The Effect of Chronic Sleep Disruption on Glymphatic System Function and Neuropathological Disease Outcomes in the 5xFAD Mouse Model
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The glymphatic system, which is primarily active during sleep, is a network of astroglial perivascular channels within the brain that allow for Cerebrospinal Fluid (CSF) influx and exchange. Glymphatics play a crucial role in the waste clearance of amyloid beta, a hallmark in the development of Alzheimer’s Disease and neurodegeneration. Recently, a bidirectional relationship between Alzheimer’s Disease and sleep has also been suggested with the aggregation of amyloid beta associated with mid-life sleep disruption. However, the mechanistic link between sleep disruption, particularly over chronic time scales, and the development of Alzheimer’s pathology remains unclear. This study investigates whether chronic sleep disruption, similar to that experienced in humans, will impact downstream neuropathology. We hypothesize chronic sleep disruption will result in decreased glymphatic function and subsequently increased amyloid plaque burden. This experiment utilizes a chronic sleep fragmentation model in 120 5xFAD mice from 8 weeks to 16 weeks of age. In the Lafayette Sleep Fragmentation chambers, 60 animals are disturbed every two minutes during normal sleeping periods (daylight hours). 60 mice were placed in normal sleeping conditions. After eight weeks of sleep fragmentation or sham exposure, glymphatic function is assessed by in vivo near infrared imaging following stereotactic CSF tracer injection. Animals are perfusion fixed, cryosectioned, and glymphatic function is assessed by measurement of fluorescent cerebrospinal fluid tracers in brain tissue. Aquaporin-4 localization, amyloid plaque deposition, and markers of astroglial and microglial activation are assessed by immunofluorescence. In this project, I specifically work on cryosectioning the tissue, and understanding glymphatic function through the processes of immunofluorescence imaging and analysis. The collected data demonstrated that sleep disruption did increase neuropathological outcomes. The measured impact of glymphatic function was also correlated with these downstream pathological effects. These findings could be an indicator of interactions between neurological disease progression and an inflammatory expression after sleep disruption. They can also shed more light on the complex relationship between Alzheimer’s disease progression, the glymphatic system, and chronic sleep disruption.

Impact of Chronic Sleep Disruption on Cognitive Performance in the 5xFAD Mouse Model
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Chronic sleep disruption, present in 25-60% of patients suffering from Alzheimer’s Disease (AD), often precedes cardiovascular disease symptoms. While little is known about the mechanisms underlying chronic sleep disruption and the development of clinical pathology, both acute and chronic sleep deprivation have been found to increase biomarkers of AD including neuroinflammation and amyloid-beta accumulation. Additionally, in people without AD, sleep deprivation can result in a deterioration of working memory and attention. In this study, we examine the impact of chronic sleep disruption on cognition both at baseline and in the 5xFAD mouse model. The 5xFAD mouse model is a transgenic mouse model of familial amyloidosis which expresses neurocognitive impairment as early as 2 months. To define the effect of chronic sleep disruption on cognition in the absence of AD pathology, 60 wild type mice were exposed to chronic sleep...
disruption or sham procedure for 8 weeks between 10 and 18 weeks of age. At 18 weeks of age, I evaluated the animals for changes in spatial memory (Barnes maze), short-term memory (Y-maze), locomotion and anxiety (open field test), and activities of daily living (burrowing trials). To test whether chronic sleep disruption specifically exacerbates AD-related neurocognitive decline, the same cognitive tests were performed on 60 5xFAD+ animals exposed to 8 weeks of sleep disruption or sham treatment. I then analyzed the collected data to isolate any trends of cognitive performance, finding that chronic sleep disruption impaired cognitive performance in 5xFAD+ and littermate controls, with a more significant impact on 5xFAD+ animals. These findings highlight the critical association between dysfunctional sleep and the development of cognitive impairment with AD disease progression which then guides us toward better preventative care and treatments.

**Glymphatic Impairment in a Murine Model of Repetitive Blast Mild Traumatic Brain Injury**  
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Mild traumatic brain injury (mTBI) is a major public health issue, frequently resulting in long-term sequelae such as sleep disruption, headaches, and cognitive impacts. In recent years, mTBI has emerged as a risk factor for the development of neurodegenerative diseases, such as Alzheimer’s disease (AD). Blast-related mTBI has been experienced by large numbers of Servicemembers during the conflicts in Afghanistan and Iraq; therefore, their potential vulnerability to downstream neurodegeneration is a major concern among Veteran populations. Recent evidence demonstrates that TBI impairs the glymphatic system, a brain-wide network of perivascular channels along which cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange facilitates the clearance of interstitial solutes such as amyloid β and tau. However, these findings were in an impact TBI model, which is a brain injury caused by a blow to the head; therefore, relatively little is known about the possible effects of blast mTBI. Here, we hypothesize that glymphatic function is impaired following repetitive blast mTBI. Using a murine blast model, we measured glymphatic function at both 7-day and 28-day timepoints following a repetitive blast induced TBI. Glymphatic function was quantified using intracisternal fluorescent tracer injection and measuring the fluorescent intensity of CSF tracer movement. We found a delayed impairment in glymphatic function at 28 days post-injury. These findings may provide further insight on the mechanisms that may render the blast-injured brain vulnerable to neurodegeneration and may give rise to improved treatments for patients exposed to blast injury.

**Defining Circadian Regulation of the Choroid Plexus**  
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Alzheimer’s disease (AD) is an age-related neurodegenerative disease characterized histopathologically by amyloid plaques and neurofibrillary tangles in the brains of affected individuals. The impairment of cerebrospinal fluid (CSF)-mediated clearance of proteins including amyloid beta and tau from the brain is proposed to underlie the development of AD pathology. Sleep and circadian disruption are both linked to the development of AD. CSF clearance is regulated through both sleep and circadian processes, while CSF production by the choroid plexus (CP) is diurnally regulated. The CP acts as a blood-CSF-barrier, provides nutrient delivery, and clears toxic proteins. Studies to date document reduction in CSF production, impaired blood-CSF-barrier function, and altered protein uptake in both aged and AD conditions. It is currently unknown whether the CP is itself regulated by sleep and circadian rhythms and whether disruption of these two governing processes contributes to disease development. Our initial analysis across awake, asleep, and acutely sleep-deprived young mice indicated no gene expression differences between sleep states; however, significant circadian-dependent transcriptional changes were observed. We then examined the circadian-dependent gene expression profile of the CP in aged (12-14 months) mice and in an AD mouse model. Preliminary analysis reveals a shift in the transcriptional profile of aged mice and a near complete loss of circadian regulation in the AD model. Ongoing analysis and validation are being carried out to reveal functional pathways disrupted in the CP that could provide a further understanding of AD pathology.

[Unable to Present] Quantitative Analysis of Aquaporin 4ex (AQP4ex) Expression in the Human and Murine Brain  
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Alzheimer’s Disease (AD) is a neurodegenerative disease that affects more than 5 million Americans. The glymphatic system (a network of perivascular spaces that facilitate fluid movement and solute clearance from the brain) and its dysfunction associated with aging has been implicated in the development of AD. The water channel aquaporin 4 (AQP4), located in astrocytic endfeet bordering the perivascular spaces,
is crucial for the proper functioning of the glymphatic system. Data suggests that loss of AQP4 localization results in amyloid-β deposition, a hallmark of AD pathology, and loss of AQP4 localization accompanies aging in rodents as well as AD in humans. In this study, we quantitatively analyze the expression of aquaporin-4ex (AQP4ex)—a translational readthrough variant of AQP4 believed to play a role in its localization—to identify any correlation with aging and AD pathology. Selective deletion of AQP4ex results in the mis-localization of AQP4 all over the astrocytic membrane, indicating that AQP4ex is a crucial element in the localization of AQP4. We analyze young, old and AD groups in the murine (mouse) brain as well as AD versus control in a human case series. Currently, we see a trend towards decline in cortical perivascular AQP4ex in the AD group, with more analysis ongoing. This is the first characterization of AQP4ex expression in the murine brain and in a human case series, and these data will contribute to the small but growing body of research on AQP4ex and its relationship with AQP4 localization, creating opportunities to identify a new novel mechanism and novel target in AD pathology.

Examining the Influence of Psychosocial Stress on Telomere Length in NCAA Collegiate Swimmers

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Regular physical activity protects against cellular aging, but a recent study found shorter telomere length (TL) in professional swimmers compared to less active controls. Shorter TL is associated with increased cellular senescence and functional decline with age, suggesting swimmers may be at increased risk for age-related morbidity. Previous studies reported competitive swimmers face high levels of psychosocial stress, which, in turn, is posited to accelerate TL shortening. I hypothesize that competitive collegiate swimmers experience increased psychosocial stress, leading them to have shorter TL despite their active lifestyles. I conducted a mixed-methods study to examine whether TL differs between Division-1 and Division-3 National Collegiate Athletic Association, NCAA, swimmers (N=28 respectively) and their non-athlete counterparts (N=15) and if differences in TL is associated with psychosocial stress (Total N=43). Collegiate swimmers face a unique set of stressors to perform for scholarships and professional opportunities while simultaneously continuing their responsibilities as students. Accordingly, I measured overall psychosocial stress (Cohen’s Perceived Stress Scale; PSS) to compare swimmers and non-athletes as well as sports-related psychosocial stress (The Student Athletes’ Motivation toward Sports and Academics Questionnaire; SAM-SAQ) to compare D-1 to D-3 swimmers. Further, I conducted semi-structured qualitative interviews to better contextualize how student-athletes perceive how the psychosocial stress they experience impacts their lives and performance. I expect swimmers to report higher levels of overall psychosocial stress (PSS) and have shorter TL compared to non-athletes. Further, I expect that D-1 swimmers will report higher levels of psychosocial stress (SAMSAQ) and have shorter TL compared to D-3 swimmers. There are over 10,000 NCAA swimmers across the country and minimal studies have looked at their physical and mental health simultaneously. This study hopes to highlight the areas we can better support and improve both the physical and mental health of our collegiate swimmers, and NCAA student-athletes as a whole.