IMPACT OF TBI ON SLEEP AND ASSOCIATED NEUROIMAGING CHANGES - *A Systematic Review* -

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- Introduction -

- Traumatic brain injury (TBI) bears a number of serious neuropsychiatric sequelae (NPS), though sleep disturbances may represent the most common with prevalence of 30-70% (Viola-Saltzman *et al.* 2016)
- Many diverse types of sleep disturbance are observed after TBI including hypersomnolence, insomnia, sleep cycle disruption, night-time awakening, and others (Ouellet *et al.* 2015)
- Sleep disruption is of particular importance among post-TBI NPS as it may interact with, exacerbate, or precipitate other NPS such as impulse dyscontrol, low mood, anxiety, and others (Freeman *et al.* 2020)
- Sleep disruption after TBI has been associated with a number of specific neuroimaging abnormalities across diverse imaging modalities; **placing these results in context of one another is critical in order to characterize neurological underpinning of this impactful NPS**

Specific Objective:

To summarize and juxtapose all extant literature describing post-TBI structural and functional brain changes associated with sleep disturbance using neuroimaging modalities, including qEEG, CT, and MRI (PSG was evaluated in a separate meta-analysis in progress)

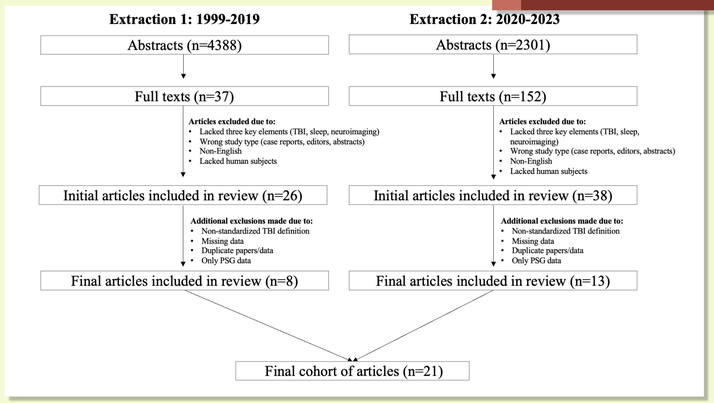
- Methods -

- A systematic search of the literature was conducted in PubMed (MEDLINE), PsycINFO, EMBASE, and Scopus databases in accordance with PRISMA guidelines for systematic reviews and meta-analyses (Page *et al.* 2021)
- ***Inclusion criteria:***
  1. Statistically analyzed the relationship between neuroimaging findings and sleep disturbance symptoms in individuals with TBI
  2. Had a clear TBI definition for participants included in the study (formalized or study-specific criteria with any combination of Glasgow Coma Scale score, loss/alteration in consciousness, and/or post-traumatic amnesia)
  3. Had a clear sleep disturbance construct (i.e., was not broadly "sleep disturbance")
- ***Exclusion criteria:***
  1. Undesirable study type (i.e., case reports/case series with n < 5, editorials, commentary letters, replies to editor, book reviews, non-peer-reviewed articles, conference proceedings, poster abstracts, dissertations)
  2. English language version unavailable
  3. No adult human subject data (<18 years)

Quality Review

- Performed using the Newcastle-Ottawa scale for observational studies
- TBI severity was evaluated as either mild, or moderate/severe using post-traumatic amnesia (PTA) where available (mild with PTA < 1 hour) or Glasgow Coma Scale (GCS ≥ 12)

- Results -



Diffusion Tensor Imaging

Study	*TBI Type*	*n (TBI)*	*n (Controls)*	*Key Findings*
Jang et al. 2016	Chronic, mild TBI	53	33	TBI participants with greater daytime sleepiness (ESS >10) had significantly lower fractional anisotropy (FA) in the hypothalamus than individuals with TBI with less daytime sleepiness and controls
Raikes et al. 2018	Subacute, mild TBI	34	18	FA in projection and association tracts (including the internal capsule, superior and anterior corona radiata, anterior and posterior thalamic radiations, and superior fronto-occipital fasciculus) was negatively associated with sleep quality (on the PSQI)
Bottari et al. 2022	Military, mild TBI (unknown chronicity)	19 (12 with PTSD)	23 (8 with PTSD)	In combat-exposed veterans with Post-Traumatic Stress Disorder and/or mild TBI (or neither), decreased FA in the right uncinate fasciculus was associated with poorer sleep quality (on the PSQI)
Muller et al. 2021	Chronic, mild TBI	40	17	In TBI+ participants, FA in the left uncinate fasciculus was negatively associated with sleepiness(on the ESS) while FA in the right cingulum was positively associated with sleepiness
Rojczyk et al. 2023	Military, mild TBI (unknown chronicity)	119 (94 with PTSD)	61 (38 with PTSD)	Whole-brain free-water corrected FA was negatively associated with sleep quality (on the PSQI) in the group with TBI and comorbid PTSD only
Mohamed et al. 2023	Military, moderate-severe TBI (unknown chronicity)	56 (33 with PTSD)	97 (53 with PTSD)	Lower FA was observed in fatigued participants with TBI and PTSD compared to non-fatigued participants with TBI and PTSD across a distributed network of tracts (including the uncinate fasciculus and other structures). No differences were observed in diffusivity measures between fatigued and non-fatigued subgroups.
Sanchez et al. 2019	Chronic, moderate-severe TBI	23	27	In TBI+ participants, fatigue (on the Fatigue Severity Scale) was significantly associated with increased axial diffusivity, sleep quality (on the PSQI) did not correlate with DTI measures. DTI measures associated with white matter damage (FA, AD, and MD) were associated with greater slow-wave power during NREM sleep in the TBI group only

Other Magnetic Resonance Imaging Findings

Study	*TBI Type*	*n (TBI)*	*n (Controls)*	*Key Findings*
Knutson et al. 2020	Military, chronic, mild TBI	28	0	Poor sleep quality (on the PSQI) was associated with weaker resting state functional connectivity between the left parahippocampal gyrus and the precuneus, cerebellum, caudate and frontal gyri
Raikes *et al.* 2021	Chronic, mild TBI	62	0	Decreased daytime sleepiness (on the ESS) was associated with pre- to post-intervention (blue light therapy) increases in gray matter volume and functional connectivity between attention and cognitive control networks and decreases in functional connectivity between visual, motor, and attention networks
Thomas *et al.* 2022	Chronic, mixed severity (mild to severe) TBI	16	16	In TBI+ participants, hippocampal and rostral anterior cingulate cerebral blood flow was negatively associated with symptoms of sleep disturbance and sleep-related impairment
Piantino *et al.* 2021	Military, chronic, mild TBI	56	0	Significant interaction observed between PSQI and number of TBIs, such that among participants with poor sleep, the effect of recurrent mild TBIs on perivascular space volume increase was greater (number of TBIs also independently associated with perivascular space number and volume)

Computed Tomography

Study	*TBI Type*	*n (TBI)*	*n (Controls)*	*Key Findings*
Fure *et al.* 2021	Subacute, mild-moderate TBI	116	0	Participants with intracranial abnormalities on CT/MRI reported decreased insomnia (on the ISI) compared to those without, although the difference lost statistical significance after controlling for prior TBI and education
Hou *et al.* 2013	Chronic, mixed severity (mild to severe) TBI	98	0	Neither presence nor location of intracerebral hemorrhage or contusion on CT was associated with the presence of sleep disorders (either insomnia or hypersomnia)
Imbach *et al.* 2015	Subacute-chronic, mixed severity (mild to severe) TBI	42	42	Individuals with intracranial hemorrhages on CT had higher total sleep duration compared to those without hemorrhages, irrespective of hemorrhage size and location
Karr *et al.* 2020	Acute, mild TBI	291	0	TBI+ participants with acute intracranial abnormalities on CT did not differ in self-reported insomnia (measured via the Checklist of Post-Concussion Symptoms) compared to TBI+ participants without intracranial abnormalities
Wickwire *et al.* 2022	Mixed severity (mild to severe) TBI (followed from 2 weeks to 1 year)	2022	0	In latent class mixed modeling of insomnia recovery course (measured by the ISI), participants with intracranial abnormality on CT had decreased odds of being placed in classes where participants had: 1) initially severe symptoms which persisted to 1 year or 2) initially severe symptoms which improved, as opposed to classes where initial insomnia symptoms were less severe

Quantitative Electroencephalogram

Study	*TBI Type*	*n (TBI)*	*n (Controls)*	*Key Findings*
Arbour *et al.* 2015	Subacute, mild TBI	34	29	TBI+ participants had increased beta power in N1, N2, N3, localized to occipital derivation
Franke *et al.* 2022	Chronic, mild-moderate, military TBI	28	0	Improvement in sleep quality (on the PSQI) with right prefrontal transcranial magnetic stimulation was not associated with delta power changes in TBI+ participants
Khoury *et al.* 2013	Subacute, mild TBI	24	18	TBI+ participants had increased beta and gamma power during N2 sleep and decreased delta power during rapid eye movement (REM) sleep
Modarres *et al.* 2016	Chronic, mild TBI	8	8	TBI+ participants had significantly higher theta:beta amplitude ratios, a greater number of EEG slow waves, and less EEG global coherence while awake
Rao *et al.* 2011	Acute, mild TBI	7	7	TBI+ participants had lower delta power and higher alpha power in N1 and higher beta power in N1 and N2
Sanchez *et al.* 2019	Chronic, moderate-severe TBI	23	27	No difference between TBI+ participants and controls in slow wave power across sleep stages, though slow wave power was associated with worse white matter damage (by FA, AD, and MD in various regions) in TBI+ group only

- Discussion -

- Post-TBI sleep disruption is associated with a diverse array of neuroimaging abnormalities detectable on structural and functional imaging
- Dysfunction of critical networks such as those involved in autonomic regulation and the reticular activating system is associated with poorer sleep quality and daytime sleepiness
- Sleep disturbance after TBI is not well predicted by presence of intracranial abnormality on CT; some studies found better initial symptoms in TBI patients with CT abnormalities
- qEEG demonstrates increased beta power in NREM and decreased delta power in REM and NREM sleep, with observable differences during wakefulness as well

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