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The bidirectional link between sleep disturbances and traumatic brain injury symptoms: A role for glymphatic dysfunction?

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Abstract

Mild traumatic brain injury (mTBI), often referred to as concussion, is a major cause of morbidity and mortality worldwide. Sleep disturbances are common after mTBI. Moreover, subjects who develop subjective sleep complaints after mTBI also report more severe somatic, mental health, and cognitive impairment and take longer to recover from mTBI sequelae. Despite many previous studies addressing the role of sleep in post-mTBI morbidity, the mechanisms linking sleep to recovery after mTBI remain poorly understood. The glymphatic system is a brain-wide network that supports fluid movement through the cerebral parenchyma and the clearance of interstitial solutes and wastes from the brain. Notably, the glymphatic system is active primarily during sleep. Clearance of cellular byproducts related to somatic, mental health, and neurodegenerative processes (e.g., amyloid-β and tau, among others) depends in part on intact glymphatic function, which becomes impaired after mTBI. In this viewpoint, we review the current knowledge regarding the association between sleep disturbances and post-mTBI symptoms. We also discuss the role of glymphatic dysfunction as a potential link between mTBI, sleep disruption, and

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post-traumatic morbidity. We outline a model where glymphatic dysfunction and sleep disruption caused by mTBI may have an additive effect on waste clearance, leading to cerebral dysfunction and impaired recovery. Finally, we review the novel techniques being developed to examine glymphatic function in humans and explore potential interventions to alter glymphatic exchange that may offer a novel therapeutic approach to those suffering from poor sleep and prolonged symptoms after mTBI.

Keywords

Glymphatic system; sleep; traumatic brain injury; perivascular spaces; Virchow Robin spaces

Introduction

Traumatic brain injury (TBI) is defined as an alteration in brain function or other evidence of brain pathology caused by an external force (1). It is estimated that 3.5 million TBI cases occur in the United States per year (2). TBI is classified as mild, moderate, or severe based on five clinical signs (Supplementary Table 1): a period of decreased consciousness, post-traumatic amnesia, alteration in mental state (i.e., confusion, disorientation, slowed thinking), neurological deficits (i.e., weakness, imbalance, change in vision, weakness, sensory loss, aphasia), or an intracranial lesion (3). Mild TBI (mTBI), often referred to as concussion, represents greater than 80% of all TBI (4). The Veterans Affairs/Department of Defense Clinical Practice Guideline for Management of Concussion defines mTBI is defined as any TBI with loss of consciousness of fewer than 30 minutes, Glasgow Coma Score between 13–15, and normal neuroimaging (3).

Sleep disturbances are commonly reported after mTBI (5). Post-mTBI sleep disturbances impair the recovery process and are associated with persistent symptoms such as memory problems, mood disturbances, anxiety, headaches, and poor quality of life (6). Moreover, post-mTBI symptoms such as headaches, depression, somatic pain, and post-traumatic stress disorder (PTSD) can further disrupt sleep, creating a vicious cycle. The mechanisms underlying this bi-directional relationship remain largely unknown.

The glymphatic system is a network of perivascular pathways along which cerebrospinal fluid (CSF) and brain interstitial fluid exchange (7, 8). Functionally connected to the recently-characterized meningeal lymphatic vascular drainage via the cisternal CSF compartment (9), glymphatic exchange along perivascular pathways plays a role in eliminating waste generated by the brain (8). Importantly, in rodents, glymphatic clearance increases during sleep and becomes impaired after moderate TBI (10, 11). Both in animal models and humans, the aberrant accumulation of cerebral waste, such as amyloid-β and tau, has been linked with neurodegeneration and cerebral dysfunction (12). Glymphatic dysfunction thus offers a potential biological mechanism for the observed association between sleep disturbances and persistence of post-mTBI symptoms.

This review discusses recent advances in our understanding of glymphatic biology and its modulation by mTBI and sleep. We also outline a potential mechanistic link between sleep disturbances, glymphatic dysfunction, and persistent symptoms following mTBI. This

review focuses on mTBI as it represents the most prevalent presentation of TBI. However, we also discuss more severe forms of TBI when information specific to mTBI is missing.

SLEEP DISTURBANCES POST-mTBI

Clinical manifestations

Disrupted sleep is observed in 30–70% of patients with TBI of all severities, and it is more frequent after mTBI (13–15). Insomnia and excessive daytime sleepiness are observed in 30–60% of individuals with TBI of all severities (15–17). Hypersomnia has been reported in approximately 30% of subjects with TBI of all severities (18). Other sleep disturbances such as sleep-related breathing disorders, circadian rhythm sleep disturbances, and parasomnias/movement disorders have also been described following TBI, regardless of severity (19–22). Patients with mTBI also show altered sleep architecture, with significantly higher periods of non-rapid eye movement (NREM) and decreased REM periods (23).

Basic mechanisms underlying sleep disturbances post-mTBI

mTBI causes a ‘neurometabolic’ cascade in animals and humans. This cascade is characterized by the release of excitotoxic molecules, increased intracellular calcium, microtubular disruption, and the release of intracellular amyloid-β and tau (24). In addition, mTBI causes impaired neurotransmitter function (25–27), alterations in cerebral autoregulation (28), disruption of the blood-brain barrier, and neuroinflammation (29). These changes can affect several areas involved in sleep initiation and maintenance, resulting in dysregulation of sleep after injury.

Hypothalamic dysregulation.—Orexin – a neuropeptide produced by the posterior lateral hypothalamus – is involved in maintaining wakefulness. Orexin-producing neurons have extensive projections to wake-promoting neuroanatomical structures. These include cholinergic and monoaminergic neurons located in other hypothalamic nuclei, the limbic system, thalamus, cortex, and spinal cord. Circadian levels of orexin correlate with wakefulness cycles (30). In animals, mTBI induces disruptions in orexin levels and orexin neuronal activity (31, 32).

Pineal gland, hypothalamus, and brainstem dysregulation.—Circadian release of melatonin by the pineal gland plays an essential role in sleep-wake cycle regulation (33). Low levels of evening melatonin are observed in humans after severe TBI (34, 35). However, melatonin supplementation did not improve sleep in these subjects (36). Damage to other sleep-promoting structures such as galanin and γ-aminobutyric acid (GABA) producing neurons in the ventrolateral preoptic nuclei and histamine-producing neurons in the mammillary bodies may play a role in sleep dysregulation post-mTBI (6). Alternatively, mTBI could induce damage to wake-inducing brainstem structures such as noradrenergic neurons in the locus coeruleus and serotonin-secreting neurons in the dorsal raphe nuclei of the midbrain.

Cerebral cortex.—In animals, extracellular glutamate in the prefrontal cortex increases during wakefulness and decreases during sleep (37). Animal models of mTBI-induced sleep

disruption have shown decreased presynaptic glutamate within nerve terminals contacting orexin neurons in the hypothalamus seven days after injury (38). Dietary supplementation with branched-chain amino acids (BCAA), a precursor to *de novo* glutamate synthesis, restores glutamate levels (38). In these animals, BCAA supplementation also restored the sleep-wake cycle (31). These findings suggest a link between post-mTBI imbalances in glutamate and mTBI-induced sleep disruption.

Relationship between post-mTBI sleep disturbances and chronic neurobehavioral symptoms

One of the main functions of sleep is posited to help restore cellular and neuronal processes. Even in the absence of injury, there is a clear relationship between lack of sleep and worsening psychomotor function, impaired judgment, and somatic disturbances such as immune dysregulation and impaired cardiovascular function (39–41). Importantly, there is a well-documented bidirectional relationship between poor sleep and mental health problems, including depression (42, 43) and anxiety (44). This relationship has also been observed in subjects with mTBI (41). Thus, sleep disturbances post-mTBI likely have outsized effects on mood regulation. In a study of 101 adults with closed-head injury, including mTBI, sleep disturbances in the acute period were associated with increased symptoms of depression, anxiety, and apathy at 12 months post-injury (45). Accordingly, treating post-mTBI sleep disturbances may have the potential to improve mental health (46).

Although the exact mechanism by which mTBI affects sleep is still unknown, there is a clear association between the presence of sleep disturbances and impaired recovery after mTBI. Mechanistically, post-mTBI sleep disturbances have been linked to impairment in brain homeostatic processes such as glutamate metabolism (47), maintenance of cerebral temperature (48), and maintenance of cerebral glycogen storage (49). In addition, post-mTBI sleep deprivation can also cause a release of pro-inflammatory cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α (50, 51). Neuroinflammation can lead to impairment of neuronal function and delayed recovery. Interestingly, animal models of mTBI suggest that pre-injury sleep deprivation may have beneficial effects (52). The physiological mechanisms underlying this association are still unknown. However, it has been postulated that sleep deprivation preceding injury generates a form of “ischemic preconditioning,” effectively reducing the impact of mTBI on brain function (53).

The relationship between sleep and post-mTBI symptoms is not linear. Worse post-mTBI symptoms are reported by those who experience too little (insomnia) or too much (increased daytime sleepiness) sleep (54). A possible explanation for this is that despite the increased sleep time, sleep architecture is disrupted in those with daytime sleepiness, thus impairing the restorative processes during sleep. Clinically, mTBI is usually followed by a period of hypersomnolence lasting approximately two weeks (55, 56). In most patients, as sleeping patterns improve, so do other post-mTBI symptoms. Those in whom sleep is not restored tend to have more protracted symptoms, including cognitive impairment, fatigue, anxiety, mood dysregulation, pain, and PTSD (6). It has been postulated that post-mTBI sleep disturbances simply reflect other symptoms such as mood disturbances or PTSD. However, studies suggest that sleep disturbances constitute an independent risk factor for poor

recovery. In a study of 374 adults with mTBI, persistent sleep disturbances were significant predictors of functional and social outcomes, independently of psychological distress (57). In a study of 92 workers with mTBI, insomnia six months post-injury was a significant determinant of disability level, independent of depression, anxiety, or pain (58). Last, adolescents with sports-related mTBI who reported sleep disruption also reported more severe symptoms during recovery (59).

GLYMPHATIC IMPAIRMENT POST-mTBI

Introduction to the glymphatic system

The glymphatic system is a brain-wide network of perivascular spaces that supports fluid movement into and through the brain parenchyma and interstitial solutes' clearance from the brain (7, 8). This perivascular fluid exchange is dependent upon the astroglial water channel aquaporin-4 (AQP4) (8, 60) and is functionally coupled to solute clearance via the meningeal lymphatic vasculature (9). Initially characterized in rodents, key features of the glymphatic system have been validated in humans. These include the occurrence of peri-arterial CSF contrast influx (61, 62), the demonstration that intrathecal contrast distribution into human brain tissue includes a convective component (63), and the more rapid clearance of interstitial solutes during sleep (64). However, a few important differences between rodent and human glimphatics have arisen. Dynamic contrast-enhanced (DCE)-MRI studies in rodents suggest that intrathecal contrast uptake peaks within 3 hours of administration, whereas analogous studies in humans demonstrate peak contrast uptake at least 24 hours after injection. On the other hand, the human brain is also predicted to be more dependent upon the convective CSF-interstitial fluid exchange of the glymphatic system, given the impact that distance has on the efficacy of diffusive (as opposed to convective) transport of solutes.

The confluence of four observations supports a role for glymphatic dysfunction as a novel mechanistic link between sleep disturbances and poor outcomes after TBI of all severities, including mTBI. First, repeated TBI, even in its milder forms, confers a risk of neurological dysfunction and neurodegeneration, as seen in histopathological studies of subjects with chronic traumatic encephalopathy (CTE) (65–67). Second, sleep dysfunction constitutes an independent risk factor for poor neurologic outcomes after mTBI, while sleep disruption in the middle to late life is associated with increased amyloid and tau pathology measures. Third, fluid movement through the glymphatic system is active primarily during sleep and is impaired by sleep deprivation (11, 60). Lastly, in rodents, glymphatic exchange is impaired after moderate TBI, leading to decreased clearance of cell byproducts such as amyloid-β and tau (10).

Role of the perivascular space in the exchange between cerebrospinal fluid and interstitial cerebral fluid.—According to the classic model, CSF is produced by the choroid plexi and circulates to the subarachnoid space. From there, CSF is reabsorbed into the venous sinuses by the arachnoid granulations. Recent evidence, however, suggests that CSF travels into the brain parenchyma along the penetrating arteries (7, 8, 62). This CSF influx occurs along the perivascular spaces, also known as the Virchow Robin spaces

(Figure 1). Similarly, fluid and solute movement through brain tissue occurs primarily along privileged anatomical pathways, including perivascular spaces and white matter tracks, eventually returning to cisternal CSF compartments housing dural sinuses. Fluid movement along perivascular spaces through brain tissue is driven by arterial pulsatility (68), and it is facilitated by the astrocytic endfeet water channel AQP4 (8, 69).

Glymphatic function is modulated by sleep and impaired post-TBI

Recent evidence shows that glymphatic exchange is significantly increased during sleep, and it is suppressed during wakefulness. In a foundational study using two-photon microscopy in mice, Xie *et al.* observed a significant increase in interstitial volume and CSF flow during anesthesia or naturally occurring sleep, compared to wakefulness (11). These observations suggest that sleep plays a vital role in removing neurotoxic waste produced during wakefulness via the glymphatic system.

In addition to being modulated by sleep, studies in animal models have demonstrated that glymphatic clearance is impaired after TBI. In rodents, moderate TBI results in loss of perivascular AQP4 polarity and glymphatic flow impairment (10). This impairment is characterized by markedly decreased CSF flow into the brain parenchyma and clearance of interstitial solutes and cell byproducts such as tau, starting 1-hour post-injury and persisting for up to 28 days (10, 70). Additional data in rodents show that, in addition to tau, other TBI biomarkers such as glial fibrillary acidic protein, S100B, and neuron-specific enolase are also cleared from the brain parenchyma through the glymphatic system. Genetic deletion of AQP4 results in decreased plasma levels of these biomarkers following TBI (71).

Glymphatic disruption, sleep disturbances, and persistent neurobehavioral symptoms post-mTBI

Glymphatic dysfunction may link mTBI and neurobehavioral symptoms by two distinct mechanisms. First, loss of perivascular AQP4 in the post-mTBI brain may *directly* slow cellular waste clearance from the interstitial space. Second, mTBI may *indirectly* reduce sleep-active glymphatic function by disrupting sleep phases in which glymphatic exchange is most active. Thus, by reducing both the opportunity for sleep-active glymphatic exchange and by reducing the efficacy of glymphatic function that does occur, mTBI may promote the accumulation of cellular waste, neuropeptides, and inflammatory mediators in the interstitial compartment, promoting neuronal dysfunction and propagation/persistence of symptoms (Figure 2). In order to illustrate our point, we will draw from examples of two clinical entities: post-concussive headaches (PCH) and post-traumatic dementia (including Alzheimer's disease and chronic traumatic encephalopathy or CTE). PCH may develop after a single episode of mTBI, whereas post-traumatic dementia and CTE are associated with repeated exposure to mTBI. Both these entities are closely related to and have implications for other potential processes that may lead to mTBI-associated changes in mental health. Chronic migraines have been associated with depression, anxiety, post-traumatic stress disorder, panic disorder, and bipolar disorder (72, 73). Individuals with dementia experience higher rates of depression, anxiety, and post-traumatic stress disorder (74). Chronic traumatic encephalopathy (CTE), in particular, is characterized by early and

profound changes in mental health, including mood swings, anxiety, impulse control, and depression; these symptoms can occur well before cognitive symptoms (75).

Glymphatic dysfunction and risk of PCH.—Headaches, particularly of the migrainous type, are common in the acute phase following mTBI and persist for at least one year after injury in 18–58% of mTBI patients (76). Even in the absence of TBI, sleep disturbances and headaches still share close clinical associations. Sleep disturbances are common headache triggers (77, 78). Conversely, sleep is a widely reported migraine abortive. This relationship between sleep disruption and headaches is observed in subjects following mTBI as well. However, whether sleep disturbances following mTBI contribute directly to PCH development or whether these two processes result from a common upstream mechanistic driver dysfunction is unknown. The release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP), by perivascular trigeminal afferents and central efferent projections, is proposed to underlie the vasodilation and pain associated with migraine (79). The trigeminal afferents innervating the leptomeningeal vasculature are located within the perivascular spaces comprising the glymphatic pathway. Cortical spreading depolarization, the proposed neurophysiological basis for migraine aura, occurs following mTBI and causes CGRP release. Once released, the route along which CGRP is cleared from the perivascular compartment to the blood has not yet been defined. Presumably unable to cross the blood-brain barrier, the clearance of CGRP and other trigeminal neuropeptides from these perivascular compartments are likely dependent upon glymphatic exchange. Glymphatic impairment caused directly by mTBI and indirectly by post-mTBI sleep disturbances may impair CGRP clearance, propagating PCH.

Glymphatic dysfunction and post-mTBI vulnerability to neurodegenerative disease.—Multiple studies have linked severe TBI to neurodegenerative diseases, including Alzheimer's disease (80, 81). Currently, mTBI is a less established predictor of cognitive decline and neurodegeneration than severe TBI (82). Studies linking mTBI to neurodegenerative processes are limited by referral bias, challenges quantifying single versus repeated mTBI exposure, and potential confounding (83). Despite these limitations, evidence suggests a link between mTBI exposure, cognitive decline, and neurodegeneration (84–86). Recent studies have linked sleep disturbances with Alzheimer's disease, even in the absence of mTBI (87–90). However, the mechanisms underlying these associations remain unknown. Both Alzheimer's disease and CTE are linked to abnormal deposition of cellular byproducts in the brain. In Alzheimer's disease, there is an abnormal deposition of amyloid-β in the cortex (91). In CTE, the pathognomonic feature is *perivascular* deposit of tau, starting in the cortical surface of the temporal lobes and extending to the rest of the cortex (65–67). mTBI results in axonal damage and release of intracellular amyloid-β and tau present in microtubules (24). It has been postulated that excess interstitial tau leads to cellular uptake and formation of fibrillary aggregates, resulting in intracellular tangles (92). In rodents, moderate TBI caused impaired clearance of both amyloid-β and tau by the glymphatic system (10). Sleep disturbances may, in turn, aggravate this impairment, promoting the aggregation of these proteins and the ensuing neuronal dysfunction. Thus it is plausible that a cumulative effect of mTBI and poor sleep could increase the risk of future neurodegenerative diseases. Supporting this hypothesis, recent studies in humans with

mTBI show that poor sleepers have elevated serum levels of neurofilament light, a marker of neurodegeneration, and lower cognitive function compared to mTBI good sleepers and controls (93).

Measurement of glymphatic function in humans

Glymphatic function in rodents is evaluated using dynamic imaging of contrast exchange from the CSF to the brain interstitial compartment, including by DCE-MRI following intrathecal gadolinium-based contrast agent injection (7, 8). Measuring glymphatic function in humans has been more challenging. Recent techniques to assess human glymphatic function include the use of contrast agents to trace CSF flow, the measurement of perivascular spaces, and CSF flow measurements with functional MRI.

Measurements of glymphatic flow with gadolinium-based contrast agents.—A series of seminal studies by Ringstad, Eide, and colleagues have shown that in healthy individuals, a gadolinium-based CSF tracer injected intrathecally penetrates the brain parenchyma from the subarachnoid space to the deep brain regions and drains into the cervical lymph nodes (62, 94, 95). The tracer's clearance is delayed in certain disorders associated with glymphatic dysfunction, such as idiopathic normal pressure hydrocephalus (62). These techniques, however, are invasive and not feasible for widespread clinical use. Using intravenous gadolinium-based contrast, investigators have shown time-dependent enhancement of the basal ganglia perivascular spaces (96), subarachnoid peri-arterial spaces, and meningeal lymphatic vessels (97). An additional study found time-dependent gadolinium clearance in subjects with white matter hyperintensities (found in cerebral small vessel disease) which suggest impaired glymphatic clearance (98). Although the leakage of contrast into the perivascular space in subjects with an intact blood-brain barrier is minimal, the use of intravenous contrast agents is less invasive and represents a promising method for studying glymphatic flow in healthy and diseased subjects.

Visualization of perivascular spaces and CSF flow.—Previously considered a normal neuroradiologic variant (99), MRI-visible perivascular spaces (PVS) are seen across the lifespan (100–102) and are increasingly considered a putative marker of glymphatic pathway impairment. Higher PVS burden is seen in conditions associated with glymphatic function impairment, such as Alzheimer's, cerebral small vessel disease, cerebral amyloid angiopathy, and multiple sclerosis (103–106). Dilation of these spaces is observed in patients with mTBI (107, 108). In a study of 38 veterans, Opel *et al.* found a relation between PVS burden and decreased total sleep time, but only in those with a history of mTBI (109). In a more recent study of 56 Iraq/Afghanistan veterans, Piantino *et al.* found a correlation between the number of mTBI sustained in the military and PVS burden (110). Moreover, PVS burden was further increased in those who, in addition to mTBI, also reported poor sleep (Figure 2). These findings suggest an interaction between mTBI and poor sleep on PVS burden. It has been hypothesized that translocation of AQP4 following mTBI leads to impaired CSF flow out of the PVS, thus causing a volume expansion (110). In addition to structural measurements of PVS, other methods to assess glymphatic flow have been proposed. Using simultaneous measurements of blood oxygen level-dependent (BOLD) functional MRI, electroencephalography (EEG), and CSF flow in healthy individuals, Fultz

et al. observed that during sleep, the brain exhibits waves of CSF flow on a macroscopic scale, which are coupled with hemodynamic and neural activity (111). Although a direct correlation between these CSF waves and glymphatic flow has not been established, these intriguing findings offer a glimpse at the interaction between sleep, neural activity, CSF flow, and cerebral hemodynamics.

Targeting glymphatics

The evidence suggesting impairment of glymphatic flow as an important factor in post-mTBI morbidity has led to the hypothesis that increasing glymphatic function, either pharmacologically or otherwise, could lead to clinical improvement of post-mTBI neurobehavioral symptoms.

Sleep-wake regulation of glymphatic exchange is mediated in part through central noradrenergic tone. In rodents, dexmedetomidine and xylazine (alpha-2 noradrenergic autoreceptor agonists) cause a reduction in central noradrenergic output and increase glymphatic flow (112, 113). In a study of 63 Veterans with a history of mTBI and post-traumatic headaches, Ruff and colleagues reported that a combined treatment approach including sleep hygiene and the centrally active α1 adrenergic antagonist prazosin markedly reduced both headache pain intensity and frequency, both after the 9-week treatment period and six months following initiation of treatment (114). Prazosin has also been used to treat sleep disturbances and nightmares associated with PTSD, but its treatment efficacy is still unclear (115).

Other non-pharmacological treatments have been proposed, including adjusting body posture (116) and modulation of respiration and other integrative health approaches (117), although these approaches are still in the early validation stages.

Challenges and future directions

Studies using DCE-MRI in the human brain have begun to corroborate animal data. However, rodent and human glymphatics may differ, and key preclinical findings still need to be replicated in human populations. First, we must define whether glymphatic function is more rapid in sleeping than the waking human brain and whether glymphatic function is slowed in humans following mTBI. Similarly, although glymphatic dysfunction promotes the development of amyloid-β and tau pathology in both the aging and the post-traumatic rodent brain, we must determine whether glymphatic dysfunction promotes the pathology underlying neurodegenerative conditions such as Alzheimer's or CTE in human populations. Furthermore, we must investigate whether glymphatic dysfunction represents a mechanism underlying other common sequelae of mTBI, such as headaches and depression.

Central to all of these issues is developing non-invasive approaches to assess glymphatic pathway function in humans. DCE-MRI requires the injection of intrathecal contrasts, and therefore it is not feasible for large studies. In addition, intravenous contrast requires blood-brain barrier breakdown to access the brain parenchyma (97), and therefore it may also have limited use. Recently, several contrast-free MRI sequences have been used to capture different elements of glymphatic biology, including trans-endothelial water exchange, perivascular diffusion, and MRI encephalography (118). However, none of these

non-invasive approaches have been validated against the gold-standard DCE-MRI approach to measuring perivascular CSF-interstitial fluid exchange. Despite promising preliminary data, the role of MRI-visible perivascular spaces as markers of glymphatic function remains hypothetical. Studies comparing PVS morphology to intrathecal contrast clearance (through DCE-MRI) in different disease stages may provide crucial validation of PVS as a non-invasive, putative marker of glymphatic dysfunction.

The majority of TBI in humans is mild. However, preclinical experiments of post-injury glymphatic dysfunction utilized a moderate TBI model. Replicating these findings in mTBI models may help move the field forward. Last, preclinical models may offer an alternative way to study the role of PVS in glymphatic function. Using two-photon microscopy in a mouse or migraine, Schain et al. have demonstrated rapid and nearly complete PVS closure minutes following cortical spreading depolarization, an electrical phenomenon observed during migraine auras (119). These findings suggest that PVS morphology is dynamic and that two-photon microscopy can be utilized in other preclinical disease models such as mTBI.

Conclusion

In conclusion, sleep disturbances are prevalent following mTBI and directly exacerbate neurobehavioral symptoms, including mood, anxiety, and chronic headaches. We propose a mechanistic model in which impairment of perivascular glymphatic exchange explains the bi-directional relationships between mTBI, sleep, and post-mTBI symptoms. Although evidence supporting this model is emerging, this remains a theoretical framework. The validation of non-invasive measurement of glymphatic function will allow us to delineate the role of glymphatic impairment in post-mTBI morbidity. In turn, modulation of sleep-active glymphatic exchange may emerge as a valuable therapeutic target for preventing and treating post-traumatic dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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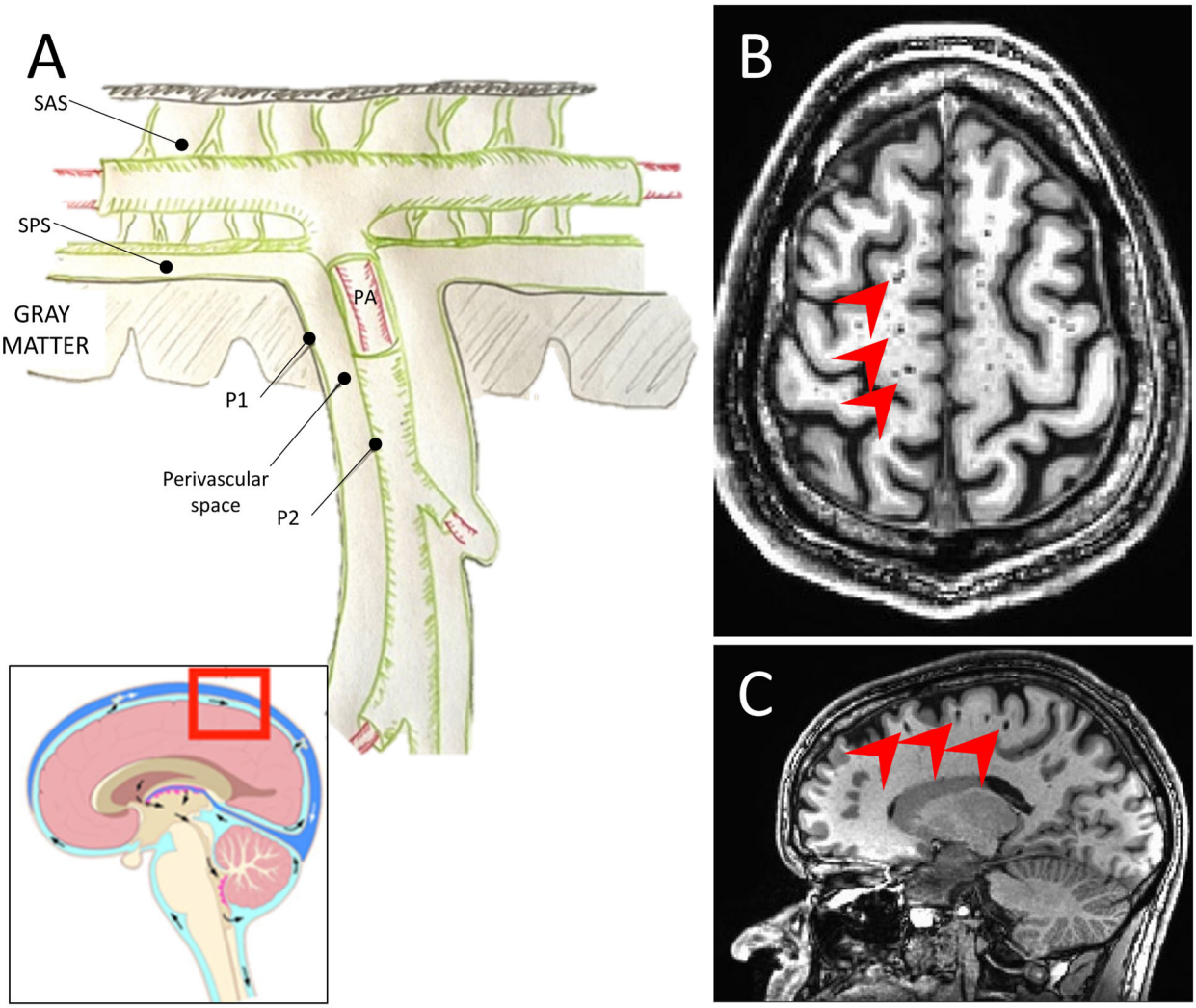

Figure 1.

Schematic representation of the perivascular space (A). The pia mater separates the subarachnoid space (SAS) from the subpial space (SPS). The perivascular space (PVS) surrounds penetrating arteries (PA) as they enter the brain parenchyma. The PVS is lined on the inside by a layer of pia mater surrounding the artery (P1) and on the outside by a layer of pia matter in contact with the brain parenchyma (P2). T1-weighted MRI, axial (B), and sagittal (C) views, showing MRI-visible PVS (red arrowheads).

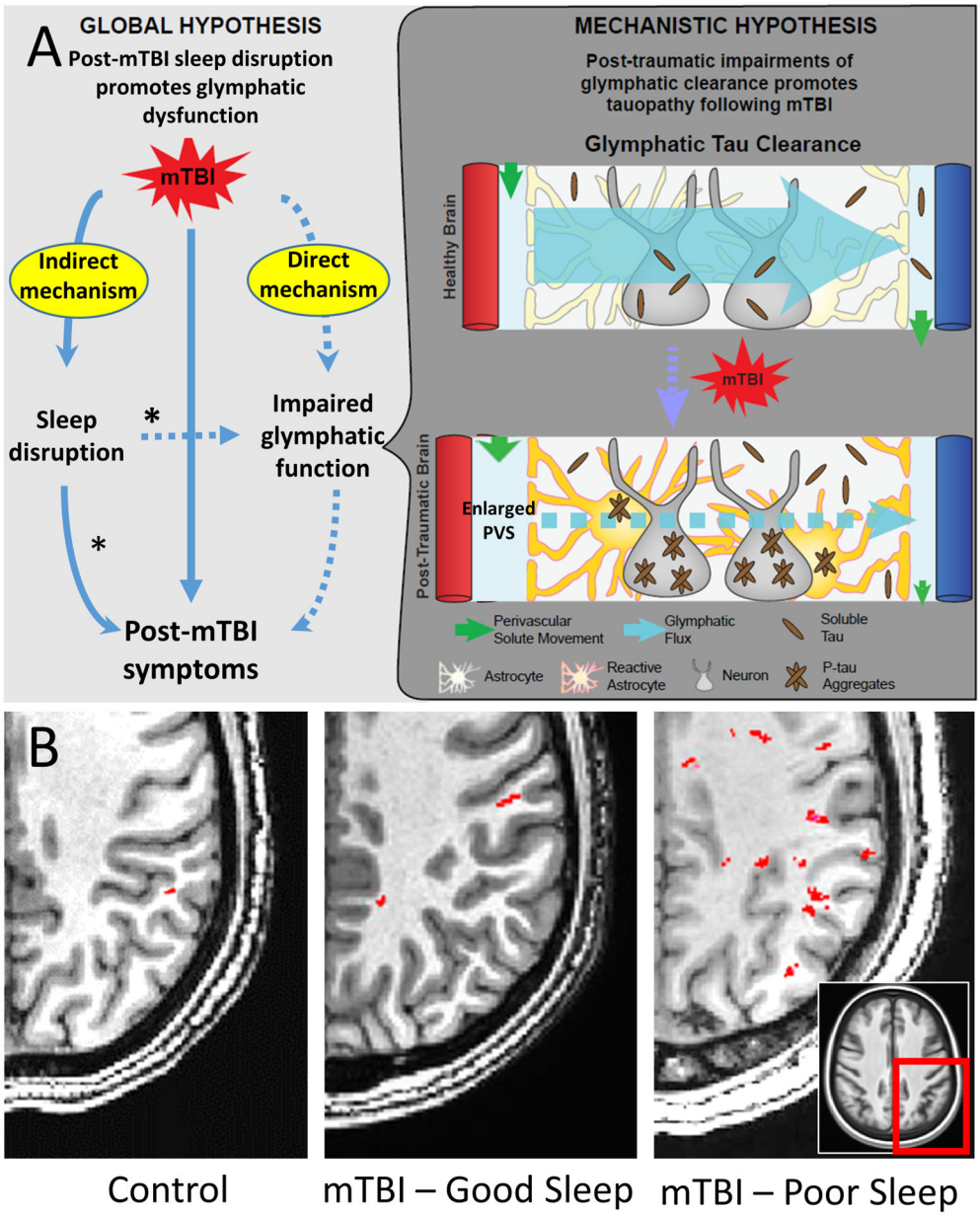

Figure 2.

Top panel (A): a proposed mechanism integrating glymphatic dysfunction, sleep disruption, and post-mTBI symptoms. The asterisks (*) indicate potential mechanisms by which improving sleep may improve recovery after mTBI. Bottom panel (B): Effect of mTBI and poor sleep on perivascular space burden. Axial T_1-weighted image slices, one cm-thick, through the posterior quadrant of the centrum semiovale (box) in a control subject with no history of mTBI and good seep, a subject with mTBI and good sleep, and a subject with mTBI and poor sleep. Perivascular spaces (PVS, in red) were identified with a semi-automated detection algorithm (100, 120, 121). Note the increased number of PVS in the posterior region in subject C.

mTBI: mild traumatic brain injury.

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