencia Ontiveros	Undergraduate Student	Thalamic Volume in Children with Traumatic Brain injury Linked to Adaptive Functioning Outcomes	Kristen Hoskinson
65	A	Neha Rao	Undergraduate Student	Oligodendrocyte progenitor cell deletion disrupts early glial scar formation following spinal cord injury	Dana McTigue
66	B	Eric Schwegler	Undergraduate Student	Printed Circuit Board to Control Remote Food Dispenser for Assessing Pig Cognition	Cole Vonder Haar
67	A	Ella Snead	Undergraduate Student	Barriers and facilitators to engaging in physical activity in individuals with chronic brain injury: A qualitative study	Catherine Quatman-Yates
68	B	Nick Sweeney	Undergraduate Student	Neuronal BAG3 attenuates AD-like pathology and cognitive deficits induced by traumatic brain injury via the regulation of autophagy-lysosome pathway	Hongjun Fu
69	A	Sheeny Vo	Undergraduate Student	MAPT R406W mutation reduces neural activity and oscillations in human neural organoids.	Hongjun Fu
70	B	Olivia VonDeylen	Undergraduate Student	Youth Sleep Quantity and Quality and Symptom Duration in the First Week Post-Concussion	Ginger Yang

#	TIME	NAME	LEVEL	ABSTRACT TITLE	MENTOR
71	A	Emily Yu	Undergraduate Student	Infrared Modulation of Motor Cortex and Related Pathways	Zeynep Saygin
72	B	Anna Lanier	Undergraduate Student	Understanding the Role of Glia in Postnatal Brain Injury	Tracy Bedrosian

Abstracts

1

Metagenomic sequencing to better understand gut microbiome contributions to TBI

Martens, K. M., Gratzol, C., Bressler, N. M., Bailey, M. T., & Vonder Haar, C.

Traumatic brain injury (TBI) causes cognitive impairment, increases risk for psychiatric disease, and exacerbates related symptoms such as risky decision-making and impulsivity. Impaired monoamine neurotransmission is a likely contributor to such symptoms, with serotonin signaling contributing to anxiety and mood-related disorders, impulsive dysfunction, and impaired decision-making. Despite this knowledge, precisely why these systems are vulnerable to TBI is unknown. However, emerging data indicate a role for the gut microbiome. Gut dysbiosis, or an imbalance in microbial populations, occurs rapidly after TBI and may persist for years in patients. In a previous study, our lab manipulated the microbiome of rodents using antibiotic dysbiosis. We then assessed function on the Rodent Gambling Task, a clinically relevant assessment of impulsivity and decision-making. The findings from the study showed a delay in the onset of TBI symptoms in the antibiotic cocktail group pointing to a potential causal role for the gut microbiome in psychiatric disease following TBI. The most common sequencing method of gut microbiome, 16S amplicon-based sequencing, identified broad changes in the microbiome, but could not identify species-level information. To better understand the mechanisms at play, we performed metagenomic shotgun sequencing which reconstructs individual genes, and then species. From these data, we were able to construct bacterial metagenome-assembled genomes (MAGs) to determine changes occurring at key time points post injury and at the species level. Ongoing analyses will determine which individual species are changed due to TBI, antibiotics, and during the post-injury recovery period as well as specific metabolic genes involved in regulating serotonin and other important gut signaling transmitters.

2

Cohesin-dependent three-dimensional chromatin looping is required for axonal regeneration after injury

Ilaria Palmisano1,2§*, Tong Liu3§, Wei Gao1, Luming Zhou1, Matthias Merkenschlager4, Franziska Müller 1, Jessica Chadwick1, Rebecca Toscano Rivolta1, Guiping Kong1, James WD King4, Ediem Al-jibury4, Yan Yuyang 1, Sree Gongala1, Francesco De Virgiliis1, Zheng Wang3§§ and Simone Di Giovanni1§§

Axonal regeneration after injury relies on coordinated changes in expression of hundreds of functionally connected regenerative genes. Gene expression changes are regulated within three-dimensional (3D) functional genomic domains, called topologically associating domains (TADs), generated by the protein complex cohesin. Within TADs, cohesin generates chromatin loops that allow functional interactions between enhancers and target gene promoters, critical for transcriptional activation. Despite the crucial role of 3D genome architecture in gene regulation, whether chromatin looping mechanisms play a role in axonal regeneration after injury remains elusive. To address this question, we performed Hi-C, promoter-Hi-C, CUT&Tag for H3K27ac and RNA-seq in purified dorsal root ganglia (DRG) sensory neurons from wildtype and cohesin conditionally depleted mice following sciatic nerve crush. We found that genes involved in axonal regeneration were enriched within cohesin-dependent TADs and formed long-range, complex chromatin loops in response to nerve injury in a cohesin-dependent way. Accordingly, loss of cohesin resulted in failure in activation of the regenerative transcriptional program and in severely impaired nerve regeneration. Complex enhancer-promoter loops during nerve regeneration were also enriched in human foetal cortical plate, where the axonal growth potential is highest, and lost in mature adult neurons. These data reveal for the first time a central role for 3D genome architecture in the control of regenerative gene expression and identify cohesin as a novel regulator of nerve regeneration. Accordingly, overexpression of the cohesin loading factor -Nipped-B-like protein- was sufficient to enhance regenerative growth of DRG sensory neurons in vitro. We also present preliminary data showing that, after crush of the DRG central branch in the dorsal columns, regenerative genes displayed a lower frequency of chromatin interactions. This suggests that the failure in regenerative gene activation after spinal cord injury might be due to the failure of cohesin to establish stable chromatin interactions within TADs at regenerative genes.

3

Quality of Life in Concussed and Non-concussed Children with Symptomatic Eye Teaming, Focusing, and Tracking Problems

Ruth Lu, PhD, Penny A. Pasque, PhD,Marjean Kulp, OD, MS

Purpose: This study investigated the Quality of Life (QoL) of children (with and without concussion) experiencing binocular vision, accommodative, and tracking disorders.

Methods: Phenomenology was used to explore how children with and without concussion experience these vision disorders. In-depth qualitative interviews and focus groups were conducted using a semi-structured interview guide and follow-up questions. Responses were collected and coded. Themes were generated through inductive and deductive processes using NVivo and developed into a codebook through group consensus. Codes within each QoL domain were grouped based on similar meanings and constructs (binning) and refined to form a representative and manageable set (winnowing).

Results: Across the five national clinical sites, 83 children (32 with a history of concussion) participated. Eleven QoL domains emerged: visual symptoms, ocular symptoms, general symptoms, activity limitation, mobility, social impact, inconveniences, economic impact, concerns, emotional impact, and coping. The majority of interviews and focus groups with children, both with and without concussion, revealed general symptoms, activity limitations, visual symptoms, ocular symptoms, coping, concerns, emotional impact, and inconveniences. Common general symptoms included headaches, tiredness, dizziness, and difficulty concentrating. Common activity limitations included difficulties playing sports, reading, using computers and phones, and looking between the board and paper. Common visual symptoms included double vision, blurred vision, and difficulty focusing. Common ocular symptoms included eye pain, tired eyes, sore eyes, and difficulty using the eyes together. Common coping strategies included using a finger/guide to read and taking breaks. Social impact was reported more often in those with concussion than in those without (58% versus 19% of groups and interviews, respectively), with reports of feeling isolated and difficulties maintaining friendships and participating in social activities.

Conclusions: Experiences of children with binocular vision, accommodative, and tracking disorders (both with and without concussion) show QoL impacts across multiple domains (general symptoms, activity limitations, visual symptoms, coping, concerns, ocular symptoms, emotional impact, and inconveniences).

4

Combined Transplantation of Mesenchymal Progenitor and Neural Stem Cells to repair cervical spinal cord injury.

Seok Voon White[2,3] Ethan Ma[1] Cole McGuiness[1] Christine D Plant[2], Alan R Harvey[3], Giles W Plant[1,2]

Mesenchymal progenitor cell (MPCs) transplantation is a promising strategy to improve recovery following cervical spinal cord injury (SCI). While being effective in reducing tissue loss, preserving white matter and improving forelimb function (White et al., 2016) a bridging strategy is also required to reconnect spinal cord pathways. We have developed a combinatorial cellular transplantation approach, using intravenous (IV) delivered MPCs after 24 hours followed by intraspinal delivery of neural stem cells (NSCs) at 3 or 7 days after injury. The intravenous delivered MSCs would provide (a) protection of the injured cervical spinal cord by reducing tissue loss and immune cell infiltration; and (b) reduce inflammation, thereby increasing NSC transplant survival and promote NSC differentiation. The transplanted NSCs would provide (a) tissue bridge across the lesion and (b) provide a substrate for axonal regeneration and myelination (c) reconnect lost neuronal pathways to induce forelimb functional return after cervical injury. Our results show that initial protection of the injury site by IV MPCs transplantation resulted in no increased survival of the NSCs transplanted at Day 7. However, integration of transplanted NSCs was increased at the Day 3 time point indicating MPCs influence very early immune signaling rather than the later adaptive immune suppressive effect on NSCs transplantation. We show in this study that two cellular transplantation techniques, each previously shown to improve functional and anatomical outcomes in rodent SCI, do not result in a co-operative improvement when combined at Day 7 post injury but were able to at Day 3 post injury. In addition to increased survival at day 3 there was an increasedifferentiation of NSCs into oligodendroglia at this early time point but no neuronal differentiation was seen. These observations provide important information regarding the combination, delivery, and timing of two cellular therapies in treating SCI. The evidence obtained in this experiment provides an understanding of the inflammatory signaling within the host tissue and the need to find the best timing for cellular transplantation survival and differentiation.

5

Human Corticospinal Neurons Derived from iPSC Transplanted to Repair Chronic Cervical Spinal Cord Injury

Doulames, VM[2], Weimann J[2], Palmer TD[2], Ma, E[1] , Boring M[1], McGuiness C[1], Chen R[1], Wasanwala H[1], Putta A[1], Mueller, P[1], Vonder Haar C[1], Singh E[1], **Plant GW[1,2]**

In this project, we transplanted human corticospinal motor neurons (hCSMNs) derived from induced pluripotent stem cells into a rat model of chronic cervical spinal cord injury. A total of 72 rats were used in the study divided into 2 cohorts of 36 rats. Each cohort was subsequently split into 3 groups which consisted of injury only (12), injury plus fibrinogen (n=12) and injury plus hCSMNs (n=12). We have used AAV reporter virus's to quantitate descending host corticospinal tract regeneration. Transplanted GFP+ human iPSC derived corticospinal neurons (CSMNs) were transplanted 2 months post injury and the survival, integration and phenotype were ascertained by gene therapy and immunohistochemistry. In addition, we have correlated behavior with these subsequent anatomical changes by monitoring the rats biweekly for changes in sensory and motor function. Transplanted GFP+ CSMNs showed excellent integration within the injured spinal cord of chronic injured rats and showed extensive regenerative growth of transplanted neurons and host supraspinal tracts. Transplanted animals showed significant reduction in spinal cavitation. At 20 weeks post injury, control rats have an average cavity volume of 0.80 mm^3 compared to 0.40mm^3 in a transplanted spinal cord. This increased supraspinal axonal growth and preservation also correlated with functional recovery of the right forelimb after transplantation (eg. Catwalk, ladderwalk and sensory tests). Based on this promising outcome we can begin tailoring parameters to better promote regeneration and connectivity between the injured nerve tracts and the transplanted human corticospinal neurons and strengthen the relay system being formed. This project represents an integral first step in developing a new translational therapy that restores motor function by repairing nerve tracts responsible for critical voluntary motor function.

6

Using virtual technology to address home safety concerns for adolescents with brain injury: results from an exploratory mixed-methods pilot study

Sarah E. Anderson, Taylor Stamper, Sarah Pierce, Jennifer P. Lundine, Emily S. Patterson, Carmen P. DiGiovine, Scott Swearingen, Lauren R. Wengerd, Amy R. Darragh

Introduction: Adolescents with acquired brain injury (ABI) are at an increased risk for additional injuries and other negative outcomes. However, the home safety hazards and concerns of this population are minimally understood. This study consisted of two aims: 1) to identify safety hazards and concerns for adolescents with ABI in home environments and 2) to identify adaptations to improve the relevancy and usability of an existing virtual simulation training system, the Home Healthcare Virtual Simulation Training System (HH-VSTS), for this population.

Methods: Using a mixed-methods, participatory approach, we engaged three stakeholder groups in interviews: adolescents with ABI, their caregivers, and clinicians who work with this population. Participants completed surveys on demographics, adaptive function, home hazards, and HH-VSTS usability. Semi-structured individual and group interviews were conducted in-person or via Zoom and included facilitated discussion, a priority hazard identification activity, and demonstration of the HH-VSTS through video and live-play. Quantitative data were analyzed descriptively, qualitative data were analyzed using grounded theory analysis of coded transcripts, and mixed-methods analysis of these data are also employed.

Results: Preliminary data are presented. 13 providers, 5 caregivers, and 5 adolescents with ABI participated in the study. A variety of clinical experts addressed home safety: ~30% OT, ~30% PT, ~23% SLP, and ~15% other. Adolescents ranged in age from 13-17 yrs., had all experienced a traumatic brain injury, and all reported being very comfortable using new technologies. All caregivers who participated were mothers or grandmothers of adolescents with ABI. Many safety concerns were discussed during the interviews including slips, trips, and burns resulting from wet surfaces, rugs, and stove/oven use. While most participants responded positively to the HH-VSTS, a range of modifications (e.g., gamification, visual improvements) were identified.

Discussion: This study uniquely focuses on home safety concerns and investigates the usefulness, usability, and desirability of the HH-VSTS for adolescents with ABI, as expressed by clinicians, caregivers, and the adolescents themselves. Results indicate that home safety concerns are present across all stakeholder groups, but adolescents express the least concern. All participants liked the program, but significant improvements were suggested to make the information more useful, the program more usable, and the experience more fun. These findings contribute to the long-term objective of this study: to increase the home safety of adolescents with ABI by improving their ability to identify and respond to common household hazards using virtual reality intervention.

7

Examining the role of the arcuate fasciculus on reading development by studying repetitive head impact

Nii-Ayi Aryeetey[1], Kelly Hiersche[1], Jeff Pan[1], Ginger Yang[2], Sean Rose[2], James Onate[1], Jaclyn Caccese[1], Zeynep M. Saygin[1]

1. The Ohio State University, Columbus, Ohio
2. Nationwide Children's Hospital, Columbus, Ohio

A myriad of changes occur as a child learns to read including in gray matter (e.g. word-selectivity in the visual word form area (VWFA)) and white matter (e.g. fractional anisotropy (FA) of the left arcuate fasciculus (AF)). Further, pre-readers at risk for developing dyslexia show lower FA in left AF, revealing potential white matter mechanisms driving reading development. While we cannot know whether arcuate development is *causally* responsible for much of early reading ability without disrupting the system, here we explore this question by studying head impacts in otherwise typically-developing 8-12 year-olds. Youth football leagues usually start tackle football around age 8, when most children acquire literacy. We scanned children before their initial season of tackle football and followed them longitudinally after the season, and compared their neurodevelopment to a matched control cohort. Preliminary findings show that at preseason, there are no significant between-group reading differences, VWFA selectivity, and FA in AF; however, we observed FA differences in the left AF postseason. Children who played their first season of tackle football showed no developmental changes in the left AF while control children showed increasing FA longitudinally (4-5 months). These white matter differences might precede observable deficits in reading, as we found no significant between-group differences in reading scores postseason (albeit trending, with modest reading score improvements in children in the control but not football group). Significant reading ability changes in typical development are expected after 1 year, minimum. Overall, these results suggest that exposure to repetitive head impacts may lead to atypical white matter development, and that the growth of the left AF may be especially important in driving reading development. Ongoing longitudinal investigations will explore whether children catch up in AF growth with increasing time post-season, and dose-response relationship of head impacts on reading and other cognitive outcomes.

8

Sample Procurement in the Operating Room: Advancing Clinical Research in a Learning Health System

Maria Balch, PhD[1]; Dana McTigue, PhD[1]; Carmen Quatman, MD, PhD[2,3]

Depts. of [1]Neuroscience, [2]Orthopaedic Surgery, and [3]Emergency Medicine

The Ohio State University Wexner Medical Center

After central nervous system (CNS) injury, patients face life-altering disability. Neuromuscular studies in animal models of spinal cord injury (SCI) give insight on paralyzed muscle pathophysiology, yet gaps remain between preclinical findings and clinical validation. Though routine and beneficial, needle biopsies yield small cores of muscle and are rarely performed outside of the neuromuscular clinic. Orthopaedic surgical procedures, however, provide ready access to muscle tissue (e.g., fracture stabilization, hardware removal) and may require removal of tissue, discarded as biohazard waste (e.g., joint replacement, debridement, amputation). Taking a Learning Health System (LHS) approach, we sought to leverage the operating room (OR) as a bridge between patient care and research stewardship in translational science.

In collaboration with Orthopaedic Surgery, and in partnership with the Neuroscience Research Institute Brain Bank & Biorepository (NRI-BBB), we designed a study to obtain open muscle biopsies during already-scheduled orthopaedic procedures in patients with (or without) history of SCI; enrollment is ongoing. From an LHS perspective, we used this pilot study to develop a novel pipeline for research sample procurement in the OR. We applied implementation science methods of process mapping, key driver diagrams, and time series analyses to identify process pitfalls, update procedures, and improve resource utilization and communication.

Here, we summarize the barriers faced and traction made while launching a workflow to obtain research samples in the OR. Project initiation-to-enrollment took 9 months, a critical period that required coordination across departments, personnel, and hospital sites; addressing obstacles to ensure policy adherence and regulatory compliance; developing a motor point biopsy protocol; streamlining patient enrollment; and tackling complexities of human muscle tissue transport and processing in a translational research laboratory.

Building a tissue procurement process for an LHS requires a complex, multi-faceted initiative that employs strategic quality improvement and implementation science. Continued application of lessons-learned and refinement of our intraoperative muscle biopsy workflow will bolster institutional efforts for an LHS and provide a foundation upon which other tissue types and patient populations can be investigated. The OR's unique accessibility of clinical samples without additional inconvenience to the patient - and its potential for repurposing discarded tissue - opens avenues for groundbreaking research.

9

Dynamic balance and gait, but not static balance, are positively associated with episodic memory performance across the adult lifespan

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Objective: Both mobility and cognition are multi-faceted constructs that decline with age. The primary objective of this study was to examine the relationship between different aspects of mobility (dynamic balance, gait, and static balance) and episodic memory (verbal and visual) in aging.
Participants and Methods: Data from 116 adults (age range=18-85 years, mean age=52.3, SD=18.5) were obtained from the Fitness, Aging, Stress, and Traumatic Brain Injury Repository (FASTER). Episodic memory was assessed with the following standardized tests: the California Verbal Learning Task-II, Wechsler Memory Scale Logical Memory Subtests, Brief Visuospatial Memory Test-Revised, and the Picture Sequence Memory Task from the NIH Toolbox. Composite scores of dynamic balance, gait, and static balance were generated. The dynamic balance composite score included time to complete a figure 8 walk test and a 5 times sit-to-stand task. The gait composite score included spatiotemporal gait measures during a 40-foot walk test, assessed with the LEGSys™ wearable device. The static balance composite score included indices of sway on firm or foam surfaces with eyes open or closed, collected via the BalanSens™ wearable device. Relative importance analyses were used to examine the relative contribution of different components of mobility to verbal and visual episodic memory. Hierarchical linear regression models were used to examine whether different components of mobility were significantly associated with verbal and visual episodic memory.
Results: After adjusting for age, sex, and education, relative importance analyses showed that gait accounted for the most variance in verbal episodic memory (lmg=0.032), followed by dynamic balance (lmg=0.019) and static balance (lmg=0.016). Hierarchical linear regressions confirmed that dynamic balance ($\hat{\beta}$ =0.19, p=.018) and gait ($\hat{\beta}$ =0.40, p=.006) were significantly and positively associated with verbal episodic memory. For visual episodic memory, dynamic balance (lmg=0.040) and gait (lmg=0.030) accounted for the most variance, and follow-up regression analyses confirmed these associations were significant: dynamic balance ($\hat{\beta}$ =0.26, p<.001) and gait ($\hat{\beta}$ =0.42, p<.001)
Conclusions: Gait and dynamic balance metrics were positively associated with both verbal and visual episodic memory, whereas static balance components of mobility were not. These findings support the notion that there may be domain specific associations between mobility and cognitive performance.

10

The effect of a low-glycemic index diet on postprandial hypotension in spinal cord injury: a case-series

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Background
Individuals living with a spinal cord injury (SCI) have a greater risk of developing cardiovascular disease (CVD) compared to the general population. One in two individuals with SCI experience a clinically meaningful decline (>20 mmHg) in systolic blood pressure (SBP) in the 2-h after eating. This is referred to as postprandial hypotension (PPH) and is associated with CVD. Post-meal glucose levels, which are typically elevated in individuals with SCI, are likely to exacerbate this but provide a possible target for the treatment for PPH. Glycemic index (GI) is a measure of how quickly food increases blood glucose, rated on a scale of 0-100 (Low: <55, Medium: 56-69, High: >70). In theory, consuming meals with a slow rate of glucose release (i.e., low GI) could prevent or lessen PPH.
Aim
To determine the effect of consuming a low-GI diet on PPH in individuals with chronic (>1-year post-injury) SCI.
Methods
In a case-series design, three individuals (A: 32-year-old male with C5 incomplete injury, B: 38-year-old female with T4 complete injury, C: 49-year-old female with C6 incomplete injury) met the threshold for PPH in a screening visit. They then completed two conditions in a randomized order: i) low GI diet (55), and ii) high GI diet (95). On each occasion, participants reported to the laboratory after an overnight fast. BP was measured at rest, and then every 6 minutes for 2-h after consumption of a breakfast meal that corresponded to the diet condition. All meals were matched for macronutrient composition (55% carbohydrate, 30% fat, 15% protein) and the calculated caloric needs of each participant.
Results
The average decrease in SBP during the in-lab breakfast meals was less in the low-GI conditions compared to high-GI for all three participants (A: 10 vs. 29 mmHg, B: 8 vs. 10 mmHg, C: 21 vs. 43 mmHg). Participant A remained within the PPH cut-off for 24 minutes during the high GI condition, and 0 minutes for the low GI condition. Participant B remained within the PPH cut-off for 108 minutes during the high GI condition, and 6 minutes during the low GI condition. Participant C did not exhibit PPH in either trial.
Conclusion
In three individuals with SCI, consuming a low-GI diet was effective at reducing the magnitude and incidence of PPH. It appears to be a promising treatment for the condition to reduce CVD risk.

11

Individual differences impact the relationship between cardiorespiratory fitness, visual episodic memory, and parahippocampal cortex thickness.

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Objective: Cardiorespiratory fitness (CRF) has been associated with visual episodic memory performance and cortical thickness in older adults. Although women are diagnosed with Alzheimer's disease (AD) at a greater rate than men, sex and age-differences in CRF, episodic memory, and cortical thickness has not been fully explored. The present study aimed to investigate potential individual differences in the relationship between CRF, visual episodic memory, and cortical thickness.

Participant and Methods: Adults (n = 93; age range: 18-85 years, M = 50.9 years) were recruited as part of the Fitness, Aging, Stress, and TBI Exposure Repository. CRF (peak VO_2) was measured via maximal graded exercise testing. A composite z-score comprised of the Brief Visuospatial Memory Test-Revised (immediate and delayed recall) and the Picture Sequence Memory Test was used to summarize visual episodic memory performance. T_1- and T_2-weighted MRI scans were processed and analyzed using FreeSurfer. Surface based analyses revealed that older age was negatively associated with cortical thickness in right parahippocampal cortex, among other regions. Given previous work demonstrating a link between visual episodic memory and right parahippocampal cortex, we identified this as a primary region of interest (ROI). Hierarchical regressions were conducted to assess the relationships between age, sex, peak VO_2, visual episodic memory, and right parahippocampal thickness. A mediation analysis was conducted to investigate the relationship of parahippocampal thickness on CRF and visual episodic memory.

Results: Age was negatively associated with right parahippocampal thickness. Sex was also associated with right parahippocampal thickness, with greater right parahippocampal thickness observed in females. After accounting for sex and age, peak VO_2 was positively associated with right parahippocampal thickness. Finally, an Age X Peak VO_2 X Sex interaction was observed. Peak VO_2 predicted greater right parahippocampal thickness in females regardless of age. In contrast, peak VO_2 only predicted greater right parahippocampal thickness in older males. Subsequent mediation analysis found that parahippocampal thickness mediated the relationship between peak VO_2 and visual episodic memory, regardless of sex or age.

Conclusion: These findings indicate that associations between CRF and cortical thickness may be dependent on both age and sex. An association was observed among females across the adult lifespan and only observed in males during older adulthood. Right parahippocampal cortex thickness exhibited an indirect effect on the relationship between CRF and visual episodic memory. Implementing a CRF intervention early in adulthood may decrease the negative effects of aging on cortical thickness and cognition, especially in females.

12

Breast cancer remotely induces bilateral pain through excitation of the anterior cingulate cortex

Yasufumi Hayano, Hiroki Taniguchi

Pain syndrome experienced by cancer patients and survivors needs to be appropriately managed for their quality of life. However, current analgesics are often ineffective or associated with severe side effects. Therefore, developing novel pain management strategies stands as urgent clinical needs, and systematic understanding of the mechanisms underlying the cancer-induced pain is required to achieve this end. Assessing the direct impact of peripheral cancer on human patients' pain is challenging due to individual case complexities. Utilizing animal models offers ideal opportunities to test the direct effects of peripheral cancer on pain induction. Previous studies in a rodent model have shown that inoculation of cancer cells into the tibia unilaterally induced the mechanical allodynia at the hind paw through neuronal hyperactivation in the anterior cingulate cortex (ACC). However, since in these studies, cancer cells likely cause neuropathic pain via damage to sciatic nerve branches, it remains obscure whether they indirectly induce pain through physical nerve damage or directly impact on the pain-related signaling system. It also remains poorly understood whether and how local tumors remotely affect pain sensation across body parts. To address these issues, we first evaluated pain sensation in hind paws of animals that unilaterally have breast cancer cells in the mammary fat pad. We found that the pain threshold is progressively decreased as tumors develop, implying the remote induction of mechanical allodynia by breast cancer. Immunohistochemical analysis using c-fos, an indicator of neuronal activity, showed significant increase of neuronal excitability in several cortical areas including the ACC. Intriguingly, allodynia and cortical hyperexcitation were observed bilaterally without glial activation in the spinal cord at the level of the hind limb, a phenomenon observed in neuropathic and inflammatory pain models with hind limb manipulations. This breast cancer-induced allodynia was significantly ameliorated by bilaterally silencing activity in ACC excitatory neurons with AAV-mediated chemogenetics. Taken together, these findings suggest that local breast cancer globally increases cortical activity and remotely induces a bilateral pain syndrome. Moreover, like the findings in bone cancer, the ACC plays a pivotal role in allodynia induced by breast cancer. Our study provides a clue to find novel mechanisms by which peripheral cancer remotely affects pain sensation.

13

Stroke Diagnosis and Monitoring Using Microwave Imaging

M Shifatul Islam, M Asiful Islam, Yousef Hannawi, and Asimina Kiourti

A stroke occurs in the United States every 40 seconds, with a fatality every 4 minutes. The ability to differentiate ischemic/hemorrhagic strokes in the pre-hospital setting and to monitor stroke evolution by the bedside has the enormous potential to improve outcomes and reduce mortality.

Unfortunately, state-of-the-practice Microwave Resonance Imaging (MRI) and Computed Tomography (CT) systems are expensive and bulky, restricting imaging to the clinical setting and sparse intervals. CT also uses ionizing radiation that poses safety risks and further prohibits frequent imaging. Microwave imaging (MI), i.e., imaging of the permittivity properties of biological tissues using antennas around the head, has been explored as a possible alternative due to its simplicity, cost-effectiveness, and use of non-ionizing radiation. However, MI methods are challenging as the lossy nature of biological tissues imposes a limitation on spatial resolution.

In this work, we report novel MI algorithms to overcome limitations in the literature. We show that 12 dipole antennas placed conformally around the head can: (a) yield high-precision classification of ischemic vs. hemorrhagic stroke (using normal imaging), and (b) allow for stroke progression monitoring (using differential imaging). Imaging quality has already superseded the state-of-the art through careful choice of operating frequencies for normal and differential imaging; the theoretical study of antennas that send energy directively towards the head; and with novel ideas for enhancing the permittivity difference of stroke locations.

Currently, our MI framework provides excellent image quality over different realistic head models, developed numerically and through simulations, with the current resolution allowing the minimum detectable stroke radius of around 1cm. Future work will focus on further improving resolution using Deep Neural Networks, as well as collecting experimental data using realistic head-emulating phantoms. Efficient bio-matched-antenna (BMA) design to achieve optimal radiation characteristics for stroke applications is also on the agenda.

14

Concussion Symptoms in Law Enforcement Cadets Undergoing Defensive Tactics Training

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Law enforcement cadets (LECs) are trained in defensive tactics, which can result in injuries, including concussions. Concussion symptoms are non-specific and may indicate brain trauma, as well as other physiological states (e.g., fatigue).

PURPOSE: To determine day-to-day variability of concussion symptoms concussion and changes across types of defensive tactics training.

METHODS: An electronic version of the SCAT6 22-symptom severity scale was distributed to LECs immediately before and after 9 defensive tactics training sessions, including 6 subject control trainings (Jiu-Jitsu-inspired), 2 boxing classes, and 1 defensive tactics assessment (all tactics).

RESULTS: 252 pre- or post-session surveys were completed by 18 participants (4 females), including 111 pre/post paired surveys. Pre-session (N=137), within-subject standard deviations ($SD_{w/i}$) ranged from 0-3.58 for number of symptoms on the 22-item scale, and 0-7.2 on the 0-132 total severity score (TSS) scale. The symptoms with the largest within-subject variability were Feeling slowed down (average $SD_{w/i}$: 0.36 on the 0-6 scale), Fatigue (0.36) and Headache (0.30). Across all sessions (N=111), the average pre/post number of symptoms increased by 0.20 (1.40 to 1.60) and the TSS increased by 0.54 (2.25 to 2.79). Pre/post changes varied by activity (ANOVA, $p<0.01$), showing larger symptom increases for the second boxing class (7 min of sparring, TSS +4) than the first (2 min of sparring, TSS -0.47) and the subject control sessions (TSS -0.18 to +1.80)(Tukey-Kramer comparisons, $p<0.05$). The number of symptoms and the TSS stayed the same pre/post in 54% of cases, increased in 24-26%, and decreased in 20-22%. Fatigue and Headache symptoms increased most often (14% of cases and mean of 0.30 on the 0-6 scale, 21% and 0.20, respectively). Large increases (>3 symptoms or >5 TSS points) were seen in 9 sessions (<1%) across 6 subjects, averaging 6.43±2.37 symptoms and 11.00±8.86 TSS points.

CONCLUSIONS: The large within-subject variability for pre-session symptoms, along with the low increases in symptoms, supports the use of pre/post comparisons to identify changes that may present a clinical interest. The increase in symptoms was larger for the session involving a longer exposure to head impacts, which will be investigated in future analyses.

15

Arachidonic acid mobilization and peroxidation promote microglial dysfunction in Ab pathology

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Abstract: Aberrant increase of arachidonic acid (ARA) has long been implicated in the pathology of Alzheimer's disease (AD), while the underlying causal mechanism remains unclear. In this study, we revealed a link between ARA mobilization and microglial dysfunction in Ab pathology. Lipidomic analysis of primary microglia from *App*$^{NL-GF}$ mice showed a marked increase in free ARA and lysophospholipids (LPLs) along with a decrease in ARA-containing phospholipids, suggesting increased ARA release from phospholipids (PLs). To manipulate ARA-containing PLs in microglia, we genetically deleted Lysophosphatidylcholine Acyltransferase 3 (*Lpcat3*), the main enzyme catalyzing the incorporation of ARA into PLs. Loss of microglial *Lpcat3* reduced the levels of ARA-containing phospholipids, free ARA and LPLs, leading to a compensatory increase in monounsaturated fatty acid (MUFA)-containing PLs in the *App*$^{NL-GF}$ mice. Notably, the reduction of ARA in microglia significantly ameliorated oxidative stress and inflammatory responses while enhancing the phagocytosis of Aβ plaques and promoting the compaction of Aβ deposits. Mechanistically, sc-RNA seq suggested that LPCAT3 deficiency facilitates phagocytosis by facilitating de novo lipid synthesis while protecting microglia from oxidative damage. Collectively, our study reveals a novel mechanistic link between ARA mobilization and microglial dysfunction in AD. Lowering brain ARA levels through pharmacological or dietary interventions may be a potential therapeutic strategy to slow down AD progression.

16

Traumatic brain injury increases risk aversion in a probability discounting task and risky decision-making on a gambling task.

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Traumatic brain injury (TBI) frequently results in cognitive-behavioral impairments such as risky decision-making. Although this correlates with a higher risk of developing addiction-related disorders, the specific mechanisms remain elusive. Complex behaviors require isolating the individual elements that underlie heightened addiction vulnerability. Pilot data suggests that TBI may generate novel neurological and/or behavioral mechanisms that contribute to the development of gambling disorders.

This study investigated how TBI affects sensitivity to probabilistic outcomes and whether reduced sensitivity is linked to disordered decision-making in rats. Rats were given a severe bilateral, frontal CCI TBI or sham procedure (N = 32). Subjects tested on a probability discounting task (PDT) in which a choice was given between a guaranteed small or uncertain large outcome. The probability of receiving the large outcome decreased across 4 blocks in a session. Rats were then assessed on the more complex rodent gambling task (RGT), where subjects chose amongst four options, each associated with varying probabilities and magnitudes of reinforcement or punishment. Lesion analysis and immunohistochemistry stains of ΔFosB, a transcription factor associated with learning and addiction, are ongoing.

Preliminary data demonstrates that TBI rats display lower preference for risky outcomes on the PDT ($p = 0.002$), suggesting risk aversion. The overall downshift of the curve in TBI rats suggests that this risk aversion leads to suboptimal decision-making, including when large reinforcement is guaranteed. Despite this risk averse behavior, TBI still increased risky decision-making on the RGT ($p < 0.001$). This data highlights discrepant relationships with probabilistic outcomes on behavior after TBI. Continued research in this area will inform the novel mechanisms by which it appears addiction may develop after TBI, further increasing the likelihood of successful future therapies and interventions.

17

Assessing non-invasive spinal Stimulation and PT/OT for motor Improvement Response with ExaStim (ASPIRE)

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Background. Currently, there is no cure for spinal cord injury (SCI) and many rehabilitative techniques are focused on preserving strength and compensatory strategies to safely perform activities of daily living. This is especially true for upper extremity (UE) function, and its restoration is one of the highest priorities for those with tetraplegia from SCI. Promising impacts from neuromodulation have emerged in recent years, including epidural and transcutaneous spinal stimulation (TSS). In addition to potential physical function improvements, spinal stimulation may also impact autonomic function, quality of life, and pain. TSS may be preferred by clinicians and individuals with SCI over epidural stimulation due to its similar efficacy and non-invasive technique. **The purpose of this study** is to examine the effectiveness of the ExaStim® TSS on UE function after chronic SCI, with results from a case series of 2 participants. **Hypotheses:** TSS with UE therapeutic activities will improve i) UE function and (ii) measures of health and recovery compared to sham stimulation with therapy. **Methods**: Ten individuals with chronic, traumatic SCI between C2 and T2 will be randomized to a TSS or sham stimulation group. Each group will participate in 45-60 minute treatment sessions 3 times a week for 8 weeks. Treatment sessions consist of stimulation with group-specified parameters while participating in UE rehabilitation activities with an occupational or physical therapist. Outcome measures include: strength [Upper Extremity Motor Scores (UEMS)], gross [Capabilities of Upper Extremity Test (CUE-T)] and fine (9-Hole Peg Test) motor function, International Standards for Neurological Classification of SCI (ISNCSCI), sitting balance [Function In Sitting Test (FIST)], spasticity [Modified Ashworth Scale (MAS)], health (SF-39), life participation [Canadian Occupational Performance Measure (COPM)], bowel and bladder management (SCI-QOL), pain [Neuropathic Pain Symptom Inventory (NPSI)], and blood biomarkers of inflammation and neurorecovery. **Case Series Results:** Two participants completed the study, 1 per group. Blood biomarkers and neuropathic pain data were not collected. Participant A (49y female, C5, AIS C) received TSS. Participant B (54y male, C2, AIS D) received sham stimulation. Both participants improved in UEMS, CUE-T, SCI-QOL bladder, and SCI-QOL bowel scores. Participant A did not demonstrate improvement in fine motor and sitting balance scores. There were no serious adverse events. **Discussion**: This project is ongoing; therefore, results are inconclusive. However, based on the first 2 participants, TSS appears to be safe and feasible with a similar impact on clinical outcomes compared to standard rehabilitation.

18

Developmental Stages of First Concussion and Psychological Outcomes in Young Adulthood

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Introduction: Concussions are common among youth athletes, and those occurring during critical periods of neurodevelopment may have lasting repercussions in adulthood. However, few studies have explored the longer-term psychological effects of concussions sustained during childhood and adolescence. Recent research has shown that younger age at first concussion is associated with increased psychological distress among college women. Nonetheless, it remains uncertain whether there is a specific developmental phase that is most closely linked to psychological distress in young adulthood.

Methods: Participants consisted of collegiate athletes who completed a baseline assessment as part of the Concussion Assessment, Research and Education (CARE) Consortium. Participants self-reported the age of their first concussion and were divided into developmental groups based on concussion timing: childhood (10y - 12y), early adolescence (13y - 15y), and late adolescence (16y - 18y). A healthy control group with no reported concussion history was also included. Participants completed the Brief Symptom Inventory-18, which assesses psychological distress through Depression, Anxiety, Somatic, and Global Symptom Severity scores. Generalized linear models were employed for men and women separately to investigate the association between a concussion during critical developmental periods and clinical outcomes in college.

Results: The final sample included 704 men (176 with no concussion history) and 388 women (97 with no concussion history). Results showed that relative to the control group, men who sustained a concussion during childhood (Exp(B)=1.84, P=0.015) and early adolescence (Exp(B)=1.71, P=0.044) had greater somatic symptoms in college. Moreover, men who sustained a concussion in late adolescence reported a broader range of symptoms including global (Exp(B)=1.69, P=0.011), depressive (Exp(B)=1.76, P=0.021), and anxious (Exp(B)=1.72, P=0.029) psychological distress. Women reported greater somatic psychological distress relative to control participants only when concussions occurred in childhood (Exp(B)=1.71, P=0.044).

Conclusion: Both men and women reported greater somatic psychological distress for concussions sustained early in their lifespan relative to control subjects. However, particularly in men, a greater range of psychological distress symptoms was observed in later developmental periods. Overall, these findings suggest that concussions sustained during particular periods of development influence psychological distress later in life. However, additional research is necessary to determine the clinical significance of these results. Future research should examine mechanisms underlying sex differences as well as longer-term outcomes.

19

Transcriptional regulations underlying the terminal differentiation of murine cortical chandelier cells

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Diverse types of cortical GABAergic interneurons (INs) that differ in morphology, physiology, and connectivity underlie a variety of neuronal computations in the brain. They are generated from the medial and caudal ganglionic eminences and the preoptic area, migrate tangentially to the pallium, are settled in proper laminar locations, and then are integrated into the cortical circuits. Although previous studies indicated that diversification of cortical INs occurs in the cortex at the postmitotic stage rather than in the progenitor domains at the mitotic stage, little is known about the molecular mechanisms underlying postmitotic specification/differentiation of each unique IN subtype.

Chandelier cells (ChCs) innervate axon initial segments of excitatory pyramidal neurons and thus powerfully control generation of action potentials. They have been implicated in several brain disorders such as epilepsy, autism, and schizophrenia. Because their axonal/synaptic organization and developmental trajectories are largely stereotyped, ChCs serve as a great model to study development of bona-fide IN subtypes.

To identify transcriptional regulators that dictate ChC specification/differentiation, we first explored genes that are enriched in ChCs by comparing gene expression profiles among ChCs, somatostatin-expressing INs, and vasoactive intestinal protein-expressing INs using bulk RNA sequencing (RNA-seq). Our analysis of RNA-seq data resulted in the identification of 19 transcription factors that are preferentially expressed in ChCs. We are currently in the middle of further validating RNA-seq results using RNA scope. To systematically perform CRISPR/Cas9-based functional screening of these candidates, we have generated single guide RNAs for each gene. We have also established an experimental method that allows us to efficiently obtain developing ChCs transfected with CRISPR/Cas9 plasmids, where exo utero electroporation of ChC progenitors is combined with their transplantation into host animals. Although this loss-of-function screening is still at the early stage, we already found that St18, a transcription factor that is known to determine globus pallidus projection neuron identity, is essential for ChC synaptic development. This project will provide fundamental insight into transcriptional regulations underlying postnatal specification/differentiation of cortical IN subtypes and open the floodgates to understanding the principle of cortical IN diversification. In this presentation, we will present our recent progress.

20

Promoting CNS axon regeneration by manipulating cholesterol

Debasish Roy, Andrea Tedeschi

Spinal cord injury (SCI) causes devastating neurological deficits due to axon regeneration failure.
Disruption of cellular membranes and myelin sheaths leads to cholesterol accumulation in the extracellular space after SCI. Cholesterol is crucial for normal brain function. High cholesterol levels, however, can be detrimental for neurological function. Thus far, how changes in cholesterol levels influence axon growth and regeneration remains elusive.
Here, we screened the whole transcriptome of DRG neurons and searched for druggable targets that correlate positively with axon growth and regeneration and negatively with cholesterol metabolism and uptake. Using a systematic approach, we found that the expression of the gene IDOL correlated inversely with loss of axon growth at later stages of embryonic development and positively with gaining growth competence in the adult. Mechanistically, IDOL targets the intracellular tail of the LDL receptor (LDLr) for lysosomal degradation. Given that LDLr acts as major carrier for ApoE-bound cholesterol, IDOL inhibits the uptake of exogenous cholesterol by downregulating the LDLr pathway. Our data showed that Idol gene deletion impaired axon growth of adult DRG neurons. Forcing Idol expression was sufficient not only to rescue axon growth defects in Idol knockout DRG neurons, but also to promote axon outgrowth in WT neurons. In vivo, lack of IDOL impaired regeneration after a peripheral nerve lesion. We found that Idol knockout DRG neurons have increased LDLr expression and >50% increase in cellular cholesterol when compared to WT. Moreover, our data suggest that lowering cholesterol is sufficient to rescue axon growth defects in Idol knockout DRG neurons. Finally, we demonstrated that forcing Idol expression in vivo is sufficient to promote axon regeneration after SCI. Given that cholesterol metabolism can be pharmacologically targeted, completion of this study may facilitate the design of translational research aimed at regaining neurological functions after SCI.

21

Association of Elevated Concussive Symptoms on Driving Performance: A Comparison between Adolescent Drivers with Mild Traumatic Brain Injury and Matched Healthy Controls

Christopher R. M. Rundus, Fangda Zhang, Ginger Yang

Purpose:

Mild traumatic brain injury (mTBI), the most common form of TBI, impacts approximately 2 million children (<18 years). Inadequately managed mTBI can lead to both immediate and long-term physical and cognitive consequences, including compromised driving abilities. This study aimed to investigate the changes in post-concussion symptoms (PCS) score before and after a simulated driving assessment, and their associations with driving performance in adolescent drivers with mTBI as compared to their matched healthy controls.

Methods:

Adolescent drivers ages 16 to 24 with a physician-confirmed isolated mTBI were enrolled within 96 hours of injury from two study sites (OSU and UAB), along with healthy controls. Enrolled participants completed the first driving performance assessment on a high-fidelity simulator under 4 scenarios for total of 30 minutes. The driving performance measures included reaction time, minimum distance between the participant vehicle and a lead vehicle, mean velocity, standard deviation of velocity, and standard deviation of lane position. Prior to and immediately following each driving performance assessment, participants rated their PCS scores using the Post-Concussion Symptom Scale. The changes in PCS scores from before and after the simulated driving assessment between mTBI cases and matched healthy controls were compared using t-tests. The associations between changes in PCS scores and driving performance between the two groups were assessed using linear mixed models, controlling for scenarios.

Results:

Participants included a total of 25 mTBI participants and 25 matched control subjects, 22 males and 28 females, with an average age of 18.6 and 20.2 years, respectively.

The average PCS score for cases was 21.1 (SD=13) pre drive and 29.7 (SD=14.7) post drive. For controls, the average PCS score was 3.1 (SD=5.9) pre drive and 5.9 (SD=8.6) post drive. Increased scores from the pre drive to post drive were observed in both groups, but the case group increased significantly more ($p=0.0486$).

Additionally, significant driving performance differences between the cases and controls were observed. Specifically, cases had a lower SD of velocity ($p=0.0005$), quicker reaction time ($p=0.0056$), and greater minimum headway distance ($p<0.0001$) than controls.

Finally, the changes in symptom scores were associated with changes in driving performance between mTBI cases and matched controls, with an increased difference in PCS scores being associated with faster reaction time ($\beta=0.0164$, $p<0.0001$) and slower mean velocity ($\beta=-0.0212$, $p=0.0325$) even after adjusting for scenarios.

Conclusions:

This study illuminates the intricate relationship between mTBI and driving performance in adolescent drivers. Those with mTBI have demonstrated greater increases in PCS scores post drive compared with the matched controls, and the increase in PCSS was associated with poor driving performance. Additional research with a larger sample is needed to confirm these results.

Keywords:

Traumatic Brain Injury (TBI), Mild TBI (mTBI), Post-Concussion Symptom Scale (PCSS), Simulated Driving, Driving Performance, Teen Drivers.

22

Genetic diversity drives extreme responses to traumatic brain injury and post-traumatic epilepsy

Tyler Shannon, Bin Gu

Traumatic brain injury (TBI) is a complex and heterogeneous condition that can cause wide-spectral neurological sequelae such as behavioral deficits, sleep abnormalities, and post-traumatic epilepsy (PTE). However, understanding the interaction of TBI phenome is challenging because few animal models can recapitulate the heterogeneity of TBI outcomes. We leveraged the genetically diverse recombinant inbred Collaborative Cross (CC) mice panel and systematically characterized TBI-related outcomes in males from 12 strains of CC and the reference C57BL/6J mice. We identified unprecedented extreme responses in multiple clinically relevant traits across CC strains, including weight change, mortality, locomotor activity, cognition, and sleep. Notably, we identified CC031 mouse strain as the first rodent model of PTE that exhibit frequent and progressive post-traumatic seizures after moderate TBI induced by lateral fluid percussion. Multivariate analysis pinpointed novel biological interactions and three principal components across TBI-related modalities. Estimate of the proportion of TBI phenotypic variability attributable to strain revealed large range of heritability, including >70% heritability of open arm entry time of elevated plus maze. Our work provides novel resources and models that can facilitate genetic mapping and the understanding of the pathobiology of TBI and PTE.

23

Profiling acute immune and chronic behavioral effects of pediatric traumatic brain injury in rats

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Abstract

Background: Traumatic brain injury (TBI) is one of the leading causes of emergency room visits in children under 10. Children are especially vulnerable to the adverse effects of TBI, given that their brains are still developing at the time of the injury. Children who experienced this early life insult are more likely to exhibit social, cognitive, and mood impairments later in life. The immune system has been implicated in adult TBI mechanisms and plays numerous roles in brain development, making it an interesting candidate potentially governing the link between pediatric TBI and long-term behavioral consequences. Here we seek to understand these neuroimmune mechanisms in a rat model of pediatric TBI, with a particular focus on microglia and mast cells.

Methods: At postnatal day (P)15, male and female rat pups were randomly assigned to 3 groups: Naïve, Sham, or TBI. Naïve rats received no surgery or injury, Sham rats received surgery but no injury, and TBI rats received both surgery and injury. The injury consisted of a 2atm lateral fluid percussion injury. Rats were either sacrificed at 3 days post injury (DPI) for neuroanatomical analyses or aged out to adulthood for behavioral testing. Neuroanatomical endpoints included IBA1/CD68 immunohistochemistry for microglia phagocytosis analysis and toluidine blue staining for mast cell analysis. Behavioral testing began at P60 and consisted of spatial and spontaneous Y maze, paired social interaction, novel object recognition, and elevated plus maze.

Results: At 3 DPI, both microglia and mast cells were impacted by TBI. Microglia in the parietal cortex medial to the injury expressed significantly more CD68 in rats who received a TBI than rats who received Naïve or Sham treatment. Mast cells were more abundant and more degranulated throughout the brain in TBI rats. These results indicate a heightened immune response acutely following pediatric TBI. No sex differences were noted, although these studies are not yet powered to properly analyze sex effects. Preliminary behavioral results indicate that TBI animals exhibit increased spontaneous alternation, along with a potentially sex-dependent impairment in spatial memory. Analyses of the other behavioral tasks are ongoing.

Conclusions: Early life TBI leads to enhanced immune activity in both microglia and mast cells. Given the many important roles of microglia in development, this activation has the potential to contribute to long-lasting consequences of this early life insult. Continuation of these studies will seek to better understand the relationship between pediatric TBI, immune cells, and behavioral outcomes.

Supported by NIH R01 NS1030517 to KML

24

Tissue-specific bulk RNA sequencing reveals effects of traumatic brain injury and post-injury sleep fragmentation on the microglial transcriptome.

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Traumatic brain injury (TBI) is a global source of injury-related death and disability, and survivors suffer functional and psychiatric consequences that often persist long after injury. Neuroinflammation, mediated in part by microglia, perpetuates chronic dysfunction after TBI, including dysregulation of the stress response. Psychological and physical stressors often disturb sleep in TBI survivors, which can influence chronic recovery. Previous work from our lab has shown that 30 days of mechanical sleep fragmentation (SF) aggravates microgliosis and increases neuroinflammation, resulting in worsened behavioral outcomes compared to TBI alone. We hypothesized that the combined effects of TBI and SF would also result in robust transcriptional changes, and that there would be a distinct effect on microglia compared to the rest of the brain. Here, we used RNA sequencing to analyze gene expression in microglia and coronal slice brain tissue of C57BL6/J mice who received TBI or sham injury followed by 30 days of SF or control housing. We analyzed the independent effects of TBI and SF on differential gene expression within each tissue type. We also compared differentially expressed genes (DEGs) in microglia to DEGs from coronal slice tissue to uncover subsets of genes that are specifically dysregulated in microglia. Furthermore, we identified a set of DEGs which are uniquely dysregulated by the combination of TBI and SF. Gene set enrichment analysis reveals numerous pathways and ontologies correlating to these groups of genes. Of particular interest, we find distinct subsets of genes related to olfaction and G protein-coupled-receptor (GPCR) activity that are differentially downregulated by SF and upregulated by TBI. In ongoing analyses, we will identify molecular targets that shed light on the mechanisms of TBI-induced microglial activity and inform how post-TBI SF alters the microglial response. TBI survivors are highly vulnerable to stress during recovery, making it crucial to investigate the relationship between TBI and post-TBI stress. In depth transcriptional analysis will help reveal novel molecular mechanisms that contribute to worsened recovery from TBI in the presence of stress, and a better understanding of these mechanisms could help improve therapeutics for TBI survivors.

25

Chandelier cells in the anterior cingulate cortex play a critical role in determining the pain threshold in physiological and pathological states

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Pain serves as a warning signal to protect the body from actual or potential tissue damages in a physiological condition. However, several causes such as nerve/tissue injuries as well as chronic disorders (e.g. cancer and diabetes) induce persistent pain. The somatosensory, cingulate, and insular cortices work as the pain matrix of the cortex, and activity in principal neurons (PNs) of these cortical areas is upregulated in a chronic pain condition. Among these cortical areas, the anterior cingulate cortex (ACC) plays a crucial role in higher order pain processing, sending direct and indirect descending signals to the spinal neurons. Although much progress has been made in understanding the role and alterations of the ACC in physiological and pathological pain, respectively, it remains poorly understood how the basal level of the pain threshold is maintained in the normal brain, and whether and how such a regulatory mechanism is disrupted in a pathological pain condition.

Cortical inhibition mediated through GABAergic interneurons plays a pivotal role in balancing activity in neural networks. Among various types of interneurons, chandelier cells (ChCs) are thought to provide PNs with the most powerful inhibitory control by innervating hundreds of PNs at their axon initial segments. Therefore, we reasoned that ChCs can be involved in normal and abnormal pain processing in the ACC. To test this hypothesis, we examined activity in ChCs and surrounding putative PNs of the ACC in physiological and pathological conditions using antibodies against c-fos, the protein product of the immediate early gene, that represents the levels of neuronal activity. We also manipulated activity in ChCs of the ACC through cell type specific expression of chemogenetic tools and tested neuronal activity and pain thresholds in physiological and pathological states. Most ChCs in the ACC were active in a normal state, and reducing their activity increased that in surrounding putative PNs. Interestingly, this manipulation also reduced a pain threshold. Consistent with these results, induction of pathological pain by cancer and injury reduced activity in ChCs and increased that in PNs in the ACC. Furthermore, increasing activity in ChCs in chronic pain models mitigated the pain phenotype. Together, our preliminary results suggest that ChC activity is necessary for maintaining the appropriate level of PN activity and the threshold for physiological pain. They also suggest that ChCs are a part of pathogenic cells in chronic pain and can be a cellular target in drug discovery for pain management.

26

A simulator study assessing the association between symptom severity and driving performance post mild traumatic brain injury in young drivers

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Purpose
This research aimed to investigate the association between symptom severity and driving performance within 96 hours of injury among young drivers with mild traumatic brain injury (mTBI).

Methods
Data were extracted from a larger ongoing longitudinal driving simulator-based study aimed to assess the trajectory of driving performance among young drivers with and without mTBI. This evaluation focused on only those participants with mTBI who completed their first driving assessment within 96 hours of injury. Participants' post-concussion symptoms were assessed by the Post-Concussion Symptom Scale (PCSS). Each participant completed 4 experimental drives (varied by the presence of cognitive load and/or safety-critical events) with each drive including a "car-following" task. Our analysis focused on the "car following" portion of the simulated driving. Driving performance was assessed by 1) mean driving velocity; 2) standard deviation of velocity; 3) standard deviation of lane position (SDLP) measuring lane maintenance ability; 4) reaction time to the sudden brakes of the lead vehicle; and 5) minimum headway distance maintained with the lead vehicle. We leveraged linear mixed models to assess the association between PCSS at injury and the simulated driving performance while adjusting for pre-injury and pre-assessment PCSS scores, as well as driving scenario.

Results
Of the 38 participants, the mean age was 19.7 years (SD=2.0 years) and 18 (47.3%) were males. The mean PCSS at injury was 39.1 (SD=20.1), which was higher than that at the pre-driving assessment (mean=26.0; SD=16.2). Results showed that PCSS at injury was significantly associated with mean driving velocity ($\beta = -0.05$, $p = 0.028$), but not with the other driving performance metrics. Specifically, participants with higher PCSS scores had significantly slower driving speed relative to their lower score counterparts during the "car-following" task. Furthermore, compared with driving under scenarios without cognitive load, when participants drove under the scenarios with cognitive load, they had significantly lower mean driving velocity ($\beta=-0.37$, $p<0.001$), larger SDLP ($\beta=0.02$, $p=0.039$), and longer reaction time ($\beta=0.53$, $p<0.001$) when following the lead vehicle.

Conclusions
The significant association between symptom severity and slow driving speed suggests injured young drivers with more severe mTBI symptoms may drive more cautiously post-injury. However, when symptom severity and driving scenario were mutually adjusted in the regression model, driving with/without cognitive load appeared to have a more pronounced impact on driving performance. Future research with a larger sample size is needed to better understand the influence of symptom severity on driving following mTBI.

27

The Effects of Sleep Fragmentation on Plasma Corticosterone in Mice with Traumatic Brain Injury.

Zachary Zimomra, Olga Kokiko-Cochran

Coordinated activation of the hypothalamus pituitary adrenal (HPA) axis results in production of corticosterone (CORT) in rodents. Traumatic brain injury (TBI) is highly associated with endocrine dysfunction, which can substantially modulate the plasma CORT response to stress and influence chronic recovery. We hypothesize that an impaired plasma CORT response to sleep fragmentation (SF) exaggerates post-injury inflammation through dysregulated glucocorticoid receptor (GR) signaling. To study this, C57BL/6 mice with jugular catheters were given a lateral fluid percussion TBI or sham injury over the right parietal lobe. Mechanical SF occurred 6AM to 10AM for 30 days post injury (DPI). Dexamethasone (DEX), a potent GR agonist, or vehicle was administered intraperitoneally 2 hours prior to SF 7, 14, 21, and 30 DPI. Blood draws were taken at 4AM, 6AM, 6:45AM, and 7:30AM for plasma corticosterone analysis by enzyme immunoassay. Mice were euthanized and tissue harvested 30DPI for histology. RT-PCR was performed on the hypothalamus, pituitary, and adrenal gland to examine genes relating to the HPA axis and CORT production. Because of the multiple repeated measures with multiple variables across the time-course of this study, a mixed model analysis was used with random subject effect to account for the within subject correlation using AUC across the four days examined (7DPI, 14DPI, 21DPI, and 30DPI). Overall, TBI mice and SF mice had a significantly higher AUC for plasma CORT across the 30 days compared to Sham mice and control mice. Sub-group analysis revealed that DEX administration significantly lowered plasma CORT AUC in both Sham control and Sham SF mice across the time-course. However, DEX significantly lowered plasma CORT AUC in TBI control mice but not in TBI SF mice across days. Preliminary gene expression analysis suggests that coordinated communication between the hypothalamus, pituitary, and adrenal gland is uniquely compromised in TBI SF mice. Together, these data confirm that post-injury SF increases plasma CORT. The DEX challenge revealed dysregulated GR signaling and HPA axis negative feedback in TBI SF mice. Chronic elevated CORT can be deleterious to long-term outcome. Future studies will be directed to understand the underlying causes of this dysregulated GR signaling and compromised HPA axis feedback both peripherally and centrally.

28

Does Neck Strength Predict Head Impacts in Youth Football Players?

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Background: Neck strength and pubertal development may contribute to the number and magnitude of repetitive head impacts (RHIs) in youth football athletes. Greater neck strength is associated with decreased head movement (i.e., peak linear acceleration [PLA] and rotational velocity [PRV]) during laboratory testing,[1] but not throughout a season in teenage hockey players.[2] The pubertal development scale (PDS) accurately assesses physical maturation[3] and may provide a more global representation of strength not captured by isolated neck strength. Determining the relationship between RHIs, PDS, and neck strength will provide insight into physical factors associated with RHI exposure during youth football.

Purpose: The purpose of this study was to determine whether neck strength and pubertal development predicted RHI number and magnitude across a youth football season in 6th grade youth football athletes.

Methods: Athletes were provided a custom-fit instrumented mouthguard (iMG);[4] athletes with braces received a "boil and bite" iMG. iMGs contained a tri-axial accelerometer and gyroscope collecting data at 3.2kHz. Games were recorded to video verify RHIs. RHI counts were defined as the number of true positive RHIs divided by the number of games (i.e., athlete exposures [AE]). Parents completed the PDS prior to the season and isometric neck strength was collected using a hand-held dynamometer for flexion, extension, bilateral lateral flexion, and bilateral rotation; the average of 3 trials was used for data analysis. Stepwise linear regressions were performed to determine if neck strength or total PDS score predicted RHIs/AE, median PLA, or median PRV.

Results: 23 athletes (Age:11-12 y.o., all male) participated in 1 to 7 games with exposure data (median = 4.5). There were no statistically significant predictors of head impacts per exposure, median PLA or median PRV for any strength models or PDS models ($p>.05$ for all models, Adjusted R^2 range .001 to .083). Only the PDS had a p value < .2 at $p = .196$.

Conclusions: Isometric neck strength is not associated with RHI number or magnitude during youth tackle football, suggesting isometric neck strengthening may not be a potential modifiable risk factor. Other physical attributes contributing to the number and magnitude of RHIs should be explored in youth football athletes.

Examining Variability of High-Level Visual Categories Across Development

Anna Quatrale, Kelly Hiersche, Zeynep Saygin

The brain is a patchwork of regions, each devoted to different mental functions. Some of the most robust and replicable regions include high-level visual areas within ventral temporal cortex (VTC), such as the word-selective visual word form area (VWFA), face-selective fusiform face area (FFA), and object-selective posterior fusiform sulcus (PFS). The existence and functions of these areas have been thoroughly investigated, but it remains unclear whether these regions vary more in their selectivity and spatial location or extent in childhood. Additionally, brain injury can introduce variations in brain activation, but without a clear understanding of typical variation throughout periods of development, it is difficult to know the extent of variance that may be introduced by trauma, especially along temporal cortex. To understand typical variation in selectivity and location of activation, we scanned 73 healthy children (ages 3-13) and 15 adults on a high-level visual localizer. We defined bilateral VWFA, FFA, and PFS subject specific functional ROIs in each participant and calculated selectivity to the preferred category in independent fMRI runs. Participants were divided based on age (3-6, 6-9, 9-12, adult) and matched based on motion during the task. To measure variability, we calculated the coefficient of variation (CV) for neural selectivity of each fROI (i.e. calculating how far off each participant's) and used two-sample t-tests to compare the CV across groups. All groups showed expected selectivity for faces, objects, and words. Younger children showed significantly greater variability in the bilateral FFA, but not other regions. Continuing investigations include comparisons with spatial location of these fROIs across development, as well as comparisons to children and adults who have sustained chronic or traumatic brain injuries.

30

Examining the relationship between gait, balance, processing speed, and executive function across the lifespan

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Introduction: Mobility deficits are associated with negative health outcomes including fall risk and cognitive impairment. Mobility is a multifaceted construct including both balance and gait components. These components of mobility may be differentially associated with cognitive performance. The current study examined the association of spatiotemporal gait measures and static balance measures with executive function and processing speed performance in young, middle-aged, and older adults.

Methods: Participants (n=104;18-85 years; mean age=51.5, SD=18.6) were recruited from the Fitness, Aging, Stress, TBI Exposure Repository (FASTER). LEGSys™and BalanceSens™ devices were used to measure spatiotemporal gait measures during a 40-foot walk test and static balance was quantified as sway on firm or foam surfaces with eyes open or closed. Standardized neuropsychological tests were used to assess executive function and processing speed. Participants were classified as young (18-34 years), middle-aged (35-64 years), or older adults (65+ years). Relative importance analyses explored the contribution of balance and gait metrics (variance explained) to composite executive function and processing speed scores using the Lindeman, Merenda and Gold (“lmg”) method. Hierarchical linear regressions were used to examine the relationships between aging, mobility, and cognition.

Results: After adjusting for covariates (age, sex, education), variability in balance-related measures including double support time while walking, sway while standing with eyes open on a foam surface, and sway while standing with eyes closed on a foam surface were relatively important predictors of executive function. In contrast, gait-related measures such as stride velocity, stride time, and stride length were relatively important predictors of processing speed. Separate hierarchical linear regressions controlling for sex and education showed that variability in double support time was positively associated with executive function whereas greater sway during eyes open foam surface static balance and eyes closed foam surface static balance were negatively associated with executive function. Slower stride time was negatively associated with processing speed. Significant Age Group x Mobility metric interactions demonstrated that sway during eyes open foam surface static balance was negatively associated with processing speed in older adults, but not young adults or middle-aged adults.

Conclusion: Balance-driven metrics explained variance in executive function whereas speed-based components of the gait cycle explained variance in processing speed. The relationship between balance and processing speed performance was dependent on age such that greater sway on a foam surface was associated with slower processing speed among older adults. These data provide evidence that different aspects of mobility may be linked to function within specific cognitive domains.

31

Investigating the Role of NG2+ Glial Cells in Chronic Spinal Cord Injury Recovery using Transgenic mice

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Traumatic spinal cord injury (SCI) is a severe condition resulting in neuronal tissue damage and profound motor and sensory impairment. This study investigates the role of NG2+ glial cells, specifically oligodendrocyte progenitor cells (OPCs), in long-term SCI recovery and scar formation. OPCs proliferate extensively in response to SCI. OPCs have long been known to give rise to remyelinating oligodendrocytes, but emerging evidence suggests they also play an important role in the SCI lesion border formation. To explore this, we use a novel transgenic mouse model to selectively delete OPCs immediately after SCI to determine if chronic scar formation was altered. PdgfrDTR mice are crossed to Olig2-cre mice to generate a transgenic mouse line (Olig2-DTR) expressing human diphtheria toxin receptor (hDTR) only in Olig2+PDGFRa+ cells (OPCs). OPCs were eliminated by injecting 20 ng/g of diphtheria toxin (DT) daily for 2 weeks after SCI, (0.4ug/100 ul sterile saline for a 20g mouse). Both Olig2-DTR and Olig2-WT littermates received DT, as Olig2-WT mice do not express hDTR and are therefore unaffected by the drug. OPC deletion was targeted to the first two weeks after injury, which is both the peak proliferative response time for OPCs and critical timeline for glial and fibrotic scar formation in and around SCI lesions. Our lab has shown that OPC depletion paradigm causes early delays in glial scar formation. In this study mice survived for 4w after DT treatment to determine long-term effects of acute OPC deletion on lesion formation and fine motor recovery. All mice received a unilateral contusion spinal cord injury at the C5 vertebral level and were assessed for fine forelimb motor recovery with a horizontal ladder task, cylinder task, and activity box. Acute OPC cell deletion caused enduring deficits in motor coordination, forelimb recovery, and overall mobility for Olig2-DTR mice through 6 weeks post injury (6wpi). Histological analysis at 6wpi revealed Olig2-DTR mice (n=6) had larger lesions compared to Olig2-WT (n=6) littermates. Using a GFAP to label astrocytes in the glial scar, there was no significant difference in glial scar border width or astrocyte density. Laminin density, which labels ECM deposition in the lesion core associated with the fibrotic scar, also did not differ between groups. We performed a comparable study using mice aged to 1 year before receiving SCI. Interestingly, aged Olig2-WT (n=5) and Olig2-DTR (n=5) mice did not have significantly different lesion sizes. GFAP border width also remained unchanged in the aged cohort. These mice had worse overall recovery outcomes than their unaged counterparts, though fine motor deficits did not significantly differ between aged Olig2-DTR and Olig2-WT groups. Overall, OPC deletion alters lesion size in young mice, which corresponds to recovery deficits through 6wpi, indicating that they play a role in motor recovery and that their loss is disruptive for long-term glial scar formation. Additionally, the analysis of aged cohorts showed that OPCs play a diminished role in glial scar formation with age, possibly driven by less responsive or fewer OPCs in aged mice overall.

32

Investigating the Role of the Peripheral Immune System in post-TBI SF

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Traumatic brain injury (TBI) induces microglia priming, which results in an exaggerated response to subsequent immune stimulus. TBI rarely occurs in isolation and therefore recovery can be impeded by external stressors that elicit an immune response. Indeed, we have shown that the stress of mechanical sleep fragmentation (SF) after TBI increases cortical and hippocampal CA1 microglial reactivity, exaggerates hippocampal long-term potentiation synaptic deficits, and impairs learning compared to controls between 7 and 30 days post-injury (DPI). However, stress signaling is associated with coordinated communication between the central and peripheral immune systems. Therefore, primed microglia may contribute to poor outcome via peripheral immune cell signaling. The goal of this study was to investigate the role of the peripheral immune system in outcomes after post-TBI SF. We hypothesized that post-TBI SF would elicit a heightened immune response via peripheral cell infiltration from multiple peripheral tissues. To test this, male and female mice received a moderate lateral fluid percussion TBI or sham injury. Then, half of the mice were undisturbed in control cages, and half were exposed to daily, transient SF for 3 or 7 DPI. Brain, blood, spleen, and bone marrow were collected for flow cytometry at either 3 or 7 DPI.

Differences in the percentage of peripheral immune cell populations were detected primarily at 3 DPI. Specifically, monocyte and B cell populations were decreased in the blood, while the spleen demonstrated increased monocyte infiltration. Only subtle differences in the percentage of peripheral immune cells were detected 7 DPI within the spleen and blood. No significant differences were found amongst immune cell populations within the bone marrow at either time point. TBI resulted in elevated neutrophils, monocytes, and macrophages within the ipsilateral brain at 3 DPI, primarily driven by the TBI SF group. At 7 DPI, TBI resulted in elevated monocytes within the ipsilateral brain; however, this response was not exaggerated by post-TBI SF. Together, these data show that the neuroinflammatory effects of post-TBI SF may be due to peripheral immune cell signaling acutely, but not subacutely. Although other models of stress have demonstrated increased hematopoiesis acutely, we are interested to determine the role of the peripheral immune response in long-term recovery from injury. Previous data from our lab has demonstrated that many deficits related to post-TBI SF were revealed at 30 days. Therefore, we plan to investigate the peripheral influence of post-TBI SF at this chronic timepoint in the future.

33

Sleep Fragmentation compromises Sleep Recovery Patterns Following Traumatic Brain Injury

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Sleep disturbances affect 30-70% of survivors following traumatic brain injury (TBI) however the regulation of sleep expression, or the control of the duration and frequency of wakefulness, non-rapid eye movement sleep (NREM), and rapid eye movement sleep (REM), is a complex homeostatic process that is influenced by a variety of environmental and biological factors. One factor of interest that adversely impacts the regulation of sleep, is the role of chronic stress. How this stress may change the regulation of sleep following TBI is not clearly understood but is important for post-TBI outcomes. We hypothesize that sleep fragmentation (SF) serves as a biologically relevant stressor that will compromise the regulation of sleep recovery following TBI. To investigate this, equal numbers of male and female mice received sham injury or lateral fluid percussion injury (LFPI). Subsequently, all mice were implanted with a wireless telemetry sensor to monitor wakefulness, NREM, and REM sleep. Half of the mice in each group were exposed to control housing and the other half were exposed to SF for 4 hours a day (6AM to 10AM) for 30 days post injury (DPI) resulting in 4 groups: Sham control, Sham SF, TBI control, and TBI SF. Following the SF period, all mice were undisturbed for the remaining light and dark phase each day. This model of SF revealed a selective loss of REM sleep bouts greater than 60s and NREM sleep bouts greater than 120s. This difference indicates a change in NREM and REM sleep quality that was persistent for 30 DPI. TBI SF mice had decreased total REM at 3 and 14 DPI while Sham SF mice had increased total REM. During the undisturbed light phase (10 AM-6PM) SF mice displayed an increase in the frequency of short REM bouts but no changes in the length of these bouts compared to Sham SF and TBI controls 1-7 DPI ($p=0.005$). These differences resolved 14-28 DPI. There was no significant difference in either sleep bout total length or frequency for NREM, sleep, or wake These data reveal there are differences in sleep regulation that are impacted both by SF and TBI however, these differences are specific to REM sleep regulation within the first 14 days post injury. SF TBI mice fail to compensate this type of sleep regulation which may be informative to TBI related defects within this time phase of injury.

34

Interleukin-1 Receptor-1 Signaling mediates Neuroinflammation, Neuronal Dysfunction, and Cognitive Decline after Diffuse Traumatic Brain Injury

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Traumatic brain injury (TBI) increases the risk of developing neuropsychiatric illness and cognitive impairment. Previous work indicates that inflammatory pathways associated with interleukin (IL)-1 and IFN signaling persist in the brain chronically after TBI. Several cell types in the brain express the interleukin-1 Receptor-1 (IL1R1) including endothelia, astrocytes, and neurons. Therefore, the purpose of this study was to determine if IL-1R1-mediated signaling after TBI promoted neuroinflammation and disrupts neuronal homeostasis and hippocampal-dependent cognition. Here, IL1R1-TdTomato reporter, wild type $^{(WT)}$ and global (g) IL1R1 knock-out (KO) mice were exposed to midline fluid percussion injury to induce a moderate and diffuse brain injury. In the Td-Tomato reporter mice, ILR1 was localized to endothelia as well as the neurons of the dentate gyrus. Moreover, IL-1R1 was markedly enhanced in the hippocampus 7 days post injury (dpi). In the global IL-1R1 knockout mice, TBI-induced inflammation (3 and 7 dpi) in the cortex and hippocampus was attenuated compared to IL1R1 mice. For instance, TBI-IL1R1^{KO} mice had less leukocyte accumulation in the brain (3dpi), decreased astrocyte restructuring (3 dpi), and reduced neuroinflammatory mRNA expression (3 & 7 dpi) compared to TBI-WT mice. Next, RNA profiles of hippocampal neurons were assessed 7 dpi in gIL1R1^{WT} and gIL-1R1^{KO} mice using single-nucleus RNA sequencing (snRNAseq). There was a robust influence of TBI and TBI x IL1R1 interactions on neuronal RNA profile that were neuron sub-type specific. The CA1 of the hippocampus had 828 differentially expressed genes (DEGs) influenced by TBI that were reversed by the KO. These DEGS were associated with pathways for cognition, neurogenesis, and synaptic plasticity. Furthermore, TBI-associated deficits in hippocampal-dependent fear conditioning 7 and 30dpi were attenuated in gIL-1R1^{KO} mice. Consistent with this neuronal dysfunction in the hippocampus, there was decreased neuronal activation (pCREB) after fear conditioning 30 dpi that was IL1R1 dependent. Overall, IL-R1 signaling after diffuse TBI mediated neuronal deficits associated with impaired hippocampal-dependent cognition.

35

Youth Football Head Impact Exposure Differences Based on Four Data Cleaning Methods

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Youth tackle football athletes commonly experience repetitive head impacts (RHIs). Instrumented mouthguards (iMG) are capable of quantifying frequency and magnitude of RHIs. Using iMGs requires cleaning recorded data to confirm impacts. Data cleaning techniques include filtering, timestamping, and video verification. Video verification is currently regarded as best practice; however, several different cleaning methods are utilized in the literature.
PURPOSE: To determine differences in number and rate per athlete exposure (IR) of RHIs among four data cleaning methods. **METHODS:** Participants (N=18, age=9±1years, height=139.7±10.2cm, mass=36.2±8.6kg) wore iMGs for six tackle football games. Impact rate ratio (IRR) and intraclass correlations (ICCs) along with 95% confidence intervals (CIs) were calculated to compare four different data cleaning methods. IRRs represent a ratio of compared methods(Table 1). IRRs with a 95% CI not containing 1.00 were considered significant. Method 1: Timestamp cleaning removed impacts occurring before or after gameplay and during breaktimes (e.g., halftime). Method 2: Video-verified impacts completed by a trained researcher. Method 3: iMG algorithm-determined real impacts. Method 4: iMG algorithm-determined real impacts only within timestamp bounds. **RESULTS:** RHI data collected resulted in 62 athlete exposures across six games. Data cleaning methods resulted in different numbers of RHIs and IRR (Table 1). ICCs indicated moderate agreement between methods 2 and 3 (ICC=0.514,p=0.012) and methods 2 and 4 (ICC=0.616,p=0.003), and excellent agreement between methods 3 and 4 (ICC=0.975,p<0.001). **CONCLUSION:** Method 1 produced the highest IR, 22 times more impacts than method 2, which utilized video verification. Overall, our results suggest that the method of data cleaning can affect IR and certain methods may result in an overestimation of RHIs. Therefore, video verification should still be considered best practice.

36

Examining self-reported moderate-to-vigorous physical activity, actigraphy metrics, and subjective cognitive complaints across the lifespan

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Objective: There is a growing need to identify modifiable health behaviors that may reduce the risk of cognitive decline. Moderate-to-vigorous intensity physical activity is one behavior that has been previously linked to improvements in subjective cognitive complaints, which have been identified as an early indicator of future cognitive impairment. Objective indices of physical activity may provide more accurate estimates of activity levels compared to self-report measures currently utilized in the literature. This study examined the associations between self-reported measures of moderate-to-vigorous physical activity, objective metrics of physical activity, and subjective cognitive complaints.

Methods: 93 participants (age range: 18-86 years, mean age = 53.6 years, SD = 19.0, mean education = 16.5 years) were recruited from the Fitness, Aging, Stress, and TBI Exposure Repository (FASTER). Self-reported moderate-to-vigorous physical activity in the last seven days was measured using the International Physical Activity Questionnaire. Objective metrics of moderate-to-vigorous physical activity were collected over seven days using a wrist-worn ActiGraph GT9X accelerometer. Subjective cognitive complaints were assessed using the Cognitive Change Index questionnaire. Hierarchical linear regressions were conducted to determine main effects of age, self-reported or objective physical activity, and Age x Physical Activity interactions. Significant interactions were followed up with post-hoc simple slopes analysis.

Results: After adjusting for sex, education, and Depression Anxiety Stress Scales scores, a main effect of age on subjective cognitive complaints was observed, such that older age was associated with more reported cognitive complaints. Main effects of self-reported or objective metrics of physical activity were not significant. There was a significant Age x Objective Physical Activity interaction: a negative association between objective physical activity and subjective cognitive complaints was stronger in older adults compared to younger adults. Post-hoc analyses confirmed that lower objective physical activity was associated with more subjective cognitive complaints among older adults. This association was not significant among younger adults.

Conclusions: The negative association between objective metrics of physical activity and subjective cognitive complaints may be age dependent. Younger adults tend to be at their peak cognitive performance, and therefore modifiable lifestyle variables may have weaker associations with subjective cognitive complaints. In contrast, associations with subjective cognitive complaints and physical activity may be more readily observable in older adults, many of whom may have experienced decades of gradual cognitive decline. These findings also highlight the importance of objective metrics of physical activity, which may be more accurate than retrospective questionnaire-based assessments of physical activity.

37

Stress Exposure Following Traumatic Brain Injury Dampens Acute Inflammatory Gene Transcription.

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The central nervous system has two phases of response to traumatic brain injury (TBI). First, primary injury is acute and caused by mechanical damage from impact, rotation, or penetration and results in tissue damage and irreversible cell death. In the following days, the secondary phase is driven primarily by microglia and subsists of a hyperactive immune response that can cause lasting, elevated neuroinflammation. Following TBI, microglial activity is vital for assisting in debris clearance and synaptic remodeling. However, this microglial activity can be exacerbated by exposure to stress and can actually impair recovery. Environmental sleep fragmentation (SF) is known to exact a stress response and is highly reported in TBI survivors. Here, we hypothesize that SF stress will exaggerate the acute expression of genes responsible for regulating the inflammatory response to TBI and stress. Following lateral fluid percussion injury or sham surgeries mice were either exposed to four hours of SF daily (6am – 10am) to induce a stress response or were left undisturbed. 3 days post-injury (DPI), injured cortices were collected, and RNA was extracted for analysis via Nanostring nCounter glial profiling panels.

Contrary to what we hypothesized, acute post-TBI SF did not result in exacerbated neuroinflammatory gene expression in the injured cortex. In fact, post-TBI SF decreased many genes that are increased as part of the response to both SF and TBI. Therefore, these data suggest TBI and SF can synergize to impair the acute neuroinflammatory response to injury or stress. Genes with increased expression due to TBI that were suppressed by SF are involved in a variety of inflammatory mechanism such as the regulation of microglial responses to injury (*Tlr4, Aif1, Cd68, Csf1R, Cd84*), interferon signaling (*Stat1, Stat2, P3mbb, Tap1, Bax*), and the complement cascade (*C1q, C1r, Itgam, Cr3, C3ar1*). Pathway enrichment analysis reveals that several pathways are increased by TBI and suppressed by post-TBI SF. These pathways include MHC class I presentation, Macrophage activation signaling, Neuroinflammation signaling, Interferon signaling, and the Complement cascade. Altogether, these data show that stress following TBI dampens the expression of genes and inhibits pathways that are typically activated as part of the TBI response. Future studies will be needed to determine the downstream effects of such inhibition, including whether stress impairs the ability of microglia to engage in debris clearance during the acute response to TBI.

38

Estimating Heart Rate Variability (HRV) Using a Wearable Magnetocardiography (MCG) Sensor

Ali Kaiss and Asimina Kiourti

Heart Rate Variability (HRV) is a physiological phenomenon that measures the variation in the time intervals between successive heartbeats. Rather than providing a single number of heart beats per minute, HRV looks at specific changes in the duration between consecutive heartbeats. Estimating HRV can be significant in monitoring the sympathetic (activated in response to stress or excitement) and parasympathetic (associated with relaxation and recovery) branches of the autonomous nervous system. For example, HRV can be used to classify cognitive workload as relevant to several brain injury applications.

In the state-of-the-art, HRV is acquired through various methods including, but not limited to, electrocardiography (ECG) and photoplethysmography (PPG). However, the skin-contact requirement of ECG and PPG's dependency on skin perfusion, among other limitations, introduce obstacles to calculating HRV. In our previous work, we introduced a wearable magnetocardiography (MCG) sensor that detects the weak magnetic field generated by the electrical activity of the heart and overcomes most of the limitations introduced by the previously mentioned techniques. However, our MCG sensor exhibited poor reliability due to low signal-to-noise ratio levels.

In this work, we introduce a new signal processing method to accurately detect heartbeats from within the MCG recording despite the high noise levels. When testing the system on six (6) recordings from human subjects, we achieved a 96.43% average heartbeat detection accuracy. The detected beats were later used to estimate HRV, showing great agreement with "gold standard" values acquired from ECG.

Our future work will focus on improving our current signal processing techniques to make the MCG sensor robust against motion artifacts and other sources of noise that may affect the quality of the recording. We then plan to validate the sensor's ability to quantify cognitive workload on healthy individuals as well as individuals with concussion.

39

The E3 Ubiquitin Ligase IDOL Regulates Microglial Phagocytosis in Alzheimer's Disease

Sarah Kaye, Jeff Atkinson and Jie Gao

Abstract:
Alzheimer's Disease (AD) is a chronic neurodegenerative disease characterized by the accumulation of disease-associated microglia (DAM) surrounding amyloid beta (Aβ) plaques. Previously, we discovered a novel E3 ubiquitin ligase IDOL that serves as a major post-transcriptional regulator of three brain ApoE receptors in the low-density lipoprotein receptor (LDLR) family. We showed that both genetic deletion and pharmacological inhibition of IDOL led to a reduction in the number and size of Aβ plaques and increased expression of genes associated with DAM phenotype. Here we show acute knockdown of IDOL increases microglial phagocytosis of Aβ plaques and the expression of DAM markers, including ApoE and TREM2. Additionally, long-term inhibition of IDOL reduced the number and size of Aβ plaques, decreased plaque-associated neuritic dystrophy, and improved cognitive function in human APP knock-in mice. Furthermore, RNA sequencing data shows that LDLR expression is increased in phagocytic microglia following knockdown of IDOL. These findings suggest that inhibition of IDOL may serve as a potential therapeutic strategy to delay of the progression of Alzheimer's disease.

40

Excitatory neuronal PLCG2 correlates with tau pathology in Alzheimer's disease

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Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder, characterized by abnormal amyloid plaques, tau aggregation, neuronal loss, and cognitive impairments. While the causes of AD are not yet fully understood, various genetic risk factors may be involved in AD pathogenesis. Recent Genome-Wide Association Studies (GWAS) have identified novel rare coding variants (P522R and M28L variants) of the enzyme phospholipase-C-γ2 (PLCG2) in late-onset AD (LOAD). PLCG2 is known as a mediator in transmembrane signaling, functioning downstream of immune receptors in LOAD. The role of PLCG2 and its variants in AD has been largely investigated in microglia and responses to amyloid β pathology; however, little is known about the role of PLCG2 in other cell types or its role in tau pathology. Recently, our 10x Genomics Multiomic analysis shows that the mRNA level of PLCG2 significantly increases not only in microglia but also in excitatory (EX) neurons in the middle temporal gyrus of the human AD samples compared to the control. PLCG2 is a well-known second messenger that activates PKC, which phosphorylates GSK3β (p-GSK3β). P-GSK3b inhibits GSK3β function, leading to decreased tau hyperphosphorylation and promotion of the autophagy-lysosomal-pathway (ALP). Thus, we hypothesize that deficiency of EX neuronal PLCG2 enhances tau aggregation in AD via the alteration of the ALP. To evaluate the immunoreactivity of PLCG2 and its relationship with tau pathology, we performed western blot assay and immunofluorescence staining on the entorhinal cortex of human post-mortem brain tissues and a tau mice model (P301S). We found that the global protein level of PLCG2 significantly increased in human AD cases and tau transgenic mice compared to the controls. Interestingly, we found that pathological tau-positive cells had a lower level of PLCG2 than neighboring pathological tau-negative cells in both the human AD samples and the tau mice model. To investigate ALP dynamics induced by PLCG2, we used FUW-mCheery-GFP-LC3 reporter plasmid in PLCG2-overexpressed HEK293 cells and found an increase in autophagy flux in the PLCG2-overexpressed cells, even in the presence of Bafilomyacin-A1, a known autophagy inhibitor. These results suggest that repression or dysfunction of PLCG2 may contribute to tau pathology in EX neurons of AD, probably via the regulation of the ALP. Future studies will further investigate the molecular mechanism underlying the relationship between EX neuronal PLCG2 and tau pathology.

41

Primed microglia and increased hypothalamic neuroinflammation after acute stress in traumatic brain injured-mice

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Microglia are activated by neuroinflammatory insults, and this activation is usually tightly controlled and transient in duration. Following traumatic brain injury (TBI), however, microglia can become "primed." Functionally priming is characterized by an exacerbated inflammatory response to secondary stimulus that augments cognitive and behavioral deficits. Psychological stress is one stimulus that may enhance the reactivity of primed microglia. Thus, the objective of this study was to determine the degree to which TBI-induced microglial priming resulted in enhanced neuroinflammatory and neuroendocrine responses to Acute Social Defeat (ASD) stress. Here adult (2 month of age) male C57BL/6 mice were subjected to TBI induced by a midline fluid percussion injury. 14 days later, control and TBI mice were exposed to a 2-hour cycle of ASD. IBA-1 and GFAP immunohistological analysis were performed to determine the number and mark intensity of microglia and astrocyte, and to evaluate the morphology of microglia within the paraventricular nucleus of the hypothalamus (PVN). Morphological analysis of hypothalamic microglia showed a main effect of TBI, which was increased in mice that also received the ASD compared to non-stressed mice. ASD caused exacerbated neuroinflammatory pathways in the hypothalamus of mice that received TBI compared to controls. For example, transcriptional analysis revealed increased expression of key cytokines and chemokines (IL1B, IL6, CXCL1 and CCL2), protein receptors (TLR4) and neurohormones (AVP and OXT) within the third-ventricle paraventricular tissue of the hypothalamus. ASD produced increased corticosterone levels in the serum of mice, although no effect of TBI was found. Overall, these data provide evidence of primed microglia in the hypothalamus after diffuse TBI that resulted in an amplified neuroinflammatory response to an acute stressor.

42

The Neuroinflammatory Impact of High Fat Diet on Memory and Synaptic Degradation in an AD Model

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Alzheimer's Disease (AD) is a neurodegenerative disease characterized by profound memory impairments, synaptic loss, neuroinflammation, and the hallmark pathologies of amyloid beta plaques and neurofibrillary tau tangles. High fat diet (HFD) consumption increases the risk of developing AD in humans even after controlling for metabolic dysfunction pointing to a role of the diet itself in increasing risk. In AD, complement, an arm of the immune system activated by the inflammatory cascade, becomes pathologically overactivated. This overactivation leads to tagging of healthy synapses for pruning. We hypothesized HFD exacerbates this neuroinflammatory mechanism in AD. While the diet to AD link is strong, the underlying mechanisms are not well understood in part due to confounding variables associated with long-term HFD (e.g. obesity and diabetes) which can blur conclusions about responsible mechanisms. Therefore, we experimented with a short-term diet regimen to isolate the mechanism underlying diet's impact on brain function without causing metabolic dysfunction. This project investigated the effect of short-term HFD on 1) memory, 2) neuroinflammation including complement, and 3) microglial synaptic pruning in the 3xTg-AD mouse model. Following the consumption of either standard chow or HFD, AD-like and WT mice were behaviorally assessed for memory impairments. In a separate cohort of mice, inflammatory markers and complement proteins in the hippocampus were assessed. For the last set of experiments, phagocytosis of synapses was assessed. Synapses were isolated from the hippocampus of AD-like chow or HFD-fed mice and conjugated to pHrodo, an indicator that glows red when engulfed by cells. The number of BV2 microglia that phagocytosed synapses was tracked over 4 hours. Finally, we incubated BV2 microglia with a complement receptor inhibitor and repeated the assay. Behavioral analysis showed AD-like mice had significantly impaired memory which was further impaired by HFD. HFD significantly increased inflammatory markers and complement expression in AD mice. Synapses from HFD-fed AD-like mice were phagocytosed at a significantly higher rate than those from chow-fed mice, showing the synapses were altered by HFD. The complement receptor inhibitor blocked this effect in a dose-dependent manner. These data suggest HFD consumption increases neuroinflammation and over activates the complement cascade in AD mice resulting in increased synaptic stripping leading to poorer memory. These data point to complement as a potential mechanistic culprit and therapeutic target underlying HFD's influence in increasing AD vulnerability.

43

Expert Interprofessional Community Advisory Board to Inform Dementia Caregiving Research

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Purpose and Background/Significance: Black/African American people participate in research at a lower rate than non-Hispanic White persons. Community Advisory Board (CAB) engagement is one proven method used to engage Black/African American people in research to improve health outcomes within the community. This project examines a health equity-focused CAB's benefits and challenges, strategies for improvement, and advice for prospective members through the lens of members of an established interprofessional CAB. **Theoretical/Conceptual Framework**: *Baquet's Bi-directional Community-Academic Partnerships* framework, a model of sustainability that acknowledges the mutually reciprocal strengths of the community and academic researchers, was used to develop the Interview Guide. **Methods**: Semi-structured interviews were conducted with *n*=11 CAB members. **Results**: CAB members included clinicians, researchers, and local organization community partners. Thematic content analysis revealed the following themes: *Bidirectional Education*, *Inter and Intragroup Connections*, *Time Commitment*, and *Flexibility as a Strategy for Continued Participation*. For example, CAB members appreciate learning from and sharing their respective areas of expertise with other Board members. They also consider the Board's goals and their personal objectives before committing to participation. **Conclusion**: Findings may inform the development of efforts to engage the Black/African American community in research through effective and impactful CAB use to promote health equity.

44

Broadband access may influence variation in Alzheimer's disease and related dementias prevalence in Central Appalachia

Jenna Rajczyk[1], James F. Burke[2], Wendy Y. Xu[3], Jeffrey J. Wing[1]

Background: Geographical differences in the burden of Alzheimer's disease and related dementias (ADRD) exist in the US. Rural and Appalachian areas are characterized by limited access to primary and specialty health care in comparison to their urban and non-Appalachian counterparts. Better access to telehealth can improve detection of ADRD in remote regions but it highly relies on availability of broadband services. Our objective is to evaluate the influence of county-level broadband availability on Appalachian and rural variation in ADRD prevalence in Central Appalachia.

Methods: County-level ADRD prevalence among fee-for-service Medicare beneficiaries in Central Appalachia (Kentucky, North Carolina, Ohio, Tennessee, Virginia, and West Virginia) was estimated using 2015-2018 Centers for Medicare and Medicaid Services Public Use Files. Broadband availability was defined as county-level measures of broadband presence (FCC Broadband Deployment Data 2015-2019), proportion of households with broadband, household device ownership, household internet access (American Community Survey 2015-2019), and broadband usage (Microsoft 2019). ADRD prevalence by Appalachian Regional Commission's Appalachian/non-Appalachian designation, and by rural/urban classification (Rural-Urban Continuum Codes) was estimated using sequential negative binomial regression models: (1) crude; (2) adjusted for age, education, and care access (PCP and neurology visits); (3) additionally adjusted for all broadband availability measures.

Results: Among all Central Appalachian counties, 52%-97% had broadband access throughout the study period. The proportions of urban (61%) and non-Appalachian counties (60%) with broadband access were higher relative to rural (39%) and Appalachian (40%) counties. Appalachian counties had higher prevalence in both rural (Prevalence Ratio (PR): 1.02; 95% CI: 1.00, 1.04) and urban (PR: 1.03; 95% CI: 1.02, 1. 05) areas, but this was mostly explained by socio-demographic factors in rural areas (PR: 1.00, 95% CI: 0.98, 1.02). Variation in urban counties persisted after adjustments for demographics, care access, and broadband availability (PR: 1.01; 95% CI: 1.00, 1.03).

Conclusion: Variation in ADRD prevalence was largely explained by socio-demographics and care access but not broadband availability. However, the role of broadband access on ADRD prevalence needs to be clarified. Greater broadband access may reflect improved telemedicine access and higher diagnoses, yet the inconsistency in rural counties challenges this hypothesis and other explanations should be considered.

45

State-level effect of Medicaid expansion on Alzheimer's disease and related dementias mortality

Jenna Rajczyk[1], Julie Strominger[1], Parvati Singh[1], Jeffrey J. Wing[1]

Background: With the rapid aging of the US population, the prevalence of Alzheimer's disease and related dementias (ADRD) is projected to double by 2050. Improvements in ADRD prevention, management, and treatment efforts rely on accurately characterizing the population-level burden. The enactment of the Affordable Care Act and Medicaid expansion could create opportunities for detection and classification of ADRD. There are trends of increasing ADRD mortality, however, it is unknown whether Medicaid expansion increased the reporting of ADRD as the underlying cause of death (UCOD) or as a multiple cause of death (MCOD) among older adults.

Methods: State-level ADRD mortality data for those 65 years and older were downloaded from CDC WONDER for 2000-2019. ADRD was classified as ICD-10 codes: F01, F03, and G30. Staggered difference-in-difference analysis was done to estimate the ADRD mortality rate pre- and post-Medicaid expansion. An overall average treatment effect for the treated (ATT) was estimated along with estimation for ATT by post-period. Mortality measured as UCOD and MCOD were evaluated separately. Results were compared to all-cause and cardiovascular disease (CVD) mortality for the same period.

Results: A total of 29 out of 50 states expanded Medicaid by 2019. Post expansion, ADRD mortality increased by 9.02 per 100,000 persons (95% CI: 1.81, 16.23). The change in mortality (UCOD) was most pronounced by two years post expansion, gradually increasing each year (two-years post ATT: 10.02; 95% CI: 3.51, 16.52; five-years post ATT: 13.58; 95% CI: 2.82, 24.34). MCOD ADRD mortality demonstrated a similar pattern as UCOD ADRD mortality, however, the observed effect was less precise (ATT: 11.31; 95% CI -1.42, 24.05). This increasing trend was not observed across the same period for UCOD CVD mortality (ATT: 0.80; 95% CI: -12.42, 14.02) and the post-expansion difference observed for UCOD all-cause mortality lacked precision in comparison to dementia mortality (ATT: 7.43; 95% CI: -23.12, 37.98).

Conclusion: ADRD as the UCOD increased following state-level Medicaid expansion, but this increase was not observed similarly for CVD mortality nor all-cause mortality. Additionally, the same effect was not observed for ADRD as a MCOD. The lag between expansion and the increase in mortality may arise from increased detection through Medicaid supported care and in-turn being listed or correctly identified as the underlying cause of death.

46

Health Outcomes in Contact Sport Athletes: The BUCKS Study

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Objectives: Exposure to repetitive head impacts (RHI) is associated with worse later life cognitive and neuropsychiatric function in contact sport athletes. Previous research studies focus on male professional football players. The BUCKS Study aims to analyze long-term outcomes in collegiate athletes, who comprise a greater percentage of the population compared to professional athletes, and understudied demographic groups and sports in this literature. We aim to characterize the prevalence of chronic health conditions, concussion history and symptoms, and the relationship between head trauma exposure and cognitive or psychiatric symptoms in a sample of OSU athlete alumni.

Methods: Recruitment of OSU varsity athlete alumni for the BUCKS study is ongoing. Participants complete an online health questionnaire and study staff verify eligibility using OSU athletics rosters. Below, we describe characteristics of a preliminary sample of participants and regression results assessing predictors of later-life neuropsychiatric symptoms.

Preliminary Results: 47 OSU athlete alumni have completed the BUCKS Study (mean age = 43.40 years, SD = 13.33 years). Participants include 23 men (48.94%) and 24 women (51.06%). The self-reported races of our participants include White (85.11%), Black (14.89%), Asian (8.51%), multiracial (6.38%), and American Indian/Alaskan Native (2.13%).

While at OSU, these alumni competed in football (12.77%), lacrosse (12.77%), gymnastics (8.51%), ice hockey (8.51%), rowing (8.51%), soccer (8.51%), and the spirit program (8.51%), among other sports. All participants reported sustaining at least one concussion (mean number of concussions = 6.19, SD = 14.41). 36 participants (76.60%) reported experiencing neuropsychiatric symptoms, with the most common symptoms being difficulty with attention (57.44%), anxiety (44.68%), memory (42.55%), and short fuse (25.53%). Number of reported concussions was significantly and positively associated with number of reported neuropsychiatric symptoms ($p<0.001$). Participant sex and age were not significantly associated with number of neuropsychiatric symptoms ($p=0.28$, $p=0.49$).

24 (51.06%) participants indicated interest in participating in the FASTER Study, a comprehensive longitudinal study investigating factors that impact brain aging at OSU.

Conclusions: The BUCKS study will address gaps in the literature by examining long-term cognitive, psychiatric, and health outcomes in former collegiate-level athletes of various demographic and athletic backgrounds. Our preliminary results suggest that many collegiate athletes have sustained concussions, and that a greater number of concussions is associated with more neuropsychiatric symptoms. Subsequent enrollment in the FASTER Study will allow us to thoroughly characterize participants and study mechanisms underlying associations between head trauma exposure and risk for cognitive and psychiatric problems.

47

Examining Sex and Neck Strength as Risk and Protective Factors for Repetitive Head Impact Exposure in Law Enforcement Cadets

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Introduction: Law enforcement cadets (LECs) undergo subject control technique trainings that may expose them to repetitive head impacts (RHIs). Previous studies on sports-related RHIs suggest that sex and neck strength may affect RHI quantity and magnitude. We aim to examine if these factors are associated with RHIs in LECs during their training. **Materials and Methods:** We used instrumented mouthguards to record RHIs using a trigger threshold of exceeding 8g on any single axis with an inclusion threshold of >5g resultant impact from 19 civilian LECs (4 females, 26.6±6.5 years) throughout the training academy. We compared peak linear acceleration (PLA) and rotational velocity (PRV) between sexes using a mixed-effects linear model with sex as the fixed-effect predictor and number of impacts as the random effect to account for sex differences and the variation due to number of impacts. We also compared the number of RHIs per exposure between sexes using a Mann Whitney U Test. Additionally, we measured isometric neck strength in six positions using a handheld dynamometer in a subset of 15 LECs and examined the association between neck strength and PLA, PRV, and RHIs per exposure using univariate regression models. **Results:** We recorded 735 RHIs >5g across 8 days of the training academy. PLA and PRV were higher in male [median = 12.2g (IQR: 11.3-12.8); median = 7.6 rad/s (IQR:6.9-8.7)] than in female cadets [median = 9.1g (IQR: 9.0-9.7), B=4.529 (95% CI: 2.734-6.323), p<0.001; median = 6.1 rad/s (IQR: 5.2-7.8), B=2.073 (95% CI: 1.133-3.013), p<0.001)]. There was no sex difference in number of RHIs per exposure (median: females = 6.3 (IQR: 4.0-9.7), males =10.8 (IQR:3.3-14.5), p = 0.530). Neck strength and girth measures were not associated with PLA, PRV, nor RHIs per exposure (B=-0.125-0.537, p=0.235-0.971). **Conclusions:** Males sustained higher magnitude impacts than females. While not significant, exposure rates of males (10.8) were nearly double that of females (6.3). This may be due to sex-matched pairs in training, where men may strike their opponent harder and potentially more often. This analysis is limited by unequal or underpowered sex representation in the analysis. Neck strength had no effect on RHIs, suggesting this may not be a modifiable protective factor in this cohort. More research is needed to understand additional risk and protective factors for RHIs in LECs.
Abstract Disclaimer (700 characters with spaces): This work was supported by the Assistant Secretary of Defense for Health Affairs endorsed by the Department of Defense, through the Traumatic Brain Injury and Psychological Health Research Program under Award No. HT9425-23-1-0520 and HT9425-23-1-0521. Opinions, interpretations, conclusions, and recommendations are those of the author and are not necessarily endorsed by the Department of Defense.

48

Exploring the association between sedentary behavior, cardiorespiratory fitness, and episodic memory in aging.

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Objective: The goal of this study was to examine the relationships between objective metrics of sedentary behavior, cardiorespiratory fitness, and visual and verbal episodic memory.

Participants and Methods: Adults (*N* = 106; ages 18- 86 years; mean age = 53.7 years, sd = 18.7; mean education = 16.4 years, sd = 2.3; 55% female) were recruited from the Fitness, Aging, Stress, and TBI Exposure Repository. ActiGraph GT9X devices were used to collect metrics of sedentary behavior (percent time sedentary) and standardized neuropsychological tests were used to assess visual and verbal episodic memory. Hierarchical regressions were conducted to assess the relationships between percent time sedentary and two sub-domains of episodic memory: visual and verbal. Demographic variables, cardiorespiratory fitness (peak VO_2), and sedentary behavior were included in the models.

Results: For visual episodic memory, the main effect of percent time sedentary was not significant after accounting for covariates and cardiorespiratory fitness. However, there was a significant age group x percent time sedentary interaction; a significant negative relationship between percent time sedentary and visual episodic memory was observed in middle-aged adults, whereas younger and older adults had null relationships. Additionally, there was a trending main effect of cardiorespiratory fitness after accounting for covariates, which did not interact with age group. For verbal episodic memory, a main effect of cardiorespiratory fitness was observed, such that higher peak VO_2 was associated with better verbal episodic memory, even after accounting for demographics. This relationship had a trending interaction with age group, such that middle-aged adults had a significant, positive relationship between cardiorespiratory fitness and verbal episodic memory, whereas younger and older adults had null relationships. The main effect of percent time sedentary was not significant for verbal episodic memory and did not interact with age group.

Conclusions: Results revealed differential findings for visual and verbal episodic memory. Higher percent time sedentary was associated with lower visual episodic memory in middle-aged adults but not younger or older adults. For verbal episodic memory, higher cardiorespiratory fitness was associated with better performance, but only in the middle-aged adults. This suggests that decreasing sedentary time and improving cardiorespiratory fitness may be important targets for future interventions focused on maintenance of episodic memory in middle-aged adults. Additionally, our results suggest that future interventions should target younger age groups, rather than focusing only on older adults.

49

Physical fitness mediates the relationship between physical activity and executive functions in aging.

Matthew J. Stauder [1], Scott M. Hayes [1,2]

Objective: Engagement in physical activity has been associated with maintenance of executive functions with age. Extant research has shown considerable variability in the size of this effect, and limited studies have explored how different age groups and modifiable mechanisms may explain this variability. Our objective was to investigate the association between physical activity and executive function performance across a sample of healthy adults aged 36-100 years and to examine the extent to which modifiable aspects of physical fitness can explain the physical activity-cognition relationship.

Participants and Methods: Self-reported moderate-to-vigorous physical activity (MVPA), measures of physical fitness (grip strength, gait speed, cardiorespiratory fitness), and executive function performance (inhibition, working memory, cognitive flexibility) were collected from 623 adults from the Human Connectome Project – Aging dataset (mean age = 59.2 years, sd = 15.0; 57.8% female). Composite metrics of physical fitness and executive function were calculated. Cross-sectional relationships between physical activity, physical fitness, and executive functions were modeled using multiple linear regression. The mediating effect of physical fitness variables and moderation by age were assessed using conditional process analyses from the PROCESS macro.
Results: Self-reported MVPA was positively, but weakly, associated with physical fitness ($r = 0.11$, $p = 0.01$). MVPA was not significantly related to executive functions ($\beta = -0.04$, $p = 0.16$) but a higher level of composite physical fitness was associated with better executive function performance ($\beta = 0.28$, $p < 0.001$). These relationships were not dependent on age. There was a significant and positive indirect effect of physical activity on executive functions through composite physical fitness ($ab = 0.02$, $p = 0.01$). The strength of this indirect effect increased with age and was driven by cardiorespiratory fitness.
Conclusions: Our findings demonstrate that objective measures of physical fitness, specifically cardiorespiratory fitness, have significant direct relationships with executive function performance and mediate the relationship between self-reported physical activity and executive function performance. Our findings also suggest that the strength of this indirect effect increases with age. These results indicate that physical activity associated with maintained or improved physical fitness may partially account for the salutary effects of physical activity on executive functions with advanced age.

50

Density of Physical Activity Resources is Associated with Post-Stroke Physical Activity

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Background: Exercise post-stroke can improve health-related quality of life and promote physical fitness, walking, and balance. Physical activity (PA) is important in post-stroke rehabilitation and recovery through the reduction of cardiovascular risk factors and lowering the risk of recurrent stroke and mortality.

Objective: To assess if area PA resources influence the change in PA 12-months post-stroke.

Methods: Addresses of 546 mild stroke survivors from the Discharge Educational Strategies for Reduction of Vascular Events (DESERVE) study were geocoded to the census tract level and merged with the density of physical activity resources from the National Neighborhood Data Archive (NaNDA). We modeled the odds of perceived change in PA at 12-months post-stroke (more active vs. about the same vs. less active) and number of fitness and recreational sports centers per square mile using multinomial logistic regression. Selection bias due to loss-to-follow-up was accounted for using stabilized inverse probability weights with robust standard errors. Models were adjusted for age, gender, race/ethnicity, education, insurance, BMI, and intervention.

Results: A total of 333 participants had 12-month PA data with 17.2% reporting being more physically active and 48.0% being about the same at 12 months. The adjusted odds of being more active compared to less active were 1.57 times larger when comparing the 90th percentile of PA resources to the 10th percentile (range: 58 resources; 95% CI: 0.99, 2.48). Similarly, adjusted odds of reporting the same level of PA compared to less active were 1.47 times larger when the 90th and 10th percentiles of PA resources are compared (95% CI: 0.99, 2.17).

Conclusion: Stroke survivors report higher odds of both maintaining the same level of PA and being more physically active when there are more PA resources in the area. This study demonstrates the potentially important role of the physical and built environment on physical fitness post-stroke. Future directions include considering the relationship between neighborhood walkability and greenspace with change in post-stroke PA.

51

Axon-Glial Mechanotransduction Induced by a Concussive Head Impact

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(a) Purpose of the Study: This study investigates the mechanisms of mild traumatic brain injury (mTBI), focusing on how mechanosensitive cells react to a head impact and contribute to primary and secondary injuries. It aims to provide a deeper understanding of the cellular and molecular events in mTBI.

(b) Research Method: The study uses the CHIMERA model to analyze immediate axonal varicosity formation post-impact. It employs Thy1-YFP transgenic mice for direct observation of varicosities and uses Memantine to study microglia activation's effect on myelin integrity. Additionally, it involves analyzing protein expression changes in knockout mice with an ion channel deletion to understand mitochondrial and microtubule disruptions.

(c) Findings or Predicted Findings: The study finds that transverse compression caused 80% of axons in corpus callosum and external capsule at an ultra-early timepoint immediately after mild TBI, whereas uniaxial stretch does not cause significant increase in varicosities. Memantine, an NMDA receptor blocker, inhibits microglial activation and cortical demyelination, suggesting a link between axonal varicosity and excitotoxicity. Protein analysis in knockout mice reveals alterations in proteins related to microtubular and mitochondrial function.

(d) Implications: The study offers novel insights into the primary and secondary injury mechanisms in mTBI, presenting a comprehensive sequence of events. These findings have significant implications for improving the diagnosis, prevention, and treatment of mTBI.

52

Effects of Early Life Stress + Adult TBI model development: Microglia as mediators of brain and behavioral outcomes

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Background: Adverse childhood experiences (ACEs), ranging from parental neglect to violence, and are a major public health concern. They affect 64% of adults in the U.S and ~20% experience four or more. ACEs impact the response to secondary perturbations, including TBI, and both ELS and TBI increase risk for psychiatric conditions. ELS models perturb microglial function during the postnatal period. This alters microglial function during development, and could precipitate worse outcomes after TBI. Here, we aimed to validate an ELS mouse model, assessing acute microglial and behavioral changes and a post-ELS microglia manipulation in juveniles, to ultimately investigate how a preceding life history of ELS might moderate the response to adult TBI.

Methods: Mice underwent 4 hr/day maternal separation stress (MSS) from postnatal day (P)1-14 or were left undisturbed. On P17, 5-6/group were perfused, and brains processed for IBA1 immunohistochemistry. Prelimbic PFC and CA1 and DG regions of hippocampus (3 images/section; 3 sections) were imaged and % area stained calculated in Image J. Remaining mice (6-8/group) underwent behavioral testing for open field and social interaction test with a juvenile sex-matched conspecific on P56-58. In a subsequent cohort, we validated the efficacy of the CSF1R inhibitor, PLX5622, to induce forced microglia turnover (depletion and repopulation) in juvenile mice. At weaning (P22-24), mice were given PLX chow or control chow for 7d. Mice were euthanized on day 7 of treatment or 14d following treatment. Brains were processed for IBA-1 immunohistochemistry and analyzed as before.

Results: MSS increased IBA1% area in the PFC ($p=0.05$), but no differences were seen in hippocampus. MSS animals showed decreased social avoidance ($p=0.048$) and a trend toward decreased passive social interaction time relative to controls ($p=0.07$). No effects were seen in center time in the open field. For microglia forced turnover, we found that at 7d, PLX treatment decreased microglia in the PFC ($p<0.0001$), DG ($p=0.0006$), CA1 ($p=0.0004$), and hypothalamus ($p<0.0001$). Analysis of microglia repopulation at 14d is ongoing.

Future Directions: As microgliosis post-stress and behavioral results were marginal, we are optimizing the stress procedure by adding maternal stress during separation. We will then proceed with our experimental aim of investigating how a preceding history of early life stress affects adult TBI outcomes, focusing on the mediating role of microglia.

Funding Acknowledgement: Supported by CDMRP grant W81XWH-22-1-0840 to KML.

53

Comparing Horizontal Smooth Pursuit Outcomes after Concussion

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Background: Visual deficits and oculomotor impairments are common in persons following concussion[1]. Findings of oculomotor dysfunction after concussion have been linked to protracted recovery and persisting symptoms after injury[2]. Current clinical practice uses subjective measures of oculomotor function based on symptom reporting, such as the VOMS[3]. Objective assessments of oculomotor function after concussion are lacking but may provide further insight into concussion recovery. The purpose of this study was to compare horizontal smooth pursuit function using a virtual reality-based eye tracker in persons clinically recovered after concussion (RTA), in persons with persisting symptoms after concussion (PSaC), and in healthy adult control participants (Control). We hypothesized that oculomotor function of persons with PSaC will be worse than in the RTA and Control groups.
Participants: We collected horizontal smooth pursuit data in 15 persons in the RTA group (age=26±15 years, 8 females, 30±15 days after concussion), 8 persons in the PSaC group (age= 29±10 years, 5 females, 62±19 days after concussion) and 19 in the Control group (age=26±6 years, 10 females).
Methods: Participants completed testing in a virtual reality head-mounted display (Neurolign Dx-100™ (Neurolign, Pittsburgh, PA). We collected outcomes of horizontal smooth pursuit including leftward/rightward velocity gain, velocity gain asymmetry, latency, and saccadic intrusions at two frequencies (.01Hz, .75Hz).
Results: There were no statistically significant differences for horizontal smooth pursuits outcomes across the groups ($p>0.05$).
Conclusion: Based on these preliminary findings, we were unable to detect significant horizontal smooth pursuit differences between healthy controls, persons at clinical recovery following concussion, and persons with persisting symptoms after concussion. Although not statistically significant, persons at clinical recovery after concussion displayed worse mean velocity gain values. Future work should continue to investigate larger samples to determine if persons at clinical recovery after concussion continue to demonstrate neurophysiological impairments.

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54

Impaired Cortical Neuronal Homeostasis and Cognition after Diffuse Traumatic Brain Injury Are Dependent on Phosphatase and Tensin Homolog and the PI3k-AKT Pathway

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Neuropsychiatric complications including depression and cognitive decline develop, persist, and even worsen in the years after traumatic brain injury (TBI), negatively affecting the quality of life and lifespan. TBI-induced alterations to neurons lead to reduced neuronal dendritic complexity, reduced excitability, and suppressed homeostatic gene expression. As previous work by the Godbout lab showed TBI-induced neuronal dysfunction, we sought to better understand deficits in neuronal homeostasis after TBI induced by midline fluid percussion injury in mice. In our recent report, single nuclei RNA-seq data 7 dpi showed evidence that phosphatase and tensin homolog (PTEN)-mediated pathways (CREB signaling, synaptogenesis, and synaptic migration) were decreased in cortical neurons 7 dpi. Here, we provide more insight from this sn-RNAseq data where specific genes associated with the PTEN pathway increased (*Pten*, *Gsk3b*, *Rock1*, *Rock2*) while genes associated with the PI3k/AKT growth and survival pathway (*Akt3*, *Igf1r*, *Mapk1*) were suppressed. Moreover, PTEN directly acts on the PI3K/AKT signaling pathway to inhibit neuronal health, growth, and survival. Thus, PTEN was targeted for inhibition following TBI using Bisperoxovanadium ho(PIC) (BPV). This potent and specific PTEN inhibitor was administered 1h following TBI, then every 24h for six days. We confirmed that TBI increased PTEN protein expression within the cortex and that this was attenuated by BPV intervention. Notably, PTEN intervention had limited effects on TBI-induced neuroinflammation and gliosis in male and female mice. Nonetheless, TBI induced cortical injury with reduced $Neun^{+}$ cell counts and percent area. This was attenuated by PTEN inhibition 7 dpi. Furthermore, TBI-induced cognitive deficits 7dpi in the NOL/NOR were also reversed by the PTEN inhibition. Taken together, reducing PTEN signaling after TBI was effective in reducing neuronal dysfunction and cognitive impairment.

55

The Impact of Pediatric Traumatic Brain Injury on Mast Cell and Oxytocin Content in Social Brain Regions in Rats

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Introduction: Pediatric traumatic brain injury (TBI) is linked to impaired social skills and higher susceptibility to neuropsychiatric disorders. Despite the lifelong implications of pediatric TBI, minimal animal research has investigated the mechanisms causing neurological and behavioral changes. We have found that pediatric TBI impairs social behavior in male and female rats. Here, we investigated the impact of pediatric TBI on two neural substrates that may influence TBI-induced social deficits: Mast cell number and oxytocin (OT) content. Mast cells are immune cells found throughout the body. In the brain, they initiate the immune response to TBI and influence sociosexual behavior in rats. OT is a neuropeptide that regulates socio-emotional behavior in both humans and rodents, and OT dysregulation is associated with disorders characterized by atypical social behavior. **Methods:** Male and female Sprague-Dawley rats received a lateral fluid percussion injury, sham surgery, or were left unmanipulated on postnatal day (P)15, approximately equivalent to “toddler” age in humans. At 3- and 7-days post injury (DPI), brain tissue was stained with toluidine blue to visualize mast cells. Mast cells in and near the hippocampus and the thalamus were counted across a minimum of 3 sections. At 7 DPI, oxytocin cells were quantified in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus, and oxytocin innervation was quantified in the amygdala across 3-5 sections. **Results:** At 3DPI, sham and TBI significantly increased the number of mast cells in the thalamus. At 7DPI, this effect remained in females but was eliminated in males. Neither TBI nor sex impacted OT. **Conclusions:** Our results show that mast cells, but not oxytocin, may potentially mediate TBI-induced outcomes. Future work and manipulations will assess if mast cell activation is required for the behavioral consequences of juvenile TBI. Preliminary work in our lab shows a higher-intensity lateral fluid percussion TBI than used in the studies presented here may elicit more robust outcomes. This work will yield new insight into mechanisms underlying TBI-induced social impairment and provide a basis for future studies of novel therapeutic interventions.

56

Test-Retest Reliability using the Neurolign Dx-100™ for Oculomotor Testing in Healthy Adults

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Background: Visual and oculomotor impairments are common sequela following concussion[1], but recovery from a concussion is often determined via subjective testing (i.e. SCAT-5, VOMS) as opposed to objective data. Emerging eye tracking technology is an objective method to determine physiological impairments after concussion, but the psychometrics of eye tracking technology are lacking and need to be established to determine if these methods may be used in clinical practice. The objective of this study is to examine the test-retest reliability of a head mounted virtual reality eye tracker in healthy young adults. We hypothesized that test-retest reliability would be good for the eye tracking outcomes of saccades, smooth pursuits, and vergence.
Participants: There were 30 participants (age=25±5 years, females=17) who completed oculomotor testing at two timepoints (29±4 days apart).
Methods: Healthy, young adults completed testing at two time points four weeks apart on the Neurolign Dx-100™ (Neurolign, Pittsburgh, PA), a virtual reality head-mounted display. We determined test-retest reliability using intraclass correlation coefficients (ICC) with a two-way mixed-effects model, absolute agreement and ICCs were interpreted as poor (<0.50), moderate (0.50-0.75), good (0.75-0.90), and excellent (>0.90). The testing paradigm included outcomes of horizontal and vertical reflexive saccades, smooth pursuits, and vergence pursuit.
Results: Test-retest reliability for horizontal and vertical saccadic latency were good (ICC=0.71-0.83) but variable for accuracy (ICC=-0.08-0.86), horizontal and vertical smooth pursuits velocity gain were variable (ICC= 0.30-0.84) and poor for initiation latency (ICC=-0.07-0.48), and vergence pursuit outcomes were poor for inward correlation (ICC=0.22) and moderate for outward correlation (ICC=0.62).
Conclusion: The Neurolign Dx-100™ provides evidence to support saccadic latency, pursuit velocity gain, and divergence test-retest reliability. Overall, the reliability of eye tracking metrics were variable during saccades, smooth pursuit, and vergence outcomes. This study adds reliability metrics using an eye tracking tool in a healthy adult population and may provide value to clinicians to assess oculomotor function after concussion.

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57

Sleep Fragmentation Influences Sleep Behavior following Traumatic Brain Injury 3 Days Post Injury

Shannon Dobres (1), Sam Houle (1,2), Zoe Tapp-Poole (1,2), Olga Kokiko-Cochran (1,2)

Traumatic brain injury (TBI) results in immediate tissue damage and subsequent neuroinflammation. Increased neuroinflammation enhances long-term pathology and impairs cognitive recovery. Environmental stressors can disrupt sleep, potentially leading to exaggerated post-TBI neuroinflammation. We hypothesized that SF would worsen acute recovery from TBI. We investigated whether sleep fragmentation (SF) administered during the first 4 hours of the inactive phase (6am-6pm) disrupted sleep, increased plasma corticosterone (CORT), enhanced behavioral deficits, and increased neuroinflammation at acute post-injury timepoints. To test this, 8-10 week old C57BL/6 mice received sham surgeries or lateral fluid percussion TBI. Sham and TBI mice were randomly assigned either daily SF (6-10am) or control (CON) housing. The mice recovered for 3 days post-injury (DPI) before tissue collection and analyses were performed.

Sleep monitoring showed that SF decreased the average percent sleep across 3 DPI. In the active period (6pm-6am), SF increased percent-sleep regardless of injury status. Sleep bout data assessed the quality of sleep, with shorter sleep bouts representing fragmented sleep and longer sleep bouts representing consolidated sleep. During the inactive phase, TBI increased sleep bouts of 32-64s and 64-128s and TBI decreased long sleep bouts of 256-512s. During the active phase, SF increased shorter sleep bouts ranging from 8-16s, 16-32s, and 32-64s. TBI CON mice also experienced more sleep bouts ranging from 32-64s than sham CON mice during the active phase. TBI and SF interacted to increase microglial percent-area in the hippocampal CA1 Enzyme-linked immunosorbent assays (ELISA) showed that SF exposure decreases norepinephrine (NE) and TBI increases NE 2 DPI. Global gene expression from coronal brain slice was similar between groups indicating that transcriptional differences may be localized to the site of injury.

Consistent with previous data, sleep monitoring indicates that SF increases sleep when mice are typically more active. TBI and SF each affected the ability of mice to regulate sleep bouts. For both inactive and active periods, TBI increased shorter bouts. For only the inactive phase, TBI decreased longer bouts. Together, the data suggests that TBI decreases sleep quality by fragmenting sleep and impairing sleep consolidation. SF increased shorter bouts during the active period, indicating that SF also decreases quality of sleep even as mice attempt to compensate for SF. Together, the data show that post-TBI sleep may be vulnerable to further disruption by exogenous stressors like SF. However, the role of neuroinflammation in mediating or contributing to sleep-wake change remains unclear.

58

Inter-Rater Reliability Between Two Raters for Repetitive Head Impact Counts in Youth Tackle Football

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Youth tackle football players often experience repetitive head impacts (RHIs) on the field. Instrumented mouthguards (IMs) can record the number of RHIs players experience. These IMs' data must be cleaned to confirm that they reflect true RHIs. A current best practice is video reviewing time-stamped data to confirm the RHIs. As a result of the length of the cleaning process, more than one rater may clean the same study's data; this could cause inconsistencies in RHI verification.
Purpose: To determine the inter-rater reliability between two raters for number of RHIs. **Methods:** Participants (N = 18, age = 9±1years, height = 139.7±10.2cm, Mass = 36.2±8.6kg) wore IMs for six youth tackle football games. Two games were randomly selected for two trained raters to both clean independently. Intraclass correlation coefficients (ICCs) were calculated to determine the inter-rater reliability, as well as impact rate ratios (IRR) and 95% confidence intervals (CIs) to determine differences in RHI counts between the two raters. ICC values under .5 indicate poor agreement, between .5 and .75 show moderate agreement, between .75 and .9 show good agreement, and above .9 show excellent agreement. IRR CIs not containing 1.00 were considered significant. **Results:** The first rater recorded a total of 23 RHIs while the second rater recorded a total of 11 RHIs for the two games. ICC was .827 (95% CI = .595-931) which represented good agreement. The IRR was 2.09 (95% CI = 1.02-4.92), suggesting there were differences between the two raters.
Conclusion: The ICC results indicate that video review of RHIs in youth tackle football players resulted in good agreement between two raters. This suggests that when given detailed and standardized instruction for cleaning this type of data, the RHI counts could be consistent among raters. However, a potential limitation is present in the lack of a large sample size of raters as well as trials conducted. Therefore, it may be worthwhile to split up video review responsibilities among raters to improve the efficiency of the process but further studies should be conducted to confirm this finding.

59

Examining the interaction of age and objective sleep quality on episodic memory performance

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Introduction
Evidence suggests there is an inverse relationship between sleep disturbances and episodic memory performance among healthy adults. However, there are limited studies examining this relationship in middle-aged and older adults. To address this gap in the literature, we examined the relationship between accelerometer-derived sleep metrics and visuospatial and verbal episodic memory across the adult lifespan.

Methods
Data were collected from 114 adults (ages 18-86 years, mean age = 54.0 (sd = 18.6); 56.1% female) from the Fitness, Aging, Stress, and TBI Exposure Repository (FASTER) study. Sleep efficiency (SE), wake after sleep onset (WASO), sleep onset latency (SOL), total sleep time (TST), and sleep fragmentation index (SFI) were assessed using a wrist-worn Actigraph GT9X device and processed with ActiLife v6.13.3. Sleep times were validated with a self-reported sleep journal. Episodic memory was assessed using the Picture Sequence Memory Test (PSMT) and the Rey Auditory Verbal Learning Test (RAVLT) from the NIH toolbox. Participants were classified as young (age = 18-29 years), middle-aged (age = 30-59 years), and older adults (age ≥ 60 years). Multiple linear regression and analyses of relative importance were used to examine main effects, interactions, and variance explained between sleep metrics and episodic memory performance.

Results
Age was associated with sleep efficiency ($r = 0.49$, $p < 0.001$), sleep onset latency ($r = -0.55$, $p < 0.001$), wake after sleep onset ($r = -0.47$, $p < 0.001$), verbal episodic memory ($r = -0.50$, $p < 0.001$), and visual episodic memory ($r = -0.52$, $p < 0.001$). Total sleep time was the most relatively important sleep metric for verbal memory performance ($R^2 = 0.02$), but did not have a significant independent association ($\beta = -0.22$, $p = 0.19$) and did not interact with age group. Sleep fragmentation index ($R^2 = 0.035$) and sleep efficiency ($R^2 = 0.045$) had the highest relative importance for visual episodic memory performance, but only sleep fragmentation index had a significant independent association ($\beta = -0.32$, $p = 0.04$). Sleep fragmentation index did not interact with age group on visual episodic memory performance.

Discussion
Older age was associated with better sleep health but lower episodic memory performance. Of the sleep metrics, only sleep fragmentation index was significantly associated with visuospatial episodic memory. Sleep fragmentation may be specifically linked to visuospatial episodic memory across the adult lifespan above and beyond other sleep metrics.

60

Deciphering the microstructure of the central nervous system white matter extracellular space

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Myelination is essential for neural network function. Myelin development starts postnatally, and myelin remodeling persists even in adulthood. In the central nervous system (CNS), myelin sheaths are exclusively formed by oligodendrocytes, which are differentiated from oligodendrocyte precursor cells. Myelin formation is regulated by both intrinsically pre-determined programs and extrinsic factors, e.g. instructive signals from axonal activities. Oligodendrocyte lineage cells express a wide variety of receptors and ion channels. Therefore, the spread of various molecules within the extracellular space (ECS) may play a key role in regulating myelination. To directly visualize ECS of white matter during myelin development, we employed a newly developed shadow imaging technique using acute brain slices. Our data suggest that ECS volume gradually decreases from the early postnatal to the adolescent phase. To investigate whether the gradual decrease in ECS between axons leads to alteration in the diffusion of molecules in the white matter, we imaged the diffusion of a point source-released fluorescence dye. Our preliminary results suggest that dye diffusion in the white matter is isotropic, and that dye may disperse faster during development when ECS is larger. These results shed light on how neurotransmitters and other molecules spread within white matter and help us gain insights into mechanisms controlling CNS myelin formation.

62

Deferoxamine Mesylate in Serum Containing and Serum-Free Environments alters Adult Schwann Cell Survivability under Hydrogen Peroxide Induced Cell Death

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Transplanted adult Schwann cells (SCs) have been shown to improve both functional and anatomical outcomes after spinal cord injury. Schwann cells also promote axonal regeneration in the CNS after injury. The effectiveness of SCs is reduced by low survival after transplantation due to cell death via oxidative challenges in the first 24–48 hours days post-transplant. Deferoxamine Mesylate (DFO), a hypoxic mimetic, has been reported to increase survivability through stabilizing HiF1a by inhibiting HIF-prolyl hydroxylases (HIF-PHDs). We have cultured adult SCs isolated from the ventral root of Sprague Dawley rats and examined the role of pre and post H_2O_2 treatment of SCs with DFO and how this effects necrotic and cell death signaling. Hydrogen peroxide (62.5 µM) was used to facilitate cell death 24 hours following initial exposure to DFO treatment *in-vitro* for 16 hours before fixation of SCs. In addition to DFO we have also examined the combined efficacy of neurotrophic factors (Neuregulin beta1, Basic Fibroblast Growth Factor, Fibroblast Growth Factor 5) with DFO *in-vitro*. Immunocytochemistry (ICC) and a nuclear DAPI stain were used to stain cells SCs for their phenotype (p75, GFAP, HiF1a, collagen IV) in different conditions. Confocal analysis showed elevated HiF1a expression associated with DFO treated cells in both serum and serum free conditions (n=300) as well as unaltered matrix in serum and serum-free conditions (n=32). Quantitation (n=700) via semi-automated image J quantitation of DAPI labeled SCs shows increased survival of DFO treated cells in both serum and serum-free conditions therefore showing the neuroprotective effects of DFO in hydrogen peroxide facilitated cell death signaling. Transcriptomic analysis through RT-qPCR profiling of pro-apoptotic, anti-apoptotic, necrotic, and autophagy genes indicates, interestingly, an upregulation of necrotic genes in DFO treated groups upon hydrogen peroxide challenge while pro-apoptotic genes are downregulated. Our findings suggest that DFO treatment of adult ventral root isolated SCs in both serum and serum-free conditions is a useful strategy to overcome cell death signaling in transplant paradigms. However, careful consideration of the upregulation of necrotic signaling upon DFO manipulation should be addressed before moving onto transplantation studies in clinical studies.

63

Effect of Baseline Neck Strength on HAE Magnitude in Adolescent Female Soccer Players

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Background: Studies suggest that head acceleration events (HAEs) in soccer, resulting from purposeful heading, physical play, or unintentional heading, can lead to acute and chronic neurological changes. Identifying practices to mitigate HAEs in soccer can make the overall sport safer.
Purpose: The purpose of this study was to determine if greater neck strength was associated with lower median peak linear acceleration (mPLA) and median peak rotational velocity (mPRV) in adolescent female soccer players at baseline (i.e., the beginning of a soccer season).
Methods: Adolescent female soccer players (14-15 years) wore instrumented mouthguards to record the magnitude of HAEs (> 5g) during a soccer heading paradigm. Mouthguards were fitted for all players using standard boil-and-bite methods. During the heading paradigm, a 1x1m area was designated for the participants. The research team member stood 5m away and threw the ball at the participant, soccer throw-in style. The participant would head the ball back to the team member and repeat the process for 5 trials. Neck strength was assessed using a handheld dynamometer and by asking the participants to complete three, 3-second maximum contraction in six positions. Maximum force was averaged across the three trials. Positions with bilateral movements were averaged together. We examined the association between neck strength and HAE magnitude using univariate linear regression models. Independent variables were flexion, extension, anterior-lateral flexion, and rotation strength. Dependent variables were mPLA and mPRV for each athlete.
Results: There were 8 participants who completed this pilot study. There was no association between neck strength and mPLA. Flexion (B=0.147, 95% CI [0.003, 0.345], p=0.047) and rotation (B=0.240, 95% CI [0.002, 0.477], p=0.048) strength were positively associated with mPRV, such that greater strength was associated with higher mPRV.
Conclusion: These preliminary data refute our hypotheses, suggesting little to no association between neck strength and head impact magnitude. The participants were randomly assigned to an isometric or dynamic neck strengthening condition. The next steps are to follow up with participants in weeks 6-14 to see if either neck strengthening intervention reduced head impact magnitude.

64

Thalamic Volume in Children with Traumatic Brain Injury Linked to Adaptive Functioning Outcomes

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Introduction
Traumatic brain injury (TBI) can result in neuroanatomical sequelae, including damage to subcortical structures such as the thalamus, a crucial area for behavioral and cognitive functioning. Thus, TBI-related degradation of thalamic subsections may have broad behavioral implications. This project explores the effect of a TBI on thalamic volume in children with orthopedic injury (OI), complicated-mild TBI (cmTBI), or moderate-to-severe TBI (msTBI).

Methods
Forty-six 8-16 year old youth with OI (n=22; M_{age}=11.72y; 14 male), cmTBI (n=11; M_{age}=12.63y; 8 male), and msTBI (n=13; M_{age}=11.30y; 9 male) underwent MRI in a 3T Siemens scanner including a T1-weighted structural scan. Parents completed the Adaptive Behavior Assessment System (ABAS-3), measuring adaptive function. We utilized Freesurfer (v7.3.2) to obtain thalamic nuclei volumes. We fitted a general linear model to the volumes with estimated intracranial volume and gender as covariates to control for head size and gender. Due to a small sample size, we focused on group differences that approached statistical significance (p
≤≤
.10) and medium (η_p^2
≥≥
0.06) to large (η_p^2
≥≥
0.14) effect sizes. Partial correlations yielded associations between bilateral thalamus volume and adaptive function, controlling for age and gender.

Results
Groups differed in left pulvinar lateral (F(2,41)=3.88, p=.029, η_p^2=.159), right paracentral (F(2,41)=3.28, p=.048, η_p^2=.138), and right ventromedial (F(2,41)=3.36, p=.045, η_p^2=.141) nuclei volumes. Although not statistically significant, medium to large effects emerged in the right centromedian (F(2,41)=2.97, p=.063, η_p^2=.126), mediodorsal medial magnocellular (F(2,41)=2.59, p=.088, η_p^2=.112), parafascicular (F(2,41)=2.82, p=.071, η_p^2=.121), pulvinar anterior (F(2,41)=2.78, p=.074, η_p^2=.119), and ventral posterolateral (F(2,41)=3.05, p=.058, η_p^2=.130) nuclei volumes. The msTBI group had overall less volume in the right thalamic nuclei compared to cmTBI and OI (all ps<.05); the cmTBI group had greater volume in all areas except the left pulvinar lateral and right paracentral (all ps<.05). Partial correlations show overall volume of the left and right thalamus is associated with better overall (rs=.409-.517), conceptual (rs=.417-.591), social (rs=.446-.477), and practical (rs=.313-.400) adaptive skills (all ps<.05).

Discussion
Our results confirm differences in thalamic volume across the injury severity groups, especially after msTBI. Additionally, they show the thalamus supports complex behavior and damage may explain adaptive functioning deficits after TBI.

65

Oligodendrocyte progenitor cell deletion disrupts early glial scar formation following spinal cord injury

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NG2+ oligodendrocyte progenitor cells (OPCs) are a unique cell population that proliferates in response to central nervous system (CNS) injuries. OPCs can not only differentiate into myelinating oligodendrocytes after spinal cord injury (SCI) but also proliferate near the lesion and therefore may play a role in glial scar formation. We utilized a novel transgenic mouse model that selectively deletes OPCs to determine the effects of OPC loss on glial and fibrotic scar formation after SCI. This model crosses pdgfrDTR mice to Olig2-cre mice to generate a transgenic mouse line (Olig2-DTR) expressing human diphtheria toxin receptor (hDTR) only in Olig2+PDGFRa+ cells (OPCs). To delete OPCs in Olig2-DTR mice, we injected 20ng/g of diphtheria toxin (DT) daily (0.4g in 100 sterile saline for a 20g mouse). Olig2-WT littermates received the same regimen; since these mice do not express hDTR, they should be unaffected by the drug. In naïve Olig2-DTR mice treated with DT, NG2+ cells were reduced by over 50% in the cervical spinal cord (n=12) compared to Olig2-WT mice (n=9). Next, the effects of OPC deletion on glial scar formation and stabilization after SCI were examined. Mice received a C5 unilateral contusion with a 60 kD force and were treated with DT daily, and tissue was assessed at 7, 11, or 21 days post-injury (dpi) – key times for glial scar formation. At 7dpi, OPCs were significantly depleted around the lesion border in Olig2-DTR mice (n=5) compared to Olig2-WT littermate controls (n=4). Olig2-DTR mice had significantly larger lesion sizes compared to controls and GFAP expression within the lesion border was three times lower in Olig2-DTR mice. Additionally, GFAP width around the border was significantly decreased in Olig2-DTR versus Olig2-WT mice. Depletion of OPCs also significantly reduced laminin expression within the lesion core at 7dpi. At 11dpi, GFAP expression within the lesion border was significantly decreased in Olig2-DTR mice (n=6) versus Olig2-WT littermates (n=6). However, there were no significant differences in lesion size, glial scar width, and laminin expression between the two groups. The 21dpi cohorts received daily DT injections for 14dpi followed by 7d of no treatment. DT injections for 14 days cover the time of peak OPC proliferation. Analysis of this cohort is ongoing and will clarify how early OPC deletion alters longer-term glial scar formation and composition. Together, these results indicate a novel role for OPCs in contributing to glial scar formation and lesion stabilization after traumatic SCI.

66

Printed Circuit Board to Control Remote Food Dispenser for Assessing Pig Cognition

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Pigs are increasingly employed as research models for traumatic brain injury due to sulci and gyri with more similarities to human anatomy than rodents. However, behavioral research using pigs as models is limited due to a lack of equipment. To address this, the Vonder Haar laboratory developed a touchscreen system for pig behavioral testing that consists of a touchscreen unit and an input/output (I/O) interface to deliver fruit-flavored sugar pellets from across testing rooms. The I/O interface still has need for improvement as it is time-intensive to set up, has a large and fragile design, and has reliability issues leading to inaccurate experimental results. Therefore, the objective of this project was to refine the system by developing a new I/O interface with the goal of offering a user-friendly solution for connecting peripheral response and food delivery devices to the touchscreen unit. To do this, we iteratively designed a circuit board for communicating with the touchscreen. We then developed a housing for the circuit board and pellet dispenser, tested a circuit board prototype, and are now testing the final product. The redesigned I/O interface is a fully integrated printed circuit board that wirelessly connects with the touchscreen unit via a Bluetooth module, can connect to up to eight input and output devices via molex connectors, and has an easy to use python library to interface with connected devices. This ensures simplicity for experimental researchers and allows food-dispensing operant devices to be placed separately from the touchscreen to prevent damage by pigs. Its compact and simple design facilitates easy wall-mounted placement and accurate data transfers. Furthermore, the eight input and output devices give researchers a wide range of devices to include in experiments. This new I/O interface combined with the touchscreen unit could significantly lower barriers to cognitive research in pigs and increase interest in studies on traumatic brain injury, Alzheimer's disease, Huntington's Disease, and other neurological conditions.

67

Barriers and facilitators to engaging in physical activity in individuals with chronic brain injury: A qualitative study

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Purpose/Hypothesis: Physical activity (PA) is valuable following brain injuries. However, little is known about factors that affect PA in individuals with chronic brain injury (CBI) after termination of rehabilitation. The purpose of this study was to identify barriers and facilitators for engaging in PA in the CBI population.

Subjects: Eight individuals with CBI (6 females, mean age in years ± SD: 40.2 ± 18) who were >1 year out from their injury and had at least one episode of rehabilitation participated in the study. Participants were between 1 to 33 years from injury.

Materials/methods: Participants completed a semi-structured interview focused on understanding the CBI impact on their post-injury activity levels relative to their pre-injury levels. Participants were permitted a care partner to accompany them in the interview to support memory and question processing. Thematic analysis of the interview data occurred in four phases. First, three independent study members open coded the data and looked for high-level patterns and themes. Next, the data were deductively coded against the physical literacy domains and the socio-ecological model. A codebook was developed iteratively among the study team coders. Findings were then synthesized to generate themes for enhanced understanding of barriers and facilitators to PA.

Results: Analyses revealed energy expenditure and energy availability as major themes towards hindering and promoting PA. When looking at the socioecological model, barriers and facilitators for PA mainly fell into the interpersonal and intrapersonal domains. Information falling into the intrapersonal domain was further placed into all five domains of the physical literacy framework, with the highest concentration occurring in knowledge and motivation domains.

Conclusion: Participants reported both varying amounts and differing barriers and facilitators to engaging in PA. These results align with previous literature indicating that individuals with CBI face many challenges in staying physically active alongside their post injury hindrances. The results of the study can be used to design novel programs for individuals with CBIs that attempt to elicit the facilitators while minimizing the barriers.

Clinical Relevance: Individuals with CBI injury symptoms have individualized challenges to engaging in PA. Barriers and facilitators to PA after brain injury differ, and individuals may require personalized strategies for increased PA. Clinicians should consider fostering conversation directed toward physical literary and socio-ecological domains with their patients to uncover their personalized needs following a CBI.

This project was supported by the 2020 Chronic Brain Injury Pilot Award Program. The project described was supported by Award Number Grant UL1TR001070 from the National Center For Advancing Translational Sciences. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Advancing Translational Sciences or the National Institutes of Health.

68

Neuronal BAG3 attenuates AD-like pathology and cognitive deficits induced by traumatic brain injury via the regulation of autophagy-lysosome pathway

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Traumatic brain injury (TBI) is a serious cause of disability and death in the United States. People living with TBI experience an increased incidence of developing Alzheimer's disease (AD) and other AD-related dementias (ADRD). We previously identified BCL2 associated athanogene 3 (BAG3) as a hub gene that controls tau homeostasis and intrinsic excitatory neuronal vulnerability to tau pathology. BAG3 is a regulator of the autophagy-lysosome pathway (ALP). Interestingly, we found that BAG3 level is reduced excitatory neurons and oligodendrocytes with hyperphosphorylated tau after TBI in mouse models and post-mortem brain tissue. We hypothesized that decreased levels of BAG3 lead to dysfunctions of the ALP, leading to the accumulation of hyperphosphorylated tau in excitatory neurons and oligodendrocytes. We also hypothesized that overexpression of BAG3 would increase the autophagic flux, reducing hyperphosphorylated tau accumulation after TBI.

Interestingly, immunofluorescence (IF) staining in mouse and post-mortem human brain tissue revealed disruptions of the ALP after TBI, as shown by reductions in ALP related proteins like CTSD, LAMP1, while increasing p62 puncta formation.

We also wanted to see how modulating the level of BAG3 would affect the autophagic flux *in vitro* using HEK293 cells. HEK293 cells were treated with lentiviral vectors that overexpress or knock down BAG3. Then, we used an LC3-reporter virus, FUW mCherry-GFP-LC3, to visualize free autophagosome and autolysosome formation. We found that BAG3 overexpression promotes the autophagic flux, while knock down of BAG3 inhibits it, suggesting that modulation of BAG3 can affect ALP dynamics.

Finally, we wanted to see whether BAG3 overexpression before TBI could ameliorate the deficits of the ALP induced by TBI. Notably, BAG3 overexpression increased CTSD and LAMP1, while reducing p62 level after TBI, suggesting that BAG3 level can modulate the ALP *in vivo*.

In conclusion, TBI induces dysfunctions in the ALP pathway, which can be ameliorated by BAG3 overexpression, making BAG3 a promising therapeutic target to reduce tau pathology after TBI. Future studies will investigate how modulating BAG3 affects ALP dynamics *in vitro* using iPSC derived neurons. We will also investigate how ALP dynamics change in a closed-head TBI model (CHIMERA). The CHIMERA model may be more translational to the human population who suffer from TBI, as many TBI-related injuries are closed-headed and exacerbated by rotational forces.

69

MAPT R406W mutation reduces neural activity and oscillations in human neural organoids.

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The progressive cognitive decline in Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) is closely aligned with tau mislocalization and aggregation. Both tau pathology and cognitive decline have been found to be associated with alterations in neural activity and oscillations in AD and FTLD. Nevertheless, the relationship between tau pathology and alterations in neural activity and oscillations remains unclear. The MAPT R406W mutation is a unique tau variant found in FTLD patients that show AD symptoms based on previous patient reports. Thus, we use this missense mutation as a proxy to study FTLD and AD. Neural network dysfunction occurs before overt neurodegeneration in humans, suggesting disruptive neural assembly may contribute to impaired cognition. Studies have also shown that an incohesive network indicates arhythmic oscillations such as decreased gamma synchronization. Effective neuron assemblies across brain areas communicate through coordination between presynaptic and postsynaptic groups that can be detected by local field potentials (LFP). Here, we employed multi-electrode array (MEA) recording to measure the LFP in human neural organoids (hNOs) derived from human induced pluripotent stem cells (iPSCs) with the MAPT R406W mutation, which provides an in vitro model that allows us to comprehensively investigate the effect of the MAPT R406W mutation on neural functional and network activity. Besides increased tau phosphorylation, we found that the MAPT R406W organoids exhibited distinct electrophysiological features, including reduced network activity indicated by reduced burst firing rate and increased interburst intervals compared to isogenic controls. Intriguingly, we have begun to uncover oscillatory patterns in the hNOs such as gamma and theta oscillations. This identification will assist in the uncovering of 1) associations that promote neural network maturation and 2) foundational changes driving these states. Furthermore, the hNOs harboring the R406W mutation notably presented with different neural oscillatory dynamics at day 120 when compared to controls. The oscillatory states of isogenic controls encompassed a mature functional assembly in tandem with complex oscillatory states a different trajectory; in contrast to MAPT R406W hNOs. Altogether, these findings highlight the developmental timing of the electrophysiology of hNOs, the impact of the unique MAPT R406W mutation on the neural circuitry, and how we can use hNOs as a model to correlate electrophysiological dynamics with cellular development and tau pathology. These insights lay the groundwork for further studies into region-specific neural network dynamics, crucial for understanding the electrophysiological dynamics involved in the progression of tau pathology in FTLD and AD.

70

Youth Sleep Quantity and Quality and Symptom Duration in the First Week Post-Concussion

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Sleep disturbances during the acute phase of post-concussion recovery are common in adolescents but not well elucidated in current literature. Moreover, there is limited research on how the quantity and quality of sleep post-injury may affect concussion recovery. This study describes objective sleep quantity and quality during the first week post-concussion and examines its association with symptom duration in youth.

Youths aged 11 to 17 years diagnosed with a physician-confirmed concussion were enrolled within 72 hours of injury in a prospective cohort study with repeated measures. Participants were followed until symptom resolution or 45 days post-injury. Survival analysis was used to evaluate the effect of night sleep quantity (i.e., time in bed [TIB], total sleep time [TST]), sleep quality (i.e., sleep efficiency, wake after sleep onset [WASO], number of awakenings), and daytime sleep during the first-week post-concussion measured using ActiGraph (Model: wGT3X-BT) with the primary outcome being days from injury to symptom resolution.

Participants included 78 concussed youth (36% female, average age 14.2 years [SD=2.1]). The average symptom score at injury was 44 (SD=19), and the average symptom duration was 19 days (SD=12). Average night TIB and TST were 452 and 414 minutes, respectively; average sleep efficiency, WASO, and number of awakenings were 91%, 37 minutes, and 16, respectively. Night TIB and TST were not associated with prolonged symptoms. However, TST during daytime was associated with prolonged symptoms (aHR=0.66, 95%CI=0.47,0.92). No sleep quality variables were correlated with the duration of post-concussion symptoms.

Sleep quantity and quality during the first week post-injury alone neither hasten nor prolonged concussion recovery. Our results suggest increased daytime sleep is associated with sleep disturbances, which may raise the risk for protracted symptom duration in post-injury youth.

71

Title: Infrared Modulation of Motor Cortex and Related Pathways

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Parkinson's Disease (PD) and Major Depressive Disorder (MDD) are prevalent disorders of the brain which may benefit from treatment via nonpharmacological neuromodulation. Current approaches include transcranial magnetic stimulation (TMS) which has been shown to noninvasively stimulate the brain with transient effects. However, the effects of TMS are limited to superficial regions. A newer noninvasive method that can reach subcortical structures is photobiomodulation (PBM), which uses visible to near-infrared light to stimulate neurons. In this work, we have built a multi-wavelength transcranial PBM (tPBM) system to assess the effects of light of 1064 nm wavelength on brain activity and connectivity. Given that motor skills are affected by MDD and PD, we focused on stimulating the primary motor cortex (M1). Healthy adult volunteers (N=10) underwent four sessions of stimulation consisting of active tPBM and TMS along with respective sham sessions. Structural and task fMRI was taken before and after stimulation. Subjects performed a finger-tapping task to explore the effect of stimulation within each individual's motor cortices. Here we report that tPBM successfully stimulated M1 to a similar amount of activation as TMS in a safe and short-term manner. The effects of tPBM and TMS stimulation on motor activation was not significantly different within subjects, suggesting that the two types of stimulation induce similar effects on the somatomotor cortex. We also observed significant changes in functional and structural connectivity between the motor cortex and thalamus after PBM stimulation. These results are in line with previous literature. Interestingly, TMS stimulation did not seem to affect structural and functional connectivity. Our preliminary results reveal that tPBM can cause changes in activation and connectivity of the somatomotor cortex with short-term effects that are comparable to the gold standard of neuromodulation, TMS. tPBM is still a relatively novel technique with more to be explored. PBM harnesses the neuroprotective properties of brain cells and may be useful when pharmacological options are unsuccessful or cannot be tolerated. Compared to other stimulation methods, PBM can penetrate further into the brain, providing more options for treatments of mental illnesses.

72

Understanding the Role of Glia in Postnatal Brain Injury

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Introduction- In the United States, traumatic brain injuries (TBIs) are a leading cause of death in children, with 0-3 years old being the most vulnerable population due to the risk of falling and abuse. Although the prevalence of pediatric TBIs is high, they are vastly underrepresented in pre-clinical models. This alarming reality contributes to the lack of understanding of how even mild TBIs (mTBI) affect brain development. It is my working hypothesis that pediatric mTBI results in gliosis, which disrupts critical neurodevelopmental processes such as microglial-regulated synaptic pruning and delays various behavioral milestone achievements.

Methods- To test my hypothesis, we adopted a previously published pediatric mTBI model from the Fleiss lab. Mice weighing 3.5 - 4 g underwent a mild weight drop TBI or sham injury paradigm testing three different injury intensities. To evaluate injury-induced pathologies, we compared phenotypes of the injured ipsilateral side to the non-injured contralateral side from injured and sham brains from all four groups. Gliosis was assessed by immunohistological stains: Iba-1 and GFAP. To determine if microglial associated injury cascades are preferential over microglia-regulated synaptic pruning mechanisms typically present at this stage postnatally, we used western blotting methods to examine the presence of synaptic pruning markers: TREM2 and Clq/C3. Additionally, to evaluate behaviors typically reached during development, behavioral milestone paradigms and isolated ultrasonic vocalizations were performed on mice following TBI or sham injury.

Results- Our preliminary analysis has shown that there is worsened neuropathology in mTBI mice than sham mice. We observed greater microglial activation in the injured ipsilateral side compared to the non-injured contralateral side as demonstrated by increased Iba-1 staining. Western blot data showed that there is increased synaptic pruning in the injured side compared to the non-injured side as shown by increased TREM2 and C1q/C3 levels. Behavioral testing results show that mTBI mice behave differently and develop at a slower rate than sham mice. Furthermore, we have found that as we increased the magnitude of weight drop forces, we saw more dramatic injury pathologies.

Conclusion- We expect these findings to improve our understanding of mTBI glial mechanisms and their impact during postnatal development.