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METABOLIC DYSFUNCTION AND SLEEP DISRUPTION IN MODELS OF ALZHEIMER'S DISEASE

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Introduction: Metabolic perturbations and sleep disruptions are a cause and consequence of Alzheimer's disease pathophysiology. A bidirectional relationship exists where impairments in sleep and metabolism contribute to the development of Alzheimer's disease while the presence of Alzheimer's disease pathology leads to decreased cerebral metabolism, peripheral glucose intolerance, and disrupted sleep. While the effects of type 2 diabetes (T2D) and Alzheimer's disease on sleep have been explored separately, no previous studies have examined the effect of acute glycemic variability, a defining feature of T2D, on sleep in the context of Alzheimer's disease. The goal of this study is to determine how glycemic variability drives sleep disruptions by modifying the relationship between cerebral glucose metabolism and neuronal activity.
Methods: Biosensors are implanted bilaterally into the hippocampus of APP/PS1, a model of amyloid-beta (Aβ) overexpression, and P301S, a model of tau deposition and neurodegeneration, mice to measure ISF glucose and lactate, markers of cerebral metabolism and neuronal activity, respectively. Simultaneous cortical EEG/EMG recordings are used for sleep/wake scoring and analysis.
Results: Glycemic fluctuations cause a decoupling of the typical relationships between cerebral metabolism and neuronal activity, while also increasing arousal in 3-month-old, wildtype mice. The presence of AD-like pathology results in a similar, albeit muted cerebral metabolic response to peripheral glycemic variability, but a diminished effect on wakefulness, likely due to age- and pathology-dependent increases in overall time spent awake. Conversely, in aged, P301S mice, cerebral metabolic responsiveness is lost and a ceiling effect on wakefulness emerges, suggesting differential effects on sleep with tau accumulation. Moreover, aged mice show progressive disruptions to overall sleep quality and quantity, highlighting the synergism existing between AD-like pathology and glucose intolerance in sleep dysfunction. Lactate seems to be a common driver of disruption in this synergistic cycle.
Conclusion: This study represents a novel approach to defining the dynamic interplay between risk factors for AD and T2D and suggests a feedforward loop of disease progression where disrupted sleep can alter the relationship between neuronal activity, metabolism, and pathology.
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POOR SLEEP QUALITY PREDICTS SERUM MARKERS OF NEURODEGENERATION AND COGNITIVE DEFICITS IN WARRIORS WITH MILD TRAUMATIC BRAIN INJURY

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Introduction: Increasing evidence links neurodegeneration to traumatic brain injury (TBI), and a separate body of literature links neurodegeneration to sleep dysfunction, implicating increased toxin production and decreased glymphatic clearance. Sleep disorders affect 50% of TBI patients, yet the sleep-neurodegeneration connection in these patients remains unexplored. We hypothesized that warfighters with TBI and sleep dysfunction would have increased neuronal injury, revealing potential mechanistic underpinnings for TBI outcomes. We measured plasma biomarkers, cognitive function and sleep surveys for correlation analysis.
Methods: In a retrospective cross-sectional study of warfighters (n=113 chronic mild TBI patients), the Pittsburgh sleep quality index (PSQI) was compared with amyloid β42 (Aβ42), neurofilament light (NFL), tau, and phospho-tau (threonine 181) isolated from plasma and exosomes. Executive function was tested with the categorical fluency test. Exosomes were precipitated from plasma. Proteins were measured with the Single Molecule Array (Quanterix). Linear models were adjusted for age, ApoE, and number of TBIs.
Results: Poor sleepers with TBI (PSQI>8) had elevated NFL compared to good sleepers in plasma (p=0.007) and exosomes (p=0.00017), and PSQI directly correlated with NFL (plasma: Beta=0.23, p=0.0079; exosomes: Beta=2.19, p=0.0013) stronger than any other marker of neurodegeneration. Poor sleepers also showed higher obstructive sleep apnea (OSA) risk compared to good sleepers by STOP-BANG scores (3.6, SD=1.6 vs 2.8, SD=1.74; p=0.0014) as well as decreased categorical fluency (20.7, SD=4.1) (18.3, SD=4.6, p=.0067). Plasma tau and Aβ42 also correlated with PSQI (Beta=0.64, p=0.028, and Beta=0.40, p=0.049 respectively).
Conclusion: This is the first reported data correlating markers of neuronal injury and cognitive deficits with sleep complaints and OSA risk in patients with TBI - possibly identifying treatable pathophysiological mediators of TBI neurodegeneration. Limitations include a small sample size, lack of objective sleep measures, and inability to establish directionality due to cross-sectional design. Prospective trials will be required to further explore our proposed hypothesis. If confirmed, these findings would call for targeting sleep disorders in the TBI population to mitigate risk of neurodegeneration.
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ASSOCIATIONS BETWEEN REST-ACTIVITY PATTERNS AND RESTING-STATE NETWORKS IN OLDER ADULTS

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Introduction: Resting-state functional connectivity is coherent brain activity in a task-free state that strongly correlates to task-evoked sensory, motor, and higher-order cognitive systems. Certain networks show decreased functional connectivity with aging. Aging is associated with changes in circadian rhythms and sleep-wake cycles. Limited research has been conducted on how circadian activity and sleep are related to markers of functional brain aging. The purpose of this study was to explore whether rest-activity patterns and shorter sleep duration are related to functional connectivity of specific resting-state networks in older adults.