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Review

Sleep disruption and the sequelae associated with traumatic brain injury

Brandon P. Lucke-Wold[b,c,1], Kelly E. Smith[a,b,1], Linda Nguyen[a,b], Ryan C. Turner[b,c], Aric F. Logsdon[a,b], Garrett J. Jackson[c], Jason D. Huber[a,b], Charles L. Rosen[b,c], Diane B. Miller[b,d,*]

[a] Department of Basic Pharmaceutical Sciences, West Virginia University School of Pharmacy, Morgantown, WV 26506, USA
[b] The Center for Neuroscience, West Virginia University School of Medicine, Morgantown, WV 26506, USA
[c] Department of Neurosurgery, West Virginia University School of Medicine, Morgantown, WV 26506, USA
[d] Centers for Disease Control and Prevention-National Institute for Occupational Safety and Health, Morgantown, WV, USA

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ABSTRACT

Sleep disruption, which includes a loss of sleep as well as poor quality fragmented sleep, frequently follows traumatic brain injury (TBI) impacting a large number of patients each year in the United States. Fragmented and/or disrupted sleep can worsen neuropsychiatric, behavioral, and physical symptoms of TBI. Additionally, sleep disruption impairs recovery and can lead to cognitive decline. The most common sleep disruption following TBI is insomnia, which is difficulty staying asleep. The consequences of disrupted sleep following injury range from deranged metabolomics and blood brain barrier compromise to altered neuroplasticity and degeneration. There are several theories for why sleep is necessary (e.g., glymphatic clearance and metabolic regulation) and these may help explain how sleep disruption contributes to degeneration within the brain. Experimental data indicate disrupted sleep allows hyperphosphorylated tau and amyloid β plaques to accumulate. As sleep disruption may act as a cellular stressor, target areas warranting further scientific investigation include the increase in endoplasmic reticulum and oxidative stress following acute periods of sleep deprivation. Potential treatment options for restoring the normal sleep cycle include melatonin derivatives and cognitive behavioral therapy.

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* Corresponding author at: CDC-NIOSH, Morgantown, WV 26505-2888, USA. Tel.: +1 304 285 6121.
E-mail address: dum6@cdc.gov (D.B. Miller).
[1] Equal contribution for authorship.

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1. Introduction

Seven million traumatic brain injuries (TBIs) occur each year in the United States. Motor vehicle collisions, which can cause concussions, account for ~45% of exposure (Scholten et al., 2014). Additionally, blast TBI has been classified as the 'signature injury' of modern warfare (Goldstein et al., 2012). The upsurge in TBI has prompted a renewed interest by the lay and scientific communities in the chronic sequelae that follows these injuries. One of the most common sequelae in patients exposed to TBI is disrupted sleep, which is especially common following mild TBI (Stocker et al., 2014). By definition, mild TBI involves a loss of consciousness less than 30 min and no skull fracture; moderate TBI a loss of consciousness between 30 min and 24 h, with or without skull fracture; and severe TBI a loss of consciousness greater than 24 h, with contusion, hematoma, or skull fracture. A concussion may occur with or without a loss of consciousness and falls under the category of a mild TBI. Exposure to blast, on the other hand, can also produce moderate and severe TBI.

The factors contributing to sleep disruption in TBI include damage to brain areas controlling the circadian rhythm, an increase in intracranial pressure that causes changes to the parasympathetic nervous system, and alterations in vascular tone. In addition, disrupted sleep often manifests with neuropsychiatric symptoms such as cognitive deficits, depression, disorientation, and anxiety (Farinde, 2014). These sleep and neuropsychiatric changes can develop independently or as part of several chronic neurodegenerative diseases such as Alzheimer's disease (AD), chronic traumatic encephalopathy (CTE), and Parkinson's disease instigated by TBI (Cipriani et al., 2014; Goetz and Pal, 2014). Little is known about the etiology of TBI-induced sleep disturbance and emotional labiality, but the growing awareness of sleep disorders in TBI patients warrants further investigation. Moreover, the change in sleep patterns and other symptoms following the different mechanisms of brain injury may be distinct. In this review, we focus on mild TBI, as the literature suggests sleep disruption is most often associated with this form of TBI. We discuss in particular sleep disruption from maintenance insomnia as a result of mild TBI, neuropsychiatric (including cognitive, emotional, and behavioral dysfunctions) and physical symptoms of TBI, and how sleep disturbances may affect the other post-TBI symptoms. Finally, we propose potential mechanisms of brain damage following TBI that may lead to sleep dysfunction. Areas of particular interest include changes in brain metabolomics, changes in vascular flow, alterations in neurogenesis, and progression to neurodegeneration.

2. Sleep and TBI

Sleep is believed to be necessary for recovery following TBI. Sleep disturbance can lead to cognitive deficits and poor overall functioning (Duclos et al., 2014). In the following section, we discuss types of sleep disturbance and what is known from clinical studies.

2.1. Types of sleep disturbances

Sleep fragmentation, defined as a slightly reduced amount of sleep with not much slow wave activity, is the most common sleep disorder immediately following injury with increased night terrors at later time points (Macera et al., 2013). Moreover, mild TBI has long been recognized to cause sleep-wake disturbances and excessive daytime sleepiness, but the precise mechanisms behind these changes remain unclear (Verma et al., 2007). Numerous clinical studies have identified increases in excessive daytime sleepiness in 25–50% of patients, with up to half of those patients experiencing severe hypersomnia (Baumann et al., 2007; Masel et al., 2001). The increase in daytime somnolence may be associated with impaired daily function, mood changes, and alterations in circadian rhythms (Verma et al., 2007), and explained by decreased sleep efficiency and increased waking after sleep onset, maintenance insomnia, in those experiencing TBI (Shekleton et al., 2010). Sleep efficiency is the percentage of time spent sleeping during the scheduled sleep period.

In an attempt to more thoroughly explore the relationship of sleep disturbances to TBI in a controlled environment, numerous investigators have employed preclinical rodent models. In one study, injured rodents had shortened wake bouts during the normal period of activity (dark phase), indicating that injury produced wake fragmentation (Skopin et al., 2014). These changes were accompanied by a decrease in orexin-A-positive neurons–neurons important for arousal. The decrease may represent a down-regulation of orexin-A or an actual loss of the neurons. Another study by Petraglia and colleagues found that both single and repeat injury were associated with an increase in wake time and a concomitant reduction in non-rapid eye movement (NREM) sleep (Petraglia et al., 2014). Similarly, repetitive TBI was also associated with NREM sleep fragmentation, affecting both the number and length of fragmentation episodes (Petraglia et al., 2014).

Mild TBI rather than severe TBI is most commonly associated with sleep disturbances (Mahmood et al., 2004; Pillar et al., 2003). Maintenance insomnia is the most commonly reported sleep disturbance and is associated with milder TBI, higher levels of fatigue, depression, and pain (Ouellet et al., 2004). Insufficient pain management is a primary contributor to increased insomnia in patients with mild TBI (Lavigne et al., 2015). Mild TBI is also often repetitive, which increases the likelihood for insomnia (Jain et al., 2014). In a survey of 452 individuals with TBI, 50.2% reported insomnia symptoms and 29.4% fulfilled the DSM-IV diagnostic criteria for an insomnia syndrome (Ouellet et al., 2006). Of those who fulfilled the criteria, their insomnia was reported as severe and was left untreated in nearly 60% of the cases. In other studies sleep deprivation, defined as loss of hours of sleep, is reported 30–80% of the time after mild TBI (Clinchot et al., 1998; Fichtenberg et al., 2002; Ouellet et al., 2006; Parcell et al., 2006). These symptoms may persist for months to years and have been demonstrated by self-report (Cohen et al., 1992) as well as by polysomnography and actigraphy monitoring 3 years after injury (Kaufman et al., 2001). Other sleep disturbances such as sleep apnea, narcolepsy, and periodic limb movements are associated with TBI but are not the focus of this review (Castriotta et al., 2007; Verma et al., 2007).

Objective findings of sleep disturbance following TBI include frequent nighttime awakenings (Kaufman et al., 2001), higher proportions of stage 1 sleep (Ouellet and Morin, 2006) and stage 2 sleep (Schreiber et al., 2008), decreased percentage of rapid eye movement (REM) sleep (Parcell et al., 2008), and shorter REM sleep

latencies (Ouellet and Morin, 2006). Overall individuals with sleep disturbance after TBI have been found to have lower efficiency of sleep than matched controls (Kaufman et al., 2001). Disruption in circadian rhythm is found in 7–10% of individuals who initially report insomnia although this disruption may go unrecognized by patients and clinicians alike (Weitzman et al., 1981). Circadian rhythm sleep disorders, defined as a disruption in the normal 24-hour cycle of physiological processes, are associated with alterations in body temperature and melatonin secretion rhythms (Shibui et al., 1999; Uchiyama et al., 2000). In a recent case report, TBI has been shown to have an association with circadian rhythm sleep disorders (Quinto et al., 2000) and there is emerging evidence that it may contribute to their onset (Ayalon et al., 2007).

3. Neuropsychiatric and physical symptoms of TBI

TBI can result in substantive cognitive, emotional and behavioral disorders (Arciniegas et al., 2000; Rao and Lyketsos, 2000), all of which are associated with increased morbidity (Arciniegas et al., 2000). Along with the cognitive or behavioral symptoms, some physical symptoms that may arise following TBI include headache, lightheadedness, tinnitus, dizziness, blurred vision, fatigue, and muscle or joint pain (MacGregor et al., 2013). We highlight some of these changes associated with mild TBI below.

3.1. Effect of TBI on cognition

Cognitive impairment represents one of the primary deficits associated not only with acute TBI but also chronic disease following TBI, including AD and CTE (Tateno et al., 2014). In fact, cognitive abilities are impaired in nearly all individuals with a history of TBI (Rao and Lyketsos, 2000). Evidence indicates that cognitive deficits following TBI may be influenced by the severity of TBI, as they have been related to the degree of axonal injury, the presence and duration of loss of consciousness, post-traumatic amnesia, and the degree of brainstem injury (Rao and Lyketsos, 2000). In cases of mild TBI, the cognitive deficits may include but are not limited to disruptions in attention, concentration, memory, language, and even arousal/alertness (Lux, 2007; Rao and Lyketsos, 2000). The emergence of cognitive deficits is also largely brain area dependent, with frontal injury being associated with impairments of executive functioning (Lux, 2007), which affects a number of functions required for everyday survival including goal selection, anticipation, initiation, planning, sequencing, self-correction, and error-detection. Additionally, a lack of awareness and subsequent diminished insight is typically seen in those with moderate injuries affecting the frontal lobe (Lux, 2007).

3.2. Effect of TBI on behavior and mood

Behavioral and mood disturbances are also commonplace after TBI, and are likely related to disruption or damage to monoaminergic pathways important for regulating emotion and behavior (Jorge and Robinson, 2003; Lux, 2007). These disturbances range from depression to affective lability, irritability, anxiety, and psychosis, with depression occurring the most often post-TBI (Bailey et al., 2014). The incidence of reported cases of depression in this population ranges between 10 and 77% (Alderfer et al., 2005; Malkesman et al., 2013; Rogers and Read, 2007; van Reekum et al., 2000). This varied incidence range may be due to differences in diagnostic criteria, time post-injury when the diagnosis of depression is made, and differences in the mechanism of injury (Alderfer et al., 2005; Malkesman et al., 2013). Depression post-injury is especially prominent in female patients as well as those who are younger and who have a history of prior mental health treatment, substance abuse, or a self-inflicted injury (Hart et al., 2011; Valk-Kleibeuker et al., 2014). While the rate and risk of developing depression is highest in the year immediately following injury, the risk continues to remain elevated above baseline for many years (Holsinger et al., 2002; Jorge et al., 1993; Malkesman et al., 2013). Symptoms associated with depression include feelings of loss, demoralization, discouragement, dysphoria, fatigue, irritability, anhedonia, disinterest, insomnia, general apathy, and suicidal ideation (Hinkeldey and Corrigan, 1990; Malkesman et al., 2013; Rao and Lyketsos, 2000; van Zomeren and van den Burg, 1985). Suicidal ideation and suicidal attempts clearly represent the most severe form of depression. The number of suicidal attempts is elevated post-TBI with rates 2.7–4 times higher than that of the general population. This is particularly true amongst veterans; especially those who underwent repeated deployment (Burns et al., 1994; Malkesman et al., 2013; Mann et al., 1999; Persinger, 1994; Simpson and Tate, 2002; Teasdale and Engberg, 2001).

Along with depression, TBI is also associated with the development of an array of anxiety-related disorders, including generalized anxiety disorder, post-traumatic stress disorder (PTSD) and obsessive–compulsive disorder. Much like depression, the true incidence of anxiety post-TBI is unclear with reports ranging from 11 to 70% (Klonoff, 1971; Rao and Lyketsos, 2000). The most common anxiety phenotype exhibited, termed generalized 'free-floating' anxiety, consists of persistent worry accompanied by stress and fearfulness (Lewis and Rosenberg, 1990; Rao and Lyketsos, 2000). In addition, patients sustaining mild TBI are more likely to develop anxiety-based disorders than those with moderate or severe injury (Mallya et al., 2014).

Least well studied of the disorders associated with TBI are the psychotic disorders. 0.7–9.8% of TBI patients develop schizophrenic-like psychosis, despite little or no family history (AbdelMalik et al., 2003). Additionally, prior head injury has been identified in nearly 15% of patients diagnosed with schizophrenia, providing further evidence of a potential relationship or correlation (Nasrallah et al., 1981). Psychotic symptoms associated with TBI are wide ranging and all encompassing with reports of delusions, hallucinations, illogical thinking, agitation, ideas of reference, grimacing, regression, and impulsive aggressiveness (Brown et al., 1981; Thomsen, 1984). Unipolar mania and classical bipolar disorder have also been observed post-injury but these reports were in the form of case series or reports without large studies being conducted (Bakchine et al., 1989; Lux, 2007; Pope et al., 1988).

3.3. Anatomic site of TBI-induced damage influences deficits

The location of TBI damage is generally believed to be of critical importance to the genesis of neuropsychiatric symptoms mentioned above. For example, damage to the dorsolateral prefrontal convexity has been associated with cognitive executive disorders whereas behavioral disorders are generally associated with orbital frontal and ventromedial damage (Grafman et al., 1996; Lux, 2007). In patients with reported episodic dyscontrol syndromes or intermittent explosive disorder, damage is frequently observed within the temporal lobes (Grafman et al., 1996; Lux, 2007). Mood-related symptoms, such as depression, may be related to disruption of monoaminergic pathways passing through the basal ganglia and/or frontal-subcortical white matter (Rao and Lyketsos, 2000; Starkstein et al., 1987). The probability of developing major depressive disorder is highest in those with left dorsolateral frontal and left basal ganglia lesions (Fedoroff et al., 1992; Rao and Lyketsos, 2000). Apathy, often associated with depression, may be due to mesial frontal lobe damage (Duffy and Campbell, 1994; Rao and Lyketsos, 2000). Post-TBI anxiety on the other hand is the result of disruption of similar monoaminergic pathways but is confounded by inhibition of GABA networks (Paul, 1988). Notably, right-sided

lesions tend to be associated with anxiety more so than left-sided lesions (Jorge et al., 1993; Rao and Lyketsos, 2000).

3.4. Physical manifestations of TBI

Headache appears to be the most common symptom reported following mild TBI, though the prevalence has ranged from 30 to 90% in retrospective studies with around 20% lasting more than a year (Theeler et al., 2013). Moreover, Hoge and colleagues reported that after adjustment for PTSD and depression, headache was the only post-injury symptom significantly associated with mild TBI among 2525 US infantry soldiers (Hoge et al., 2008). Though the data are limited, a few human studies have assessed changes in vagal activity after TBI in the acute phase. The increase in parasympathetic activity as a result of an increased intracranial pressure (Kox et al., 2008) and/or activation of the pulmonary vagal reflex (Cernak and Noble-Haeusslein, 2010) may cause the reduction in heart rate (bradycardia) and dilation of peripheral blood vessels (hypotension) observed immediately after injury. Endocrine abnormalities such as growth hormone deficiency, hypothyroidism, and adrenal insufficiency are also common with insomnia following TBI (Englander et al., 2010). Some of these physical manifestations due to endocrine changes may be temporary and completely dissipate within days or weeks, while others may continue on for a year or more after the brain injury (Masel and DeWitt, 2010). Whether these mechanisms persist regardless of injury mechanism, location, and severity as well as their relationship to the sleep disturbances caused by TBI remains to be determined.

4. Sleep and symptoms

Sleep disturbance may exacerbate these other symptoms of TBI, impede the rehabilitation process, and limit the ability to return to work leading to poor occupational outcomes (Cohen et al., 1992; Ouellet and Morin, 2004). In the following sections we discuss how sleep affects neuropsychiatric and physical symptoms. In the final section, we address potential treatment options for patients with sleep disturbance.

4.1. Effect of sleep on neuropsychiatric symptoms of TBI

While the role of sleep has been widely accepted for years in the maintenance of the brain, recent evidence suggests that reduced or inadequate sleep impairs cognition and mood. Sleep disorders are especially common in patients with neurodegeneration, such as Alzheimer's disease (Villa et al., 2015). Emerging evidence implicates sleep in the most basic of neurological functions, namely the exchange of metabolic wastes associated with neurological homeostasis. Specifically, the Nedergaard laboratory has demonstrated that sleep is integral in the function of the glymphatic system. The glymphatic system functions in waste clearance and acts as the lymphatic complex of the brain. Natural sleep or anesthesia accounts for an increase in interstitial space that facilitates the subsequent exchange of cerebrospinal fluid (CSF) with interstitial fluid. This system works to increase the clearance of metabolic waste products and accumulated proteins through the process of sleep (Xie et al., 2013). Nedergaard and colleagues also showed that disruption of this system following TBI could lead to accumulated tau in their mouse model. This finding may explain the heightened risk of AD and CTE in those with a history of neurotrauma (Iliff et al., 2014). Orexin levels are also increased following sleep disruption, which contributes to cognitive decline (Malkki, 2014).

4.2. Relationship of sleep and physical manifestations of TBI

Sleep disturbance from mild TBI may exacerbate a number of the physical health symptoms. Several studies have cited post-traumatic headache and other pain complaints as important factors affecting sleep in mild TBI (Beetar et al., 1996; Chaput et al., 2009; Hou et al., 2013). In a study that surveyed patients in the first six weeks post-injury, those with subjective sleep complaints were 3 times more likely to develop concomitant headaches (Chaput et al., 2009). In a separate study involving patients surveyed at a long-term follow up (an average of 33 months since injury), a significant association was also observed between headache and/or dizziness and the presence of insomnia in TBI patients (Hou et al., 2013). Of note, a recent study by Khoury and colleagues found that pain affected the sleep parameters in mild TBI patients (Khoury et al., 2013). They found that mild TBI patients with pain showed an increase in rapid EEG frequency bands mostly during REM and slow-wave sleep (alpha intrusion) compared to mild TBI patients without pain and controls, suggesting pain may be a critical factor in inducing or causing poor sleep in this population (Khoury et al., 2013).

4.3. Treatment options available for treating sleep disorders

There are several psychiatric and pharmacologic treatment options available for treatment of sleep disturbance after TBI. Cognitive behavioral therapy (CBT) has been used in treatment of insomnia, but there are few reports specifically addressing individuals with TBI. CBT was used in a small study of 11 individuals with TBI and insomnia 8 weeks after injury. The techniques included stimulus control, sleep restriction, cognitive restructuring, sleep hygiene education, and fatigue management. With these techniques there was a 54% reduction in total wake time and average sleep efficiency improved from 77.2 to 90.9% at 3-month follow-up across participants compared to a control group. Improvement in sleep was accompanied by reduction in fatigue symptoms (Ouellet and Morin, 2007). Given the association of TBI with disruptions in circadian rhythms, another potential treatment modality to improve sleep consolidation (memory storage during sleep) is light therapy (Ouellet and Morin, 2004). Regarding pharmaceutical treatments, one approach is to use melatonin-like compounds. Melatonin is an endogenous neurohormone agent synthesized in the pineal gland and is involved in maintenance of circadian rhythms. Levels of melatonin are reduced in individuals who have suffered TBI (Paparrigopoulos et al., 2006). Synthetic melatonin can have anti-oxidant and anti-inflammation properties (Naseem and Parvez, 2014). It has also been shown to be anti-apoptotic and reduce calcium influx in a rat model of TBI (Yuruker et al., 2015). Ramelteon, a melatonin agonist, has been shown to decrease sleep latency and improve total sleep time in an elderly population and improve memory in individuals with chronic primary insomnia (Erman et al., 2006), but has yet to be specifically studied in the TBI population. Benzodiazepines and atypical GABA agonists are commonly used in sleep disorders but should be used with caution in the TBI population due to their effects on cognition and adverse effects on neuroplasticity (Larson and Zollman, 2010).

5. Mechanistic consequences of sleep disruption

Sleep disruption can impair the circadian rhythm and may lead to altered homeostasis. Several key systems within the body become dysfunctional with continued sleep disturbance. In the following sections, we highlight changes in metabolomics, vasculature, and neurogenesis that occur following sleep disruption. In

the final section we discuss how sleep disruption can contribute to neurodegeneration over time.

5.1. Sleep disruption and metabolomic compromise

Sleep disruption increases susceptibility to metabolic disorders such as obesity and the metabolic syndrome likely through epigenetic changes (Khalyfa et al., 2014). The epigenetic changes may lead to altered brain chemistry and metabolism (Viant et al., 2005). Recent evidence using proton nuclear magnetic resonance has shown that 24 h of sleep deprivation in humans increases a series of brain metabolites acutely (Davies et al., 2014), which may be further exacerbated by injury (Glenn et al., 2013). Brain metabolites are therefore being investigated as potential biomarkers for TBI (Wang and Yu, 2013). Aspartate, an indicator of excitatory neurotransmission, was significantly increased in a cohort of TBI patients whereas total creatinine, a bioenergetics marker, was decreased (Glenn et al., 2013). In rodents, lactate, valine, and ascorbate, measures indicative of hypoxia, specific neurochemical changes, and oxidative stress, respectively are acutely increased following TBI and may reflect pathological mechanism (Harris et al., 2012). These metabolites need further verification in human TBI patients (Lemaire et al., 2011). Recent evidence indicates that the lactate/pyruvate ratio is predictive of sleep fragmentation following TBI using mass spectroscopy. An increased lactate/pyruvate ratio is associated with abnormal metabolism as well as a unique protein profile and has been identified in the cerebral microdialysis samples collected from patients in the 96 h immediately following TBI (Marcoux et al., 2008). These unique profiles link metabolic problems and cellular damage in the early hours following brain injury. Many types of cellular stress alter protein synthesis by activating the unfolded protein response (UPR). This response is essential for eliminating misfolded and damaged proteins and would be expected to play a major role following various types of brain injury. Various animal studies indicate the UPR is compromised in aged as well as sleep disrupted subjects (Naidoo, 2009). The UPR is impaired in old mice relative to young mice (Naidoo et al., 2008). Targeting the UPR pharmacologically and restoring the appropriate response may provide an avenue to reduce the consequences of sleep fragmentation and restore metabolic homeostasis.

5.2. Sleep disruption and vascular compromise

Vascular dilation occurs in response to neuronal activity and is believed necessary to increase blood flow and supply sufficient nutrients to sustain the neuronal response. Further, this hemodynamic response is compromised following sleep disruption and the blunting of the vascular response increased as sleep loss increased (Schei and Rector, 2011). Thus, it would appear intuitive that recovery from brain trauma would require adequate sleep and that the sleep disruption accompanying TBI may be detrimental. Thus, sleep is an important activity essential for maintaining vascular homeostasis and its loss may compromise other aspects of the vasculature that further compromise the injured brain. For example, resting blood pressure increases in humans deprived of sleep although heart rate and sympathetic nerve activity do not appear to be affected (Kato et al., 2000). Interestingly, sleep deprivation does not impair the brain's reflex control of cardiovascular function in the orthostatic condition of waking (Muenter et al., 2000), but can cause changes to sleep architecture. However, sleep deprivation can increase the risk of hypertension, vasospasm, and blood–brain barrier (BBB) disruption (Plante, 2006). These alterations to the cerebrovasculature can induce more detrimental effects that lead to further neuronal injury following TBI.

Sleep apnea which involves both sleep disruption and hypoxia causes hypertension by increasing oxidative stress and inflammation, which are risk factors for ischemic stroke and neurodegeneration (Kohler and Stradling, 2010). Acute sleep loss of 34–37 h also influences the immune response by increasing the blood levels of the inflammatory cytokine tumor necrosis factor alpha (TNF-α) (Chennaoui et al., 2011). Moreover, acute as well as chronic sleep deprivation impairs human endothelial vasodilation (Dettoni et al., 2012; Sauvet et al., 2010). Endothelial function following sleep deprivation and TBI is also disrupted in rodents. A pre-clinical study revealed that endothelial dysfunction is associated with the nitric oxide (NO) synthase pathway, independent of the changes in blood pressure and the sympathetic nervous system (Sauvet et al., 2014). These results suggest sleep plays an integral role in vascular integrity and has a powerful role in recovery post-injury.

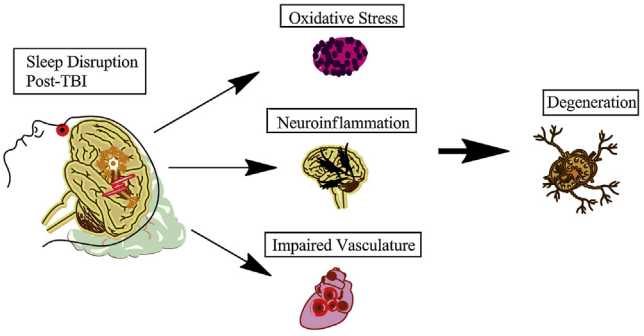

Fig. 1. Sleep disruption following traumatic brain injury triggers neurodegeneration. Sleep disruption can lead to an increase in oxidative stress and neuroinflammation. Oxidative stress damages intracellular organelles while neuroinflammation causes an increase in cytokines. Cytokines can disrupt vascular function leading to complications such as blood brain barrier breakdown and vasospasm. Over time these mechanistic changes contribute to neurodegenerative pathology such as neurofibrillary tangles.

Sleep disturbance can cause cerebral vasospasm, or an uneven expansion/contraction of blood vessels, which limits blood delivery to neuronal cells (Fletcher, 2000). TBI also can lead to severe vasospasm (Kramer et al., 2013), and in conjunction with chronic sleep deprivation can deplete energy supply to the point of neuronal cell death (Zhang et al., 2010). Sleep deprivation also increases blood oxygen saturation and reduces hemodynamic responses leading to decreased vascular compliance (Krieger and Egan, 2013). Hemodynamic alterations during sleep disruption have contributed to extended coronary vasospasm in human subjects (Somers et al., 1993).

Lastly, recent discoveries indicate that sleep deprivation can impair BBB function (Gomez-Gonzalez et al., 2013). Depriving a rodent of REM sleep leads to an increase in BBB tracer permeability and a decrease in the expression of vasoactive substances. In addition several tight junction proteins in brain microvessels of the BBB become disrupted (He et al., 2014). The breakdown of the rodent BBB can be seen from basement membrane compromise with electron microscopy and increased Evan's blue extravasation (Gomez-Gonzalez et al., 2013). Total sleep deprivation was also shown to increase human serum levels of brain specific proteins including neuron-specific enolase and S100 calcium binding protein B, which could indicate neuronal damage, BBB dysfunction or both (Benedict et al., 2014). These findings suggest that sleep deprivation can cause BBB dysfunction, and that this dysfunction allows blood–borne substances to enter the brain and promote excitotoxic events that trigger neuronal cell death (Fig. 1). TBI in a mouse model caused BBB disruption that led to damage of aquaporin channels. This in turn limits the removal of hyperphosphorylated tau by the glymphatic system during sleep (Iliff et al., 2014). Consequently, sleep deprivation and its detrimental effects on the BBB and the

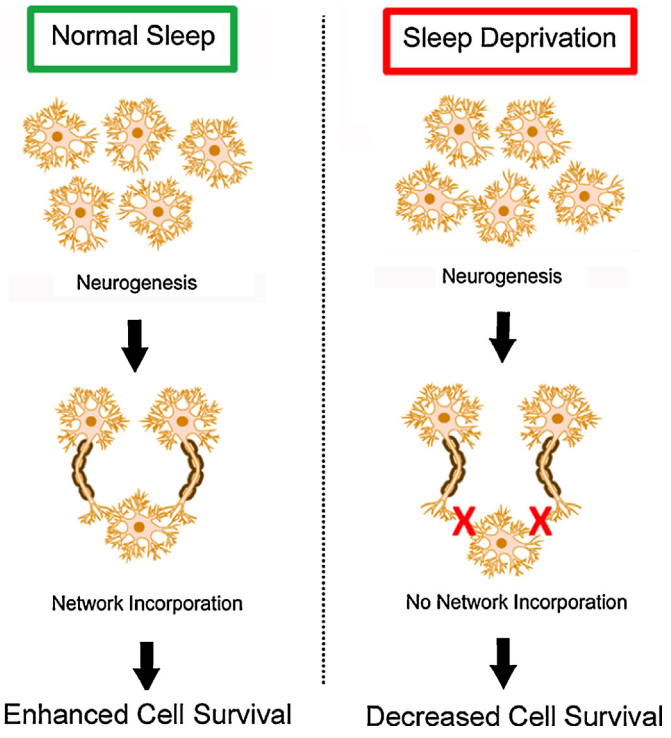

Fig. 2. Effects of sleep on neurogenesis. In the hippocampus, cells undergo neurogenesis to increase cell numbers. During sleep, these cells are integrated into neuronal networks through synaptogenesis. Once integrated into the existing cellular network, these cells have a greater likelihood of surviving. The surviving cells allow for maintenance of functions such as memory, learning, and cognition. However, when sleep is disrupted, synaptogenesis is decreased as well as memory consolidation. Ultimately, this change in synaptogenesis leads to a reduction in action potential firing. If synapses are not formed, newly generated cells fail to integrate into the existing neuronal network and the cells undergo apoptosis. The death of these cells prevents recovery and leads to memory loss and cognitive deficiencies following injury.

brain waste clearance system may work in conjunction with the deleterious effects of TBI, exacerbating neuronal damage and death

5.3. Sleep disruption and altered neuroplasticity

Sleep is also an important activity for brain plasticity (Alkadhi et al., 2013). Studies have shown that sleep disruption inhibits long-term potentiation, which may result in impaired synaptic growth and neurogenesis (Gronli et al., 2013). A recent study by Joo and colleagues demonstrated that patients suffering from chronic insomnia and sleep loss had structural differences in the hippocampus, including decreased hippocampal volume determined through magnetic resonance imaging (MRI) (Joo et al., 2014). In another study, an increase in hippocampal neurons in the dentate gyrus was observed in sleep-deprived rats (Grassi Zucconi et al., 2006), which may be a compensatory mechanism. In rats subjected to 24-hour sleep deprivation following TBI, there was a spike in initial cell number after injury that was drastically attenuated over time (Martinez-Vargas et al., 2012) (Fig. 2). These alterations in the hippocampus, a key brain area for learning and memory, may explain the prominent cognitive deficits seen in post-TBI patients. Indeed, in a rodent model of TBI, sleep disruption has resulted in impaired learning and memory (Skopin et al., 2014). Additionally, in a prospective study of humans with TBI, the duration of daytime sleep partially mediated the positive relationship between the score on the Glasgow Coma Scale and the recovery of cognitive function–controlling for total daytime sleep reduced the relationship (Chiu et al., 2014).

5.4. Sleep disturbance and neurodegeneration

Sleep fragmentation can have long-term negative consequences on recovery and can potentially contribute to the progression of injury in brain trauma. Patients with TBI subjected to more days of hourly neurologic evaluation had a significantly greater length of stay in the hospital (Stone et al., 2014). Recent evidence has found that TBI patients need more sleep than average and often underestimate their need for sleep as evidenced by sleep propensity measures. This increased sleep need may play a role in recuperation during the immediate period following TBI but the persistence of the need for many years after is difficult to explain. The persistent increased sleep need may reflect sleep insufficiency due to poor quality sleep (Sommerauer et al., 2013). Patients are often in isolated rooms as well which limits social interaction and worsens outcome (Riechers et al., 2013). When a patient is sleep deprived post-injury, one of the earliest clinical signs is the inability to sustain focused attention (Bloomfield et al., 2010). A possible reason is that extended wakefulness has been shown to contribute to alteration/deficiencies in tyrosine hydroxylase positive of wake-active neurons in the locus ceruleus (Zhang et al., 2014). Paradoxically, sleep deprivation before injury in experimental animals diminishes histopathologic changes (Martinez-Vargas et al., 2012). Further studies are needed to determine the potential neuroprotective versus neurodegenerative effects of sleep deprivation.

With sleep deprivation, the brain becomes primed to secondary injury cascades and therefore is preconditioned to glutamate excitotoxicity and NO mediated damage (Novati et al., 2012; Obukuro et al., 2013). Damaged neurons from TBI are often found in regions controlling behavior (Garcia-Garcia et al., 2011), which may result in increased neuropsychiatric symptoms characteristic of many neurodegenerative diseases. In a rodent model of sleep disruption and fragmentation, for example, animals displayed more impulsive-like behavior and had increased levels of corticosterone (Tartar et al., 2009). Not surprisingly sleep wake disturbances have been reported in diseases such as AD, Parkinson's disease, and CTE (Belaid et al., 2014; Collen et al., 2012; Lim et al., 2014). Ongoing work is needed to investigate how TBI sleep disruption can accelerate the progression toward these neurodegenerative diseases.

Two primary theories among many of sleep are currently under investigation. First, the metabolism theory posits that sleep is critical to maintain appropriate ATP production as well as restoration of the immune system and the regulation of inflammation (Zielinski et al., 2013) (Fig. 3). This beneficial process suggests that sleep allows energy stores to be generated enhancing cell functions during times of wakefulness. Additionally it prepares the body to maintain defense mechanisms and alter the inflammatory response. A second theory is the glymphatic theory of sleep (Iliff et al., 2014). During sleep, extracellular spaces are increased to permit greater flow of cerebrospinal fluid through the parenchyma allowing for greater clearance of wastes generated during times of wakefulness. This clearance removes any remaining metabolites and toxins that may be harmful to neurons (Fig. 4). Sleep deprivation following injury supports both of these theories. Without sleep to generate necessary ATP and protein synthesis, cell functions may be impaired or lost. This results in impaired synaptic plasticity and decreased neurogenesis. Additionally, the regulation of the inflammatory response is critical to neurological protection. Overactive neuroinflammation may inhibit recovery and repair as well as trigger further neural damage and death. Under the second theory, waste productions from damaged and dying cells cannot be cleared and limits the survival of regenerated neurons. Additionally, impaired clearances of wastes will result in increased activation of inflammatory responses. Thus, sleep deprivation and disruption may inhibit waste clearance and energy production resulting in inhibited neuron repair. Furthermore, sleep deprivation

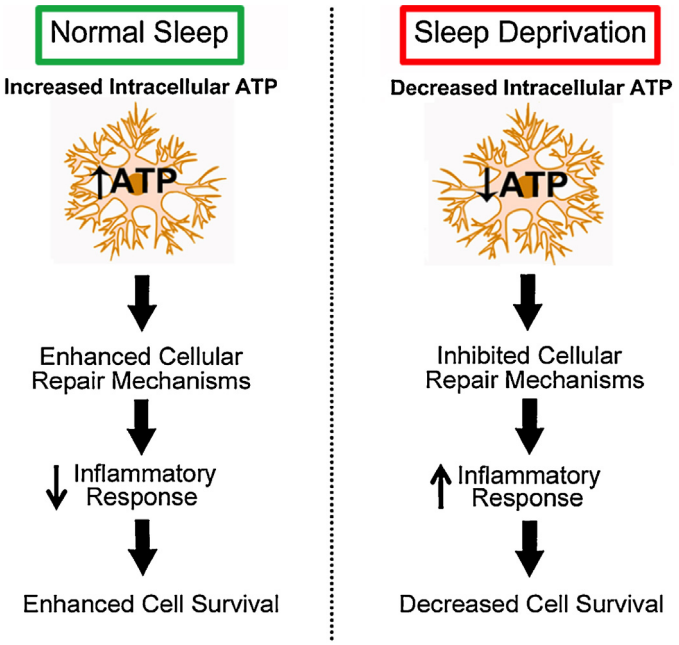

Fig. 3. The sleep theory of metabolism. ATP is crucial to cellular repair processes. During sleep, ATP production is increased allowing an elevated energy reserve that can decrease inflammation and contribute to enhanced cell survival. Following injury, sleep becomes more of a necessity for the repair and recovery of damaged and stressed cells. During sleep deprivation, ATP production is drastically reduced. The brain no longer can initiate repair and the prolonged inflammation can be detrimental, resulting in neuronal cell death. The cell death can eventually lead to affective disorders, memory and learning deficits, and cognitive dysfunction.

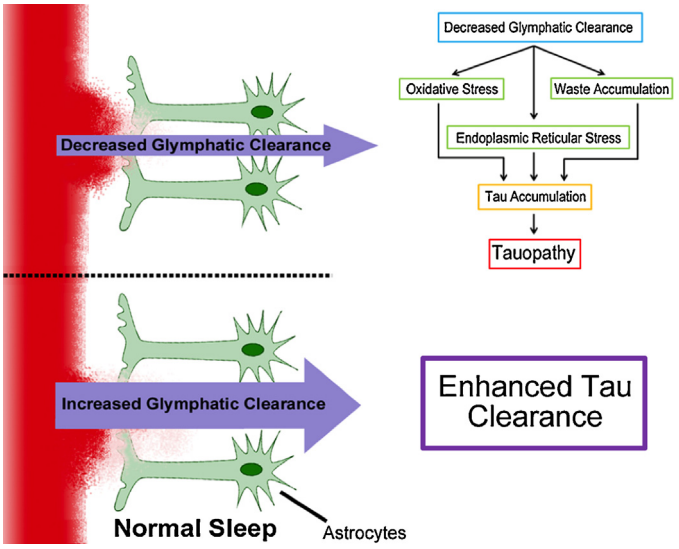

Fig. 4. Sleep disruption and the effect on the glymphatic system. During sleep, extracellular spaces are enlarged allowing for increased flow of interstitial fluid and increased clearance of wastes and metabolites. This removal of wastes lowers oxidative and endoplasmic reticulum stress, therefore reducing protein misfolding and tau accumulation. When the glymphatic system is altered during sleep disruption, the clearance of metabolites and toxins is reduced because the extracellular spaces fail to enlarge. Hyperphosphorylated tau can accumulate in this altered state, which increases the progression of tauopathies including Alzheimer's disease and chronic traumatic encephalopathy.

may activate secondary mechanisms of injury including oxidative stress and the UPR. Rodent models have shown that sleep fragmentation following injury can lead to oxidative damage of DNA (Everson et al., 2014), and the UPR has recently been shown to account for sleep fragmentation in the elderly (Brown et al., 2014). It is therefore likely that these secondary injury pathways contribute to the pathology of sleep fragmentation and early onset of neurodegenerative disease following TBI.

6. Conclusions and future directions

Sleep disruption is an important and often overlooked outcome of TBI. Although sleep disturbances have been frequently reported, research is needed to address how sleep disturbances associated with TBI change over time and what sleep disruption informs us about the injured brain. Continued pre-clinical work needs to focus on disruptions of the glymphatic system and the clearance of metabolic waste. Additionally, it will be important to determine if and how repetitive injuries impact the sleep disturbance associated with brain trauma and if the injuries cause summative or exponential decline. Current evidence suggests it is necessary to successfully manage sleep disturbance early following brain injury because sleep disruption following TBI is concomitant with multiple neuropsychiatric and cognitive symptoms. In addition, physical manifestations of TBI such as headaches can worsen with sleep disruption or can even cause sleep disruption. Future clinical work will need to evaluate if treating sleep disturbance improves neuropsychiatric and physical symptoms of TBI. In this review, we discussed potential mechanistic contributions of sleep disruption including metabolomic alterations, vascular changes, and disruption of neurogenesis. Other pathways warranting further investigation include the UPR and oxidative stress. In this review, we also highlighted how sleep disruption following TBI may contribute to the development of neurodegenerative disease. Continued exploration into how sleep disruption contributes to tauopathies in particular is warranted. We propose that treating sleep disruption will lead to healthier outcomes for patients both acutely and chronically.

Disclaimer

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