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CLINICAL REVIEW

A systematic review and meta-analysis of sleep architecture and chronic traumatic brain injury

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SUMMARY

Sleep quality appears to be altered by traumatic brain injury (TBI). However, whether persistent post-injury changes in sleep architecture are present is unknown and relatively unexplored. We conducted a systematic review and meta-analysis to assess the extent to which chronic TBI (>6 months since injury) is characterized by changes to sleep architecture. We also explored the relationship between sleep architecture and TBI severity. In the fourteen included studies, sleep was assessed with at least one night of polysomnography in both chronic TBI participants and controls. Statistical analyses, performed using Comprehensive Meta-Analysis software, revealed that chronic TBI is characterized by relatively increased slow wave sleep (SWS). A meta-regression showed moderate-severe TBI is associated with elevated SWS, reduced stage 2, and reduced sleep efficiency. In contrast, mild TBI was not associated with any significant alteration of sleep architecture. The present findings are consistent with the hypothesis that increased SWS after moderate-severe TBI reflects post-injury cortical reorganization and restructuring. Suggestions for future research are discussed, including adoption of common data elements in future studies to facilitate cross-study comparability, reliability, and replicability, thereby increasing the likelihood that meaningful sleep (and other) biomarkers of TBI will be identified.

Introduction

The conclusion of a report recently presented to the United States Congress by a TBI working group that included members from the Center for Diseases and Control and Prevention, the National Institutes of Health, the Department of Defense, and the Veterans Association leadership panel, was that there is a growing need for information on the chronic effects of traumatic brain injury (TBI) [1].

Alterations in sleep quality and quantity are common acutely after TBI. Nearly half of patients report having problems with their sleep shortly after injury [2], and objective measurements of sleep, as measured with actigraphy or polysomnography (PSG), corroborate the subjective complaints. Frequently, both subjective reports and objective measures reveal nighttime awakenings and daytime sleepiness [3–5], as well as hypersomnia/increased sleep need [5,6] and insomnia [7].

Yet it is unclear whether, and the extent to which, sleep-wake disturbances persist after injury (and after apparent behavioral recovery). Some have found that hypersomnia can persist for more than 6 months following TBI [8,9]. However, others have failed to find differences in total sleep time between those with chronic TBI and non-injured controls [10], and, conversely, some have even reported that TBI patients have shorter mean total sleep times [11,12]. Similarly, some have found evidence that individuals with chronic TBI report poorer subjective quality sleep [11], while others have failed to find an increased rate of subjective complaints [10]. Lastly, and perhaps most ambiguously, there is little agreement regarding the effects of chronic TBI on sleep architecture (i.e., differences in absolute and relative sleep stage amounts). Sleep architecture is a relatively unexplored but potentially important

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Abbreviations

CI	Confidence interval 95%
EEG	Electroencephalography
GCS	Glasgow coma scale
MOOSE	Meta-analysis of Observational Studies in Epidemiology
mTBI	mild traumatic brain injury
NREM1	Sleep stage 1
NREM2	Sleep stage 2
NREM3/SWS	Sleep stage 3/Slow-wave sleep
NICE	National institute for health and care excellence
NREM	Non-rapid eye movement
PSG	Polysomnography
PTSD	Post-traumatic stress disorder
REM	Rapid eye movement
SMD	Standardized mean difference
TBI	Traumatic brain injury
TMN	Tuberomammillary nucleus
TST	Total sleep time
WASO	Wake after sleep onset

marker of injury that reflects brain heath status [13], thus providing information regarding both prognosis and recovery status (e.g., readiness for Soldiers to return to duty or athletes to return to play). Furthermore, because specific cognitive processes have in some cases been linked to specific sleep stages, it is possible that sleep architecture abnormalities could lead to cognitive and behavioral deficits in TBI (and other) patients.

For instance, non-REM stage 2 (NREM2) has been shown to be involved in motor skill learning, and markers of NREM2 (i.e., sleep spindles) positively correlate with improved motor and cognitive performance in subjects without TBI [14,15]. Additionally, slow wave sleep [SWS] facilitates learning [16] and memory consolidation [17]. Also, in a recent study conducted by one of the co-authors (JM), sleep-dependent emotional deficits were found in mild TBI (mTBI; Glascow Coma Scale from 15 to 17) patients who exhibited reduced REM sleep [18]. It follows that a reduction in any of these sleep stages could hinder cognitive functioning. Additionally, the relationship between sleep architecture and waking cognition is complex, with some studies suggesting that at least some aspects of cognition may be mediated by the interactive effects of the various sleep stages [19–21]. Therefore, a reduction or excess of one sleep stage could broadly impact cognition, and, consequently, identifying abnormalities in sleep architecture could help guide treatment and rehabilitation strategies.

Recently, a meta-analysis with similar aims revealed no significant differences in the sleep staging of TBI patients vs. controls [11]. However, that analysis included one study with patients in the sub-acute TBI recovery phase [22]. Although it is unknown how 'time since TBI' impacts sleep, it is possible that sleep does not stabilize until the chronic phase of injury (>6 months since injury). In the current meta-analysis, we included only studies on chronic TBI patients (i.e., participants who continue to experience symptoms at 6 months or longer post-injury). Nevertheless, we were able to include five more studies (and 142 more subjects) in the current meta-analysis than the previously published work (10 studies and 187 subjects, including 24 subjects with acute TBI [22]), increasing our statistical power to perform a meta-regression for a wider array of sleep-related variables.

The current study was conducted with three goals: The first was to conduct a systematic review and meta-analysis using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines to determine the extent to which chronic TBI is characterized by specific changes in sleep architecture [23]. The MOOSE are guidelines for reporting on observational studies that contain specifications including background, search strategy, methods, results, discussion, and conclusion. The second was to determine the extent to which sleep architecture may reflect the severity of TBI (using an exploratory moderation analysis) – based on the hypothesis that mTBI is qualitatively different and physiologically distinct from moderate and severe mTBI [24] (i.e., that these three classifications of injury do not represent a physiological continuum). The third aim was to qualitatively assess heterogeneity between studies and set methodological guidelines so that between-study methodological and statistical variability in future work can be minimized. It is hoped that information gained from this investigation will lead to greater understanding of the relationship between TBI and sleep, and ultimately be used to help inform clinical decision-making.

Methods

Inclusion/exclusion criteria

Studies eligible for analysis met the following criteria: (a) the study examined at least two independent groups, (b) at least one group in the study consisted of individuals with a history of TBI, (c) at least one group in the study consisted of individuals without TBI, (d) sleep parameters were polysomonographically measured, and (e) studies comprised individuals over the age of 18.

Studies were excluded from the present analysis if (a) both of the aforementioned groups were not present, (b) polysomnography was not used to assess sleep, (c) the study was a review or commentary (i.e., contained no new or relevant data), (d) the investigation used only data from an animal model (i.e., contained no human data) (e) participants were drawn from a pediatric or adolescent population (i.e., <18 yr of age).

Search strategies

A search was conducted for relevant investigations using PudMed, a biomedical database of over 25 million records, and EMBASE, which includes citations from roughly 8500 journals from over 90 countries. The following query was used to find relevant articles: ((TBI OR Traumatic Brain Injury OR concussion) AND (polysomnography OR PSG OR REM sleep OR slow wave sleep OR slow wave activity OR NREM sleep OR delta sleep OR sleep microarchitecture OR sleep macrostructure OR sleep physiology OR EEG) AND (adults) NOT (Children OR Child)). The search was conducted on all available literature, not restricted by date. This search yielded 3764 articles from PubMed and 1762 from EMBASE.

Screening

Screening processes were conducted using Covidence (covidence.org), an online platform that supports meta-analysis collaboration between multiple researchers. A total of 5526 articles identified by EMBASE and PubMed were imported into the Covidence platform (Fig. 1). Two trained research assistants (SM and MT) screened the title and abstract of each publication study to determine which studies potentially met inclusion criteria. If the initial screening failed to result in consensus (i.e., a mismatch of yes/no/maybe), the final decision to include or exclude a particular study was made by one investigator (JM). Following this initial screening phase, the two research assistants (SM and MT)

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