Published in final edited form as:

Clin Psychol Rev. 2015 August ; 40: 195–212. doi:10.1016/j.cpr.2015.05.008.

Sleep Disturbances, TBI and PTSD: Implications for Treatment and Recovery

Karina Stavitsky Gilbert^{1,2,*}, Sarah M. Kark^{1,*}, Philip Gehrman^{3,4}, and Yelena Bogdanova^{1,2}

¹Psychology Research, VA Boston Healthcare System, Boston, MA

²Department of Psychiatry, Boston University School of Medicine, Boston, MA

³Department of Psychiatry, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA

⁴Philadelphia VA Medical Center, Philadelphia, PA

Abstract

Post-Traumatic Stress Disorder (PTSD), traumatic brain injury (TBI), and sleep problems significantly affect recovery and functional status in military personnel and Veterans returning from combat. Despite recent attention, sleep is understudied in the Veteran population. Few treatments and rehabilitation protocols target sleep, although poor sleep remains at clinical levels and continues to adversely impact functioning even after the resolution of PTSD or mild TBI symptoms. Recent developments in non-pharmacologic sleep treatments have proven efficacious as stand-alone interventions and have potential to improve treatment outcomes by augmenting traditional behavioral and cognitive therapies. This review discusses the extensive scope of work in the area of sleep as it relates to TBI and PTSD, including pathophysiology and neurobiology of sleep; existing and emerging treatment options; as well as methodological issues in sleep measurements for TBI and PTSD. Understanding sleep problems and their role in the development and maintenance of PTSD and TBI symptoms may lead to improvement in overall treatment outcomes while offering a non-stigmatizing entry in mental health services and make current treatments more comprehensive by helping to address a broader spectrum of difficulties.

Corresponding Author: Yelena Bogdanova, PhD. VA Boston Healthcare System, Psychology Research (151-A), 150 South, Huntington Avenue, Boston, MA 02130. bogdanov@bu.edu.

*Co-first authors contributed equally to the manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Contributors

All authors contributed to this review. YB and KSG designed the study and developed the search strategies. KSG and SMK conducted literature searches and provided summaries of previous research, with supervision from YB (senior author). KSG, SK, and YB wrote the first draft of the manuscript. YB, KSG, and SMK completed the review and revised the manuscript, in collaboration with PG. All authors contributed to interpretation of the literature and revisions of the manuscript, and all have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

Keywords

Sleep; PTSD; TBI; Veterans; Cognition; Interventions; Sleep physiology; Neuromodulation; Paradoxical insomnia; Actigraphy

INTRODUCTION

The prevalence of sleep disorders in the general population (Ohayon, 2007) has gained much attention in recent years, as problems with sleep have been linked to increased psychological sequelae (Vandekerckhove & Cluydts, 2010); increased health problems, particularly cardiovascular health (Lofaso et al., 1996); impaired immune function (Gamaldo, Shaikh, & McArthur, 2012); and even increased mortality (Li, Sato, & Yamaguchi, 2013). The impact of sleep disturbances is now recognized as being wide spread, affecting individuals across age groups, ethnicities, and degrees of health status.

Given the prevalence of sleep difficulties in other neurologic, medical, and psychiatric conditions, it is not surprising that sleep problems are common in individuals with traumatic brain injury (TBI), including those with mild (m)TBI¹. Overall, approximately 40–65% of individuals with mTBI report symptoms of insomnia (Beetar, Guilmette, & Sparadeo, 1996; Dikmen, McLean, & Temkin, 1986). The etiology of these sleep problems is still under investigation, though recent research has implicated neurobiological factors such as impairment in the functioning of neural circuits involved in sleep-wake regulation (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008; Saper, Chou, & Scammell, 2001). Moreover, there is a wide range of sleep-wake dysfunctions that emerge from TBI other than insomnia, including hypersomnia and circadian rhythm abnormalities (Ayalon, Borodkin, Dishon, Kanety, & Dagan, 2007). It is also not clear to what extent restorative sleep is related to successful recovery in individuals with TBI or whether there is a cumulative impact of the severity of TBI on the severity of sleep disorders. What is known is that poor sleep may exacerbate symptoms of TBI (Ouellet & Morin, 2007), impact the individual's ability to cope with these symptoms (Lew et al., 2009), increase neuropsychiatric symptoms (depression, anxiety and apathy) post-injury (Rao, McCann, Han, Bergey, & Smith, 2014), and inhibit complete participation in rehabilitation treatments (Worthington & Melia, 2006).

¹Throughout the review we refer to TBI and mTBI as both are of importance in this discussion. As elaborated on in this review, there might be overlapping and distinct sleep symptoms along the spectrum of TBI severity. As such, we attempt to be as inclusive as possible of the studies that examine TBI with relation to sleep regardless of the severity of the patients in the studies. Therefore, we wanted to present the readers with the definitions of TBI and to clarify the conceptual definition of both TBI and mTBI. **DoD/VA Common Definition:** TBI is a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by the onset or worsening of at least one of the following clinical signs, immediately following the event: any period of a loss of or decreased level of consciousness; any loss of memory for events immediately before or after the injury; any alteration in mental state at the time of the injury (feeling dazed, confused, disoriented, thinking slowly, etc.); neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient; and intracranial lesion (DOD, 2009). **Definition of mild TBI** by Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine: A patient with mTBI is a person who has had a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: any period of loss of consciousness; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and focal neurological deficit(s) that may or may not be transient, but where the severity of the injury does not exceed the following: loss of consciousness of approximately 30 minutes or less; after 30 minutes, an initial Glasgow Coma Scale (GCS) of 13–15; and posttraumatic amnesia (PTA) not greater than 24 hours (ACRM, 1993).

PTSD is another major psychiatric disorder with poor sleep being one of its principal symptoms. In PTSD, disturbed sleep is part of the diagnostic criteria, with insomnia being a symptom of alterations in arousal and reactivity (Cluster E), and nightmares as part of the re-experiencing symptom cluster (Cluster B) (American Psychiatric Association, 2013). Consequently, individuals with PTSD tend to present with extremely poor, fragmented, and variable sleep quality as measured by self-report (van Liempt, 2012). As with TBI, it is not clear to what extent the severity of sleep disturbance maintains the psychopathology of PTSD given that poor sleep is associated with increased anxiety, irritability, and deficient coping (K. Babson et al., 2011; Pietrzak et al., 2010; van Liempt, 2012). Recently it has been reported that poor sleep independently predicts the development of depression (Baglioni et al., 2011; Buysse et al., 2008; Jackson, Sztendur, Diamond, Byles, & Bruck, 2014; Peppard, Szklo-Coxe, Hla, & Young, 2006; Szklo-Coxe, Young, Peppard, Finn, & Benca, 2010), PTSD (Bryant, Creamer, O'Donnell, Silove, & McFarlane, 2010; Gehrman et al., 2013; Gerhart, Hall, Russ, Canetti, & Hobfoll, 2014; Kobayashi & Mellman, 2012; Koffel, Polusny, Arbisi, & Erbes, 2013; Spoormaker & Montgomery, 2008; Swinkels, Ulmer, Beckham, Buse, & Calhoun, 2013; Wright et al., 2011), changes in post-deployment depression and PTSD symptoms (Wright et al., 2011), suicide risk in both clinical and non-clinical populations (Pigeon, Pinquart, & Conner, 2012; Ribeiro et al., 2012; and for a review see Woznica, Carney, Kuo, & Moss, 2014), and is more related to low satisfaction with life and post-deployment community integration than other symptoms of PTSD (Kark, Stavitsky, Deluca, Lafleche, & Bogdanova, 2013). Furthermore, there is some evidence that poor sleep likely impacts the efficacy of evidence-based psychotherapy for treatment of PTSD (Nappi, Drummond, & Hall, 2012). This evidence is based on the fact that restorative sleep is necessary for the consolidation of emotional memories (Payne, Chambers, & Kensinger, 2012; Payne & Kensinger, 2011; Stickgold & Walker, 2007; Walker, 2010) and generalization of fear extinction (Pace-Schott et al., 2009; Pace-Schott, Verga, Bennett, & Spencer, 2012) - cognitive processes that are the foundation of most evidence-based treatments for PTSD (van Liempt, 2012).

Given the nature of the recent conflicts, with high rates of physical and psychological injuries due to blast exposures and multiple tours of duty, returning Veterans are often present with co-occurring TBI and PTSD (reviewed in Bogdanova & Verfaellie, 2012). Three of the largest studies evaluating OEF/OIF/OND Veterans report 5–7% of Veterans have probable co-morbid mTBI/PTSD, and in those with mTBI, the rate of co-morbid PTSD is between 33% and 39% (Carlson et al., 2011). Little is known about the overlap or differences between PTSD and TBI with respect to sleep. Few studies have compared individuals with co-occurring PTSD and TBI to those with TBI or PTSD only, to evaluate sleep quality and to determine the differential contribution of these distinct yet overlapping conditions to sleep impairment. One recent study examined PTSD vs. TBI in returning combat Veterans and found no differences between diagnostic groups (PTSD vs. TBI) with the exception of increased arousals among patients with PTSD and greater slow wave sleep (SWS) among those with TBI (Capaldi, Guerrero, & Killgore, 2011). These results suggest some sleep problems in PTSD and TBI might be distinguishable between the two conditions.

The overlap between TBI and PTSD combined with other confounding deployment- and post-deployment-related factors, present significant methodological challenges, which make it difficult to conduct research and to interpret the findings in this population. A recent prospective study explored the role of sleep as a mediating factor in the development of mental health symptoms (TBI, PTSD and depression) in a large sample (29,640) of US Navy and Marine Corps men (Macera, Aralis, Rauh, & MacGregor, 2013). Sleep problems mediated the association between TBI and the development of PTSD and depression. The results suggest that sleep problems may be an early indicator of risk for PTSD or depression in TBI. Further, there is evidence that sleep problems can be considered a separate post-deployment health problem, distinct from PTSD, TBI, and depression (Maguen, Lau, Madden, & Seal, 2012). These and other research findings highlighted in this review, despite their methodological limitations, provide future research directions and suggest that early identification and treatment of sleep disturbance may potentially prevent the development and improve the outcome of mental health disorders, such as PTSD and depression.

This review is intended to 1) provide the latest information on sleep as it relates to the pathophysiology and psychopathology of PTSD and TBI, particularly in military personnel and Veterans returning from more recent Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OEF/OIF/OND) conflicts; and 2) to discuss how sleep impacts recovery, course of treatment and outcome in these individuals. Sleep problems are prevalent among OEF/OIF/OND Veterans and are reported to be among the primary complaints (Faestel, Littell, Vitiello, Forsberg, & Littman, 2013; Hoge et al., 2008; McLay, Klam, & Volkert, 2010; Wallace et al., 2011). Veterans returning from combat present with a variety of sleep disturbances that are not limited to insomnia and include circadian rhythm disorders, Obstructive Sleep Apnea (OSA), and even possibly Rapid Eye Movement (REM) Behavior Disorder (Mysliwiec, Gill, et al., 2013; Mysliwiec, McGraw, et al., 2013). Since poor sleep may exacerbate psychological suffering related to combat-related physical (i.e., mTBI) and psychological (i.e., PTSD) trauma and given the evidence that sleep may moderate the efficacy of behavioral treatments for these conditions, it is important to understand the etiology of sleep disorders in this population.

While trauma-focused PTSD treatments have led to some improvements in sleep, nearly half of PTSD treatment positive responders report residual sleep problems, despite relief in other symptom domains (Schoenfeld, Deviva, & Manber, 2012; Zayfert & DeViva, 2004). The emergence of sleep as a distinct post-deployment factor (Maguen et al., 2012) highlights the need to address sleep disturbances in the clinical screening process and to develop sleep-specific treatment protocols. Moreover, sleep treatment has the potential to provide a non-stigmatizing entry into mental health services by focusing on a topic that Veterans may not consider to be 'mental health treatment', thereby maximizing engagement in treatment (Epstein, Babcock-Parziale, Herb, Goren, & Bushnell, 2013). For example, a recent case study found that pre-empting PTSD treatment with sleep-focused intervention facilitated successful entry into exposure-based therapy for PTSD (Baddeley & Gros, 2013). Although to date there is a paucity of studies examining the efficacy of sleep treatment for Veterans with mTBI and PTSD, the few recent treatment outcome studies in PTSD have shown a positive impact of sleep treatment on PTSD symptoms (Casement & Swanson, 2012; Germain et al., 2012; Nakamura, Lipschitz, Landward, Kuhn, & West, 2011; Nappi et al.,

2012) and may provide a good model for the development of treatment programs for returning Veterans with comorbid TBI and PTSD.

SLEEP DISTURBANCES AND PTSD

Sleep disturbance is one of the core features of PTSD (Calhoun et al., 2007; Dagan, Zinger, & Lavie, 1997). Approximately 70% of patients with PTSD have co-occurring sleep problems (K. A. Babson & Feldner, 2010). PTSD has been associated with reduced sleep efficiency, increased sleep latency, increased sleep fragmentation, and greater night-to-night variability in sleep (Breslau et al., 2004; Calhoun et al., 2007; Habukawa, Uchimura, Maeda, Kotorii, & Maeda, 2007; Mellman, Kulick-Bell, Ashlock, & Nolan, 1995; Straus, Drummond, Nappi, Jenkins, & Norman, 2015). Sleep difficulties in the Veteran population are linked to a variety of poor mental health and socioeconomic outcomes. For example, one recent study found that poor sleep quality was associated with PTSD, panic disorder, depression, suicidal ideation, and risky drinking behavior in Iraq/Afghanistan Veterans (Swinkels et al., 2013). Other studies have reported similar poor outcomes in Veterans with sleep difficulties including lower quality of life and more severe fatigue, pain, PTSD, and depressive symptoms compared to those without sleep difficulties (Lang, Veazey-Morris, & Andrasik, 2014; Wallace et al., 2011). Ribeiro and colleagues (2012) reported an association between insomnia symptoms and suicidal ideation in a sample of 311 military personnel. Specifically, sleep disturbances were found to be predictive of shorter time to suicide (57% loss of survival time) in Veterans in Veterans Health Administration care (Pigeon, Britton, Ilgen, Chapman, & Conner, 2012). Investigating the relationship between sleep disturbances and suicide is important given the high rates of reported sleep disturbances in Veterans Health Administration users (Mustafa, Erokwu, Ebose, & Strohl, 2005) and in returning OEF/OIF/OND Veterans (Hoge et al., 2004; Neylan et al., 1998; Seelig et al., 2010; Wallace et al., 2011); as the rate of suicide is not entirely attributable to a PTSD diagnosis (Lewis, Creamer, & Failla, 2009). This information may help with suicide risk identification and prevention methods as well as early and effective sleep-focused interventions for Veterans at high risk for suicide.

Sleep disturbance itself may be a risk factor for development of PTSD following exposure to trauma (Bryant et al., 2010; Gehrman et al., 2013; Gerhart et al., 2014; Kobayashi & Mellman, 2012; Koffel et al., 2013; Spoormaker & Montgomery, 2008; Swinkels et al., 2013; Wright et al., 2011). A longitudinal investigation of sleep and trauma-related distress found that initial sleep problems predicted increased PTSD and depression at 6 month follow-up, whereas initial PTSD and depression did not predict increased sleep problems (Gerhart et al., 2014). A longer follow-up study similarly found that pre-deployment sleep complaints uniquely and incrementally predicted PTSD and depression up to two years after deployment, even after controlling for baseline psychiatric symptoms and negative emotionality characteristics (Koffel et al., 2013). These findings suggest that pre-trauma sleep disturbance predicts later development of PTSD following exposure to trauma, even after controlling for pre-existing psychopathology. Sleep disturbances may also mediate the effect of mTBI on the development of PTSD and depression and may be an early indicator of risk for depression and PTSD in blast exposed OEF/OIF/OND Veterans (Macera et al., 2013). These findings highlight the importance of pre-deployment sleep symptom screening

procedures, which could allow for early identification of Veterans with pre-deployment sleep problems, and facilitate prospective post-deployment care and health planning.

Sleep problems are particularly common in returning Veterans with PTSD compared to those without PTSD or trauma history (N. Orr et al., 2010). A recent review of deployment-related insomnia in military personnel provides a thorough overview of how sleep problems develop in military personnel and Veterans and are perpetuated by the deployment experience (Bramoweth & Germain, 2013). Mellman and colleagues (1995) evaluated sleep quality among combat Veterans with PTSD and found that the most commonly reported sleep-related symptoms were recurrent awakenings, threatening dreams, thrashing movements while sleeping, and waking up startled or in a panic. One recent study by Mysliwiec and colleagues (2013) found an increased rate of comorbid diagnoses of insomnia and OSA in US military personnel returning from deployment presenting to a sleep clinic. In this retrospective cross-sectional study sleep disorders were diagnosed in 88.2% of subjects with 62.7% meeting diagnostic criteria for OSA and 63.6% for insomnia. Those with comorbid insomnia and OSA were more likely to meet criteria for PTSD and depression (Mysliwiec, McGraw, et al., 2013). Wallace and colleagues (2011) characterized sleep quality in OEF/OEF/OND Veterans with PTSD and insomnia (with and without mTBI). Fifty-six percent of the PTSD group reported severe insomnia and 44% reported moderate insomnia. Both groups (PTSD vs. mTBI) reported severe difficulties with sleep initiation, maintenance, early awakenings, and daytime fatigue, while daytime sleepiness was greater in the PTSD-mTBI group. When compared to the PTSD-mTBI insomnia group, the PTSD group showed worse sleep continuity measured by actigraphy (ACT) (sleep efficiency, nighttime awakenings, and fragmentation index). These data suggest that, while both groups reported similar insomnia severity, patients with PTSD might be experiencing more sleep quality difficulties while the PTSD-mTBI patients might be suffering from a differential set of difficulties resulting from a complex interplay between insomnia and hypersomnia.

Sleep Discrepancies in PTSD: Current Issues

While subjective sleep complaints are a core feature in PTSD, previous studies have been unable to consistently corroborate subjective sleep complaints (i.e., self-report questionnaires, sleep diaries) with objective sleep measurements (i.e., polysomnography [PSG], ACT) (Germain, Hall, Shear, Nofzinger, & Buysse, 2006; Pillar, Malhotra, & Lavie, 2000; Woodward, Bliwise, Friedman, & Gusman, 1996). One issue might be that PSG studies typically rely on only 1 or 2 nights of data collection, which is problematic if symptom severity is intermittent or highly variable. Indeed, recent evidence suggests greater intraindividual variability of sleep in military-related PTSD, relative to primary insomnia patients and healthy controls (Straus et al., 2015). Further, it has been suggested that many patients with PTSD may sleep better in a PSG laboratory because they feel safer or more protected under the observation of research staff compared to their home environment, which compromises the ecological validity of the data (Germain et al., 2006; Khawaja, Hashmi, Aftab, Westermeyer, & Hurwitz, 2014). In line with this theory, results from a small pilot study revealed a relationship between in-home PSG-measured sleep disturbances and subjective sleep problems in a sample of adult crime victims with PTSD (Germain et al.,

2006). While PSG is the gold standard for objective sleep measurement, it is also costly and might not be the most practical or ecologically-valid method to examine sleep in the PTSD population.

While the ambulatory nature of actigraphic monitoring allows for more ecologically-valid data collection and prolonged sleep recording compared to PSG, the relationship between ACT and self-reported sleep quality also remains equivocal (for a review see Khawaja et al., 2014). For example, prior work reported a significant relationship between sleep diary and ACT total sleep time (TST), but sleep diaries underestimated the number of sleep awakenings compared to ACT (Westermeyer et al., 2007). These findings suggest that ACT and diary data may align on some but not all measures of sleep quality. In a recent CBT-I intervention study for chronic PTSD that used both ambulatory PSG and ACT, the treatment group showed post-treatment improvements in both PSG-measured TST and self-reported sleep symptoms, compared to the waitlist group (Talbot et al., 2014). The PSG data were only based on one night of data collection and there were no significant improvements in continuous ACT-measured sleep to corroborate the PSG data or self-reported sleep improvements. More research is necessary to understand the accuracy of PSG and ACT-measured sleep in the PTSD population.

Although the disparities between objective and subjective sleep data are often considered a source of measurement error, it has also been suggested that the difference between objective and subjective sleep measurements, or sleep discrepancies, might capture clinically meaningful correlates of psychiatric status (Williams, Kay, Rowe, & McCrae, 2013). Prior work has been unable to demonstrate a relationship between sleep discrepancies and PTSD status (Kobayashi, Huntley, Lavela, & Mellman, 2012), which is thought to reflect sleep misperceptions in PTSD (Dagan et al., 1997; Klein, Koren, Arnon, & Lavie, 2003; Kobayashi et al., 2012). Indeed, “paradoxical insomnia”—a relatively new diagnosis that first appeared in the *International Classification of Sleep Disorders - 3rd Edition (ICSD-3; American Academy of Sleep Medicine, 2014)*—is characterized by quantifiable discrepancies between objective and subjective sleep measurements. While paradoxical insomnia is relatively rare amongst civilians with insomnia (5%), a recent study reported paradoxical insomnia in 17.2% of a large cohort of active duty military personnel with sleep disorders (Mysliwiec, McGraw, et al., 2013). Further, results of a recent study reported underestimated self-reported TST compared to ACT TST, which offers new evidence for PTSD-related paradoxical insomnia (Ghadami, Khaledi-Paveh, Nasouri, & Khazaie, 2014). These findings highlight the importance of utilizing objective sleep measures in the military population, without which paradoxical insomnia would go undetected.

Despite the prevalence of paradoxical insomnia, individuals with PTSD do likely suffer from objective insomnia. However, the experience of true insomnia related to acute PTSD may give rise to enduring thought patterns about sleep that eventually manifest as subjective insomnia in chronic PTSD (Dagan et al., 1997). A recent PSG study demonstrated fragmented and reduced REM sleep in PTSD patients with relatively proximate trauma exposure compared to unaltered REM sleep in the chronic or ‘distal’ PTSD patients, even after controlling for depression (Mellman, Kobayashi, Lavela, Wilson, & Hall Brown, 2014). Sleep state misperceptions in paradoxical insomnia might be especially common for

returning Veterans as they reintegrate into a safe sleeping environment after maintaining high levels of nocturnal vigilance during deployment (Mysliwiec, McGraw, et al., 2013). Further, a recent neuroimaging study reported a link between decreased subjective sleep quality and reduced cortical and frontal grey matter volume in Gulf War Veterans without a current psychiatric diagnosis, which may suggest an association between frontal lobe integrity and the capacity to experience sleep as restorative (Chao, Mohlenhoff, Weiner, & Neylan, 2014). These findings provide potential neural evidence to corroborate the theory of dysfunctional cognitions and thought patterns about subjective sleep quality. Further work is necessary to 1) understand the prevalence and clinical implications of sleep discrepancies or 'paradoxical insomnia' in returning Veterans with and without PTSD, 2) investigate if these discrepancies arise during the shift from acute (or 'proximal') PTSD to chronic (or 'distal' PTSD), and 3) develop early and effective interventions to alleviate sleep misperceptions that might arise in military-related chronic PTSD.

Neurobiological Correlates of Sleep in PTSD

Neuroimaging studies are beginning to explore the brain-behavior link in individuals with PTSD and have recently reported neurobehavioral correlates of sleep disturbance in those with PTSD. Structural and functional neuroimaging studies have found hyperactivation of the amygdala and impaired medial prefrontal cortex function in patients with PTSD (Germain, Buysse, & Nofzinger, 2008; Hughes & Shin, 2011). Specifically, patients with PTSD show hyperactivation of the amygdala in response to threat-related stimuli, which exaggerates the fear response (Germain et al., 2008; Hughes & Shin, 2011; Patel, Spreng, Shin, & Girard, 2012). Activation of the medial prefrontal cortex, which is critically involved in fear extinction, might be impaired in PTSD subjects compared to trauma-exposed controls (Liberzon & Sripada, 2008). With regard to sleep, investigators have found both hypo and hyperactivation of specific brain regions in individuals with PTSD during sleep. For example, Germain and colleagues (2013) found that OEF/OIF/OND Veterans with PTSD experience elevated neural activity during wakefulness and REM sleep in the REM-generating and arousal regions of the brainstem. Results showed hyperactivation of the brain in arousal-related regions involved in REM sleep regulation (midbrain reticular formation left and right locus coeruleus, raphe nuclei, pedunculo pontine, laterodorsal tegmental nuclei, cerebellum) as well as limbic structures involved in emotion and memory processing (hippocampus, amygdala, basal ganglia, insula, and thalamus).

Nightmares in PTSD may be facilitated by the hypoactivity of the dorsal medial prefrontal cortex, which modulates the activity in subcortical limbic regions, such as the amygdala, during REM sleep (Germain et al., 2008; Germain et al., 2013). In a similar vein, earlier studies found that symptomatic awakenings in those with PTSD were preceded by REM sleep, suggesting that arousal may intrude upon the sleep state via increased amygdala activity or impaired medial prefrontal cortex function (Mellman, Bustamante, Fins, Pigeon, & Nolan, 2002; Mellman et al., 1995). An electroencephalographic study by Cohen and colleagues (2013) compared sleep architecture between combat Veterans with and without PTSD and found no difference between measures of central arousal (beta and gamma activity) between groups. The authors suggest that central arousal might be indicative of primary insomnia whereas hyperarousal symptoms in PTSD might reflect increased

autonomic and limbic activity and/or dysfunction in sleep-related memory or emotional processing. The results from this study also revealed that, in combat-exposed Veterans without PTSD, REM and non-rapid eye movement (NREM) sleep sigma activity was positively correlated with level of combat exposure and NREM sigma activity was negatively correlated with PTSD avoidance symptoms. The authors concluded that these data suggest the possibility of a sleep architecture-related marker of resilience to PTSD (Cohen et al., 2013).

In 2013, van Liempt and colleagues reported the results of a study investigating Hypothalamic-Pituitary-Adrenal (HPA) axis and sleep dysfunction in Veterans with PTSD compared to trauma-exposed and healthy controls (van Liempt et al., 2013). The group collected objective and subjective measures of sleep quality as well as cortisol, adrenocorticotrophic hormone (ACTH), and melatonin levels. While no difference in sleep architecture was found between the 3 groups, the PTSD group experienced more nighttime awakenings, which were positively correlated with ACTH levels. ACTH and cortisol were also inversely related to slow wave sleep and ACTH was found to be an independent predictor of SWS in those with PTSD. The authors suggest that fragmented sleep in PTSD might be associated with increased corticotrophin-releasing hormone, which inhibits SWS. The authors did not find evidence of phase shifts in circadian rhythms of cortisol, ACTH, or melatonin in Veterans with PTSD. Of note, a recent study by the same group found a strong relationship between sleep fragmentation and blunted growth hormone secretion in PTSD, both of which might negatively impact sleep-dependent memory consolidation (van Liempt, Vermetten, Lentjes, Arends, & Westenberg, 2011). Together, the foregoing studies provide evidence for dysregulation of arousal centers of the brain related to sleep disturbances in PTSD.

The HPA axis is a neurohormonal feedback loop that functions as part of the stress response system and regulates other biological processes including mood and emotions, digestion, and physical activity. Among the more important and most easily measurable hormones released through the HPA axis is cortisol, which can serve as an index of HPA activity and marker of circadian rhythms; the release of which is activated by the feedback loop initiated by the corticotrophin-releasing hormone secreted by the paraventricular nucleus of the hypothalamus. The release of corticotrophin-releasing hormone from the hypothalamus is influenced by the sleep/wake cycle in addition to having an endogenous circadian rhythm. Studies have found that upon awakening, there is an immediate rise in cortisol, known as the cortisol awakening response (CAR), which reaches its peak approximately 30 minutes following awakening (Fries, Dettenborn, & Kirschbaum, 2009) and demonstrates gradual decline throughout the day (Clow, Thorn, Evans, & Hucklebridge, 2004; Pruessner et al., 1997; Wilhelm, Born, Kudielka, Schlotz, & Wust, 2007). This response is sensitive to a variety of inter-individual differences, including stress, health status, awakening time, and the morningness/eveningness of the individual (Bailey & Heitkemper, 2001; Brigitte M. Kudielka, Buchtal, Uhde, & Wust, 2007; B. M. Kudielka, Federenko, Hellhammer, & Wust, 2006; Pruessner et al., 1997; Randler & Schaal, 2010; Wust, Federenko, Hellhammer, & Kirschbaum, 2000). However, despite these inter-individual differences, the CAR demonstrates within-individual stability (Hucklebridge, Hussain, Evans, & Clow, 2005; Pruessner et al., 1997; Wust et al., 2000).

In so far as the cortisol response and associated HPA axis activity is an intrinsic part of circadian rhythms and is associated with sleep wake activity, it is expected that in individuals with disturbed sleep or altered sleep-wake rhythms these mechanisms would demonstrate significant modulation. However, the results of the studies examining the relationship between the CAR and sleep efficiency have been inconsistent. Some studies have reported no difference between subjective measures of sleep quality and cortisol at awakening (Zhang et al., 2011), while others have found a relationship between sleep duration and sleep disturbances and morning cortisol levels (Backhaus, Junghanns, & Hohagen, 2004; Kumari et al., 2009). Others have reported an association between poor sleep and evening cortisol levels (Rodenbeck, Huether, Ruther, & Hajak, 2002; A. N. Vgontzas et al., 2001). The implication of these equivocal findings is that it is likely that the inter-individual differences and the methods of measuring cortisol (i.e., CAR, diurnal cortisol slope) may result in inconsistent results. Moreover, the majority of these studies measure sleep quality by using conventional sleep measures such as sleep efficiency, duration, and sleep onset latency.

Dysfunction of the HPA axis has been repeatedly implicated in PTSD (de Kloet et al., 2006; Drake, Roehrs, & Roth, 2003). Particularly, the suppression of the HPA axis in PTSD has been reported, with less variability (fewer peaks and troughs) in the diurnal cortisol cycle in individuals with PTSD (Yehuda, 2002). Recently, Wahbeh and Oken (2013) reported lower cortisol across the entire day (wake, 30 minutes after waking, and bedtime) in combat Veterans with PTSD compared to combat Veterans without PTSD. Patients who develop PTSD following exposure to trauma show a sharp increase of cortisol immediately following the traumatic event followed by tapering to low basal cortisol levels over the course of a few months into the chronic phase of PTSD (Pervanidou & Chrousos, 2010). Pervanidou and Chrousos (2010) have posited that the initial spike in cortisol and subsequent low basal cortisol state in the presence of progressive norepinephrine levels characterizes the development and maintenance of PTSD, respectively. In concordance with these findings, it has been reported that symptom severity in chronic PTSD is negatively correlated with cortisol levels (Olf, Guzelcan, de Vries, Assies, & Gersons, 2006). Future work is needed to elucidate the role of HPA response in the development and maintenance of PTSD in returning service members, with the possibility that HPA function might interact with TBI status.

Prior work has also found reduced plasma brain-derived neurotrophic factor (BDNF)—a neuroprotective growth factor that directly influences sleep need (Faraguna et al., 2008)—in PTSD patients, relative to healthy controls (Dell’Osso et al., 2009). Dysregulation of BDNF might adversely affect neuroplasticity, cognition, and memory in PTSD (Deppermann, Storchak, Fallgatter, & Ehlis, 2014; Kaplan, Vasterling, & Vedak, 2010). Chronic stress and cortisol elevation are linked with BDNF down-regulation in regions of the brain such as the ventromedial prefrontal cortex (Gourley, Kedves, Olausson, & Taylor, 2009) and the hippocampus (Rasmusson, Shi, & Duman, 2002)—regions critical in the regulation of physiological arousal and memory, respectively. Re-exposure to a fear-conditioned context reduces BDNF expression in the hippocampus, which could possibly hamper hippocampal-based fear extinction learning (Rasmusson et al., 2002). These results demonstrate a link between BDNF, stress, and cognition. In regards to sleep, animal work has demonstrated

increased wakeful daytime exploration is associated with increased cortical BDNF expression and increased slow-wave activity during subsequent sleep, compared to rats awake for the same amount of time but not exploring (Huber, Tononi, & Cirelli, 2007). BDNF regulation seems to be important in the link between daytime cognition and activity with the normal drive for sleep. Future work is needed to disentangle the possible interaction between BDNF regulation, sleep drive and intensity, and cognition in PTSD.

Conclusion

Sleep problems are prevalent in returning Veterans with PTSD. Sleep problems pose a risk factor for the development and maintenance of PTSD and have substantial impact on psychosocial functioning and recovery from PTSD. Furthermore, impaired sleep might also impede upon the effectiveness of clinical treatments for PTSD, the mechanisms for which will be further elaborated on in the following section. Sleep neuroimaging studies have demonstrated regional activation differences between individuals with and without PTSD and have demonstrated increased limbic activity during sleep, which may serve as a marker for nightmares and increased arousal in PTSD that is different in patterns of arousal in insomnia. Results of studies investigating the possible link between HPA-axis dysfunction and sleep in PTSD have been largely equivocal, although the link between both PTSD and sleep-related HPA-axis circadian activity is well established. New evidence suggests a link between BDNF function, sleep, and cognition in PTSD, but this emerging line of inquiry remains open. Research on sleep problems in OEF/OIF/OND Veterans, especially those with PTSD, is beginning to explore the complexity and correlates of these coexisting disorders. However, there is more work to be done as it is imperative that we hone sensitive sleep measures in order to elucidate the neural and behavioral connection between sleep disturbance and PTSD development and maintenance, and the impact of sleep on outcomes in PTSD.

Impact of poor sleep on cognition in PTSD

Individuals with PTSD often complain of memory difficulties that have been hypothesized to be related to hippocampal dysfunction in these individuals (Bremner, 2007). The work of Vasterling and colleagues (2002) supports the association between PTSD and neurocognitive and intellectual performance deficits, citing increased problems with learning, memory, and attention in Vietnam Veterans with PTSD. Other studies have similarly found that in other cohorts of individuals with PTSD, difficulties in attention, learning, and verbal memory are also present (Bremner et al., 1995; Marx, Doron-Lamarca, Proctor, & Vasterling, 2009; Samuelson et al., 2006; Vasterling et al., 2012; Vasterling et al., 2002). Few studies have examined the circumscribed relation between sleep and cognitive function in individuals with PTSD. The potential role of sleep disturbance on PTSD has been peripherally addressed previously in work examining the role of sleep in learning and emotional memory consolidation (Nishida, Pearsall, Buckner, & Walker, 2009; Stickgold, Hobson, Fosse, & Fosse, 2001; Stickgold & Walker, 2005) or by demonstrating that even short periods of sleep such as daytime naps can diminish impulse control (i.e., reactivity to anger and fear inducing stimuli (Gujar, Yoo, Hu, & Walker, 2011). Yoo, Gujar, Hu, Jolesz and Walker (2007) demonstrated the mechanisms for how disturbed sleep can exacerbate and maintain PTSD symptoms by showing that sleep deprivation can enhance negative emotional response by

disrupting connectivity between the amygdala and the medial prefrontal cortices, a pathway that modulates emotional responsivity. However, few studies have examined specific components of cognitive difficulties in PTSD, including attention, executive function, and learning, with respect to poor sleep. One recent study by Brownlow, Brown, and Mellman (2014) demonstrated a relationship between sustained attention, verbal memory, and objectively measured sleep in PTSD. Interestingly, a full night's sleep (approximately 7 hours or greater) mitigated attention errors in PTSD.

Sleep problems and associated cognitive deficits may have an impact on treatment outcome in PTSD. Evidence-based treatments for PTSD, such as cognitive processing therapy or prolonged exposure treatment, have strong learning components involving attention and memory consolidation processes. Furthermore, extinction of conditioned fear responses, which is related to consolidation of emotional memories, is also an important part of psychotherapeutic interventions aimed at alleviating PTSD. Individuals with PTSD have impaired extinction of conditioned fear responses and impaired recall of the extinction (Bleichert, Michael, Vriends, Margraf, & Wilhelm, 2007; Milad et al., 2008; S. P. Orr et al., 2000; Wiseman-Hakes et al., 2013). Given the evidence that sleep—and particularly REM sleep—plays an important role in memory consolidation, including that of emotional memories (Bennion, Mickley Steinmetz, Kensinger, & Payne, 2013; Hu, Stylos-Allan, & Walker, 2006; Payne et al., 2012; U. Wagner, Gais, & Born, 2001; U. Wagner, Hallschmid, Rasch, & Born, 2006), and that sleep promotes generalization of extinction memory (Pace-Schott et al., 2009), it is important to consider the impact of poor sleep on treatment outcome in individuals with PTSD.

Conclusion

Overall, the impact of sleep on cognitive functioning is well studied, although due to the multiple etiologies of poor sleep and distinct methodologies of studying sleep, the conclusion of whether poor sleep has a long-term impact on cognitive function is equivocal. Additionally, the neurobiological mechanism behind the interaction between poor sleep and cognition has yet to be elucidated. However, what is clear from a multitude of studies is that there is an association between sleep and daytime cognition and consolidation of memories, particularly emotionally salient ones. Individuals impacted by PTSD are already vulnerable to cognitive deficits and are at high risk for poor sleep. Therefore, in individuals with PTSD, the additional impact of poor sleep on their everyday function coupled with the loss of benefits associated with restorative sleep is particularly burdensome. In addition to impacting their everyday function, poor sleep may also have a negative effect on psychotherapeutic treatment in those with PTSD.

Management and Treatment of Sleep Problems

Pharmacologic treatments—A thorough review of the pharmacologic treatments of sleep problems is beyond the scope of this paper and was recently reviewed by Richey and Krystal (2011). Briefly, the current first line of pharmacologic treatment for insomnia are the benzodiazepine-receptor agonists medications: zolpidem, zaleplon, and eszopiclone. The main advantage of these medications over the traditional benzodiazepine drugs is their relatively shorter duration, fewer side effects, and low abuse potential (Richey & Krystal,

2011). However, despite the general improvement in efficacy these medications are not consistently effective and have significant side effects including headaches, anxiety, and sleepiness (Krystal, Erman, Zammit, Soubrane, & Roth, 2008). For example, the most common prescribed of these, zolpidem, has not demonstrated consistent effectiveness in sleep maintenance, but is generally helpful in sleep initiation (Rosenberg, 2006). Other pharmacologic treatments for insomnia have included tricyclic antidepressants as well as serotonergic agents such as trazodone, but most medications have not been thoroughly investigated in randomized controlled trials and can have significant side effects.

Prazosin is an alpha-1 antagonist that has been used pharmacologically to treat PTSD-related sleep disturbances and nightmares. Prazosin's mechanism of action has been stipulated to be the attenuation of noradrenergic function during REM sleep, thereby reducing nightmares and related complaints of insomnia (Raskind et al., 2003; Ross, Gresch, Ball, Sanford, & Morrison, 1995). Studies have shown that prazosin-related improvement in sleep is accompanied by improvements in other daytime symptoms of PTSD (Boynton, Bentley, Strachan, Barbato, & Raskind, 2009; Germain et al., 2012; Raskind et al., 2007; Raskind et al., 2003; Raskind et al., 2002; Taylor & Raskind, 2002). A recent randomized control trial of prazosin in returning Veterans with PTSD showed favorable results with reported improvements in nightmares, overall sleep quality, global function, and PTSD symptoms (Raskind et al., 2013). However, substantial residual symptoms remained, suggesting that adjunct treatment was needed.

In addition to prescription medication, over-the-counter pharmacologic sleep enhancers include melatonin, which is a naturally occurring hormone that is endogenously produced by the pineal gland and is important in regulation of circadian rhythms by initiating the feedback circuitry of the suprachiasmatic nucleus. Melatonin has been explored as a hypnotic, but a number of randomized trials have failed to find evidence of efficacy (Richey & Krystal, 2011). Overall, although short-term effects of pharmacotherapy on sleep problems and particularly insomnia are well documented, the long-term benefits are unknown, and long-term use may be associated with multiple adverse effects (Gillin & Byerley, 1990). Some have suggested that pharmacologic sleep agents may negatively impact neural recovery/neuroplasticity in patients recovering from TBI (Larson & Zollman, 2010). Moreover, it has been recently suggested that biological treatments might be the most efficacious for short sleep duration insomnia, while insomnia with normal sleep duration might respond better to psychological treatment (A. Vgontzas & Fernandez-Mendoza, 2013). While some antidepressants prescribed for PTSD might activate BDNF pathways, further research is needed to develop agents that selectively target BDNF function, which have the potential to alleviate cognitive and sleep symptoms in PTSD and TBI (Kaplan et al., 2010). More clinical studies are necessary to understand the efficacy of BDNF-enhancing interventions, such as exercise, and combined pharmacological-behavioral approaches (Chen, Ivy, & Russo-Neustadt, 2006; Kaplan et al., 2010).

Non-pharmacologic treatments—The treatment and management of sleep disturbance has primarily utilized pharmacologic approaches that have the potential for side effects and, in some medications, development of tolerance over time. As sleep disturbances occur for a variety of reasons, including mood difficulties, behavioral factors such as poor stimulus

control, aging-related changes, pain, and other medical conditions, effective and consistent pharmacologic treatment has been difficult to achieve. There is also a growing body of evidence for effectiveness of non-pharmacological interventions, such as cognitive and behavioral treatments, for sleep disturbance in PTSD (Schoenfeld et al., 2012). Given the complexity and multitude of underlying psychological factors that commonly accompany sleep disturbance (Espie et al., 2012), including behavioral intervention in the treatment plan may be beneficial for patients with comorbid PTSD and mTBI (polytrauma for the Veteran population). The current practice guidelines developed by the Standards of Practice Committee of the American Academy of Sleep Medicine recommend using psychological and behavioral interventions for the treatment of chronic primary insomnia (Standard) and secondary insomnia (Guideline) (Morgenthaler et al., 2007). As of 2012, no guidelines specific to treatment of sleep disorders following mTBI have been established (Marshall et al., 2012). Recommendations for sleep disorders have been adopted from current practice guidelines outside of the TBI field. Practice guidelines for incorporation of sleep interventions into management of PTSD are yet to be established (Germain et al., 2013), however, the PTSD algorithm of the Psychopharmacology Algorithm Project at the Harvard South Shore Program has proposed treatment guidelines outlining that sleep evaluation and treatment should be the first step in assessing and treating PTSD (Bajor, Ticlea, & Osser, 2011).

In terms of non-pharmacologic treatments, psychotherapeutic interventions for insomnia have gained momentum in the recent years with the increase of evidence for their efficacy. Cognitive behavioral treatment for insomnia (CBT-I) is a psychotherapeutic treatment that has shown efficacy in treating poor sleep particularly in insomnia (Edinger, Wohlgenuth, Radtke, Marsh, & Quillian, 2001; Galuszko-Wielniak, Jakuszkowiak-Wojten, Wiglusz, Cubala, & Landowski, 2012; Morin et al., 2006) by targeting maladaptive thoughts and behaviors associated with maintaining the cycle of poor sleep. Specifically, the goal of CBT-I is to target factors that maintain insomnia over time including sleep-related anxiety, maladaptive or sleep-interfering behaviors, and the resultant dysregulated sleep drive (Mitchell, Gehrman, Perlis, & Umscheid, 2012). CBT-I uses stimulus control, sleep restriction, and cognitive restructuring to change sleep-related behaviors and thoughts that maintain poor sleep. The treatment is usually administered over the course of 4–8 sessions, with significant improvements often around sessions 3 or 4 (Edinger & Means, 2005; Mitchell et al., 2012). Overall, randomized control trials have found that CBT-I has medium to large effects in reducing insomnia, in comparison to placebo treatments such as wait-list and sleep hygiene programs, that are maintained post-treatment (Sanchez-Ortuno & Edinger, 2012), but unstandardized treatment adherence across protocols complicate the evaluation of CBT-I treatment outcome (Matthews, Arnedt, McCarthy, Cuddihy, & Aloia, 2013). Recently, the favorable efficacy of CBT-I in Veterans and implementation feasibility by VA providers has already been reported (Karlin, Trockel, Taylor, Gimeno, & Manber, 2013). In comparison to pharmacologic treatments trials compared CBT-I to zopiclone, zolpidem, temazepam, and triazolam and overall, found that CBT-I is at least as effective in treating insomnia when compared to these medications (Mitchell et al., 2012). Furthermore, CBT-I efficacy is likely more durable than that of medication (Mitchell et al., 2012).

In the Veteran population, CBT-I has been used to treat PTSD-related sleep disturbances. In a multi-component treatment study, those with PTSD demonstrated post-treatment improvements in their sleep onset latency, awakenings, sleep efficiency, and self-reported sleep quality in response to CBT-I (Ulmer, Edinger, & Calhoun, 2011). However, the nature of the sleep disturbances in individuals with PTSD is substantially different than those experienced by other individuals with sleep problems (see the PTSD and sleep section) and consequently some investigators have aimed at tailoring sleep treatments to sleep disturbances experienced by those with PTSD.

Imagery rehearsal therapies (IRT) are aimed at modulating post-traumatic nightmares by decreasing their frequency and severity through “rescripting” of nightmare content (Kellner, Neidhardt, Krakow, & Pathak, 1992; Kellner, Singh, & Irigoyen-Rascon, 1991) and were first shown to be an effective treatment for nightmares in individuals with PTSD by Krakow and colleagues (2001). There are several different protocols for imagery rehearsal in the PTSD population including Exposure, Relaxation, and Rescripting Therapy (Davis & Wright, 2006), Imagery Rehearsal Therapy (Krakow & Zadra, 2006), and Imagery Rehearsal and Exposure Therapy (Long et al., 2011). Regardless of specific protocol, the main components of each of these treatments are similar and include: psychoeducation, narratives about selected nightmares, and imaginal rehearsal of new dreams, as well as some forms of exposure to the selected nightmares. Over the years, empirical evidence for the efficacy of IRT has been growing and has been shown to reduce nightmare frequency in US Army Veterans (Moore & Krakow, 2007) and female sexual assault victims (Krakow et al., 2001). A recent meta-analysis confirmed that IRT reduces nightmare frequency and improves sleep quality in a variety of trauma-related study samples and protocols (Casement & Swanson, 2012). On the contrary, the largest study to date, conducted in Vietnam era Veterans did not find IRT to be effective, compared to an active control condition (Cook et al., 2010) therefore, the efficacy of IRT in Veterans with PTSD is still not fully determined. Further, a recent review of the current evidence base for IRT in PTSD revealed a lack of higher-level study designs and methodological inconsistencies across treatment protocols, none of which have been compared directly (Harb et al., 2013). These studies highlight the limited data supporting the efficacy of IRT for the treatment of PTSD.

Others have combined IRT and CBT-I treatments or components of each of these cognitive behavioral therapies in order to target both the PTSD-related nightmares as well as the general sleep dysregulation that is especially prevalent in the Veteran population. Studies of combined treatment have varied from group treatments to individual therapies and have found significant effect sizes in improvement of nightmares, sleep quality, and PTSD symptoms (Davis & Wright, 2006; Germain, Shear, Hall, & Buysse, 2007; Krakow et al., 2001; Nappi et al., 2012; Ulmer et al., 2011). Overall, these studies demonstrate a greater improvement in overall sleep quality than IRT alone (Casement & Swanson, 2012). Furthermore, at least one study comparing a behavioral intervention for sleep and nightmares found that the behavioral treatment was comparable to prazosin in reducing insomnia severity and PTSD-related daytime symptoms in Veterans with PTSD (Germain et al., 2012). Another recent study reported improved subjectively and objectively measured sleep and a reduction in PTSD symptom severity and PTSD-related nighttime symptoms in OEF/OIF/OND combat Veterans with PTSD following 4 sessions of combined CBT-I/IRT,

compared to a waitlist control group (Margolies, Rybarczyk, Vrana, Leszczyszyn, & Lynch, 2013). A recent case report described that treatment of insomnia in a Veteran patient with CBT-I improved sleep and facilitated entry into exposure therapy for PTSD (Baddeley & Gros, 2013). The preliminary results of this case study also highlight the importance of investigating the most efficacious order of evidence-based psychotherapies, particularly in comorbid insomnia and PTSD.

Conclusion

Treatment of sleep disorders has relied on pharmacologic management for many years. More recently other methods of treating sleep disorders have gained attention, particularly with sleep problems gaining recognition for their prevalence and the long-term efficacy and side effects of pharmacologic agents remaining in question. Behavioral treatments of insomnia are promising, particularly for individuals with insomnia related to mood and anxiety disorders including individuals with PTSD. For Veterans returning from the OEF/OIF/OND arenas, sleep problems are especially prevalent and are often co-occurring with both PTSD and mTBI (Wallace et al., 2011). These young Veterans are particularly encumbered by the mood, cognitive, and health difficulties that are associated with PTSD and without the additional burden of sleep problems. Behavioral treatments of PTSD do not address sleep as a primary target, yet sleep difficulties may be an important barrier for good treatment outcome (Nappi et al., 2012). This area of research is currently lacking in the literature, particularly as it pertains to PTSD.

SLEEP DISTURBANCES FOLLOWING TRAUMATIC BRAIN INJURY

Sleep and circadian disturbances in TBI

Daytime sleepiness and nighttime sleep disturbance are common following TBI (Baumann, 2012). Common post-traumatic sleep-wake disturbances (SWDs) include; poor nocturnal sleep quality, hypersomnia, excessive daytime sleepiness, impaired daytime vigilance, and circadian rhythm phase shift (Ayalon et al., 2007; Baumann, 2012; Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007; Kempf, Werth, Kaiser, Bassetti, & Baumann, 2010; Ponsford, Parcell, Sinclair, Roper, & Rajaratnam, 2013). Objective sleep studies have shown that patients with TBI exhibit reduced sleep efficiency, increased wakefulness after sleep onset, increased sleep onset latency, alterations in sleep architecture (less REM sleep, more time in “light” NREM sleep), and report more frequent insomnia (Baumann et al., 2007; Collen, Orr, Lettieri, Carter, & Holley, 2012; Mathias & Alvaro, 2012; Ponsford et al., 2012; Shekleton et al., 2010). Reports have shown that 25–81% of post-acute TBI patients suffer protracted or even permanent SWDs or other sleep disturbances (Mathias & Alvaro, 2012), regardless of localization, severity of, or time since, the TBI (Baumann et al., 2007; Castriotta et al., 2007; Kempf et al., 2010). Not only is the prevalence of sleep problems in TBI patients significantly higher than in the general population (Mathias & Alvaro, 2012), these sleep problems are chronic and have been shown to persist at 6 months and up to 5 years post-injury (Beetar et al., 1996; Fogelberg, Hoffman, Dikmen, Temkin, & Bell, 2012; Kaufman et al., 2001; Kempf et al., 2010; Masson et al., 1996; Stulemeijer et al., 2006; Tham et al., 2012; Watson, Dikmen, Machamer, Doherty, & Temkin, 2007).

There is a lack of understanding regarding the temporal relationship between primary brain injury and the subsequent emergence and maintenance of SWDs. SWDs are common during the acute TBI phase, as evidenced by objectively and subjectively measured hypersomnia and reduced sleep efficiency (Chiu, Lo, Chiang, & Tsai, 2014) and can persist up to 5 years post-injury (Masson et al., 1996). However, many of the long-term follow-up studies are based on subjective sleep measures, thus, it is possible that protracted sleep complaints are related to sleep state misperceptions following the initial experience of objective sleep problems (Orff, Ayalon, & Drummond, 2009). Prior work has also demonstrated that the spectrum of mild to severe TBI patients is affected by objectively measured chronic SWDs (Verma, Anand, & Verma, 2007). The type of brain injury (e.g., diffuse, focal) might influence the type and severity of SWD (Orff et al., 2009). Recent animal work has shown hypersomnia during the first week following induction of diffuse TBI, however post-traumatic hypersomnia did not develop into chronic sleep disturbance (Rowe, Harrison, O'Hara, & Lifshitz, 2014). These data suggest that hypersomnia following diffuse TBI (e.g., blast exposure) does not necessarily develop into persistent sleep problems. A recent study by Ponsford and colleagues (2013) demonstrated that poor sleep quality and daytime sleepiness increases with time since injury in older TBI patients relative to younger TBI patients, suggesting an interaction between sleep disturbances, aging, and time since injury in TBI. These findings highlight the importance of considering the course of sleep disturbances in TBI in Veterans across the life span as Veterans age. Future work is needed to understand the relationship between injury severity and type and the development and persistence of SWDs.

A recent meta-analysis using data from 21 studies (n=1706) examined twenty-one years of TBI and sleep literature (1990–2011) (Mathias & Alvaro, 2012). The group reported that in studies that used objective sleep measures in conjunction with formal diagnostic criteria; the prevalence of sleep disturbances was 53%. Compared to the prevalence reported in the general population, the TBI group was found to be significantly more likely to experience sleep disturbances and was more than 12 times more likely to have diagnosed sleep disorders. The authors also reported several challenges to the clinical utility of these studies due to differences in criteria, which may explain the wide range of sleep disturbance incidences described in the literature. In similar vein, a survey by the Armed Forces Health Surveillance System found that sleep disorders were among the most common sequelae following TBI in the active duty Armed Forces service members between the years 2000–2012 (AFHSC, 2013). Farrell-Carnahan, Franke, Graham, and McNamee (2013) recently found that in a sample of 114 returning Veterans with blast-induced mild traumatic brain injury, 77% reported subjective sleep difficulties. The foregoing findings highlight the need for standardized criteria and sleep measures to allow for more meaningful comparisons across studies and more powerful meta-analytic reviews.

It is the general consensus in the literature that SWDs can be considered primary to TBI and are not solely attributable to secondary physical or psychological symptoms (Beetar et al., 1996; Clinchot, Bogner, Mysiw, Fugate, & Corrigan, 1998; Fichtenberg, Millis, Mann, Zafonte, & Millard, 2000; Ouellet, Beaulieu-Bonneau, & Morin, 2006; Ponsford et al., 2012; Tham et al., 2012). The most comprehensive of these studies was conducted in 2007 by Baumann and colleagues, who investigated the risk factors and biomarkers for posttraumatic

SWDs at 6 months post injury by obtaining neuropsychiatric and lab data, computerized tomography, sleep latency tests, PSG, and ACT from 65 patients with TBI at 4 days and 6 months post injury (Baumann et al., 2007). New onset SWDs were found in 72% of the patients and 60% of those patients had a SWD that could not be attributed to any specific cause (e.g., restless leg syndrome, OSA, behaviorally induced insufficiency sleep syndrome, depression) other than the TBI itself (Baumann et al., 2007). The cumulative impact of multiple brain injuries may also increase the severity of sleep disturbances. For example, Bryan (2013) reported that, compared to a single TBI and no TBI, multiple TBIs were associated with an increased risk for and severity of sleep difficulties in male service members in Iraq. Together, these findings suggest the effect of TBI on SWDs is cumulative and potentially causal.

Mild TBI patients, who comprise 70–90% of the treated TBI population (Cassidy et al., 2004), have been shown to have a higher rate of SWDs than those patients with more severe head injuries (Mahmood, Rapport, Hanks, & Fichtenberg, 2004; Orff et al., 2009; Ouellet et al., 2006; Parcell, Ponsford, Rajaratnam, & Redman, 2006). While TBI patients are generally susceptible to SWDs regardless of the severity of the head injury, one longitudinal study suggested that those with mild injuries are more likely to report symptoms of insomnia whereas those with more severe injuries are more susceptible to hypersomnia (Masson et al., 1996). Parcell, Ponsford, Rajaratnam, & Redman (2006) collected sleep diary data and found that individuals with TBI reported more nighttime awakenings, longer sleep onset latency, lighter (fragmented) sleep, and a change in bedtime (either earlier or later) compared to their pre-injury levels. This study also reported that those patients with milder brain injuries, amongst a mixed severity control sample, reported more nighttime awakenings. While some studies (Mahmood et al., 2004; Parcell et al., 2006) have found subjective sleep quality to be more severely impaired in mTBI compared to severe TBI, a recent study by Ponsford and colleagues (2013) did not replicate these findings. The authors suggest their findings might be explained by the fact that their mTBI group did not have higher anxiety or depression compared to the moderate and severe TBI group, suggesting the role of psychiatric symptoms contributing to increased sleep disturbance in mTBI. It is important to note that inconsistencies in the literature regarding the prevalence and severity of sleep disturbances across the TBI spectra, as in PTSD, may also reflect sleep state misperceptions (for a review see Orff et al., 2009).

In mTBI there is also evidence, albeit inconclusive, of circadian rhythm sleep disorders (CRSDs) (for a review see Orff et al., 2009). Ayalon and colleagues (2007) utilized PSG, ACT, temperature and melatonin data, as well as morningness/eveningness to measure the prevalence of CRSDs in 42 mTBI patients with complaints of insomnia. The authors reported a significantly higher incidence of CRSDs in the mTBI sample when compared to the prevalence amongst people attending sleep clinics with complaints of insomnia (36% vs 10%). Based on ACT data, 8 of the patients exhibited delayed sleep phase syndrome and 7 exhibited an irregular sleep-wake pattern. True to the clinical definitions, when compared to normative sleep-wake times, the data showed that the delayed sleep phase patients experienced delayed sleep onset (Mean = 2:33 am, Standard deviation = 76 mins) and offset times (Mean=11:57 am, Standard deviation =127 mins) while irregular sleep-wake pattern patients classically exhibited a disorganized and variable sleep and wakefulness episodes

(day-to-day onset and offset variability > 2 hours). The incidences of delayed and irregular sleep phase were nearly equal in the mTBI sample, whereas amongst CRSD patients in sleep clinics rates are typically 85% and 2%, respectively (Dagan & Eisenstein, 1999). However, the authors note that patients with advanced or delayed sleep phase can exhibit normal sleep durations if allowed to choose their sleep schedule, which might mean that circadian shift disorders can go undetected if only sleep duration-related variables are examined out of the context of sleep pattern. While Ayalon and colleagues (2007) detected a significantly higher incidence of CRSDs and distinct temperature and melatonin profiles amongst the mTBI sample, Steele, Rajaratnam, Redman, and Ponsford (2005) reported no difference in sleep timing or melatonin onset in a sample of 10 TBI patients when compared to age and gender matched controls. However, the discrepant results between these two studies might be due to the fact that the majority of those from the latter study presented with moderate TBI. Moreover, anecdotally, one earlier case study published by Quinto, Gellido, Chokroverty and Masdeu (2000) describes the presence of new-onset delayed sleep phase syndrome at 4 years post mTBI. Despite a limited number of studies, these findings highlight the possibility of CRSDs following TBI.

While many TBI patients experience sleep disturbance, others report wake-related complaints such as fatigue, excessive daytime sleepiness, and hypersomnia (Baumann et al., 2007). Schreiber and colleagues (2008) reported increased daytime tiredness and a tendency to fall asleep during the day in a group of 26 mTBI patients compared to healthy matched controls. Kempf and colleagues (2010) followed a cohort of mixed severity TBI patients and reported that 67% of the patients who had endorsed sleep disturbances at 6 month post-injury continued to experience excessive daytime sleepiness, hypersomnia, fatigue, and decreased vigilance at 3 years post-injury. In fact, fatigue and hypersomnia increased at 3 years post injury and persisted up to 5 years post-injury (Bushnik, Englander, & Wright, 2008; Kempf et al., 2010). It has been reported that 20–33% of mTBI patients reported increased levels of fatigue compared to pre-injury levels (Englander, Hall, Stimpson, & Chaffin, 1992; Middleboe, Andersen, Birket-Smith, & Friis, 1992; Stulemeijer et al., 2006). It is not clear if wake-related complaints are the result of nocturnal sleep disturbance or a direct result of neuronal injury.

Recent works suggests biomarkers, such as relative cerebral metabolic rate of glucose, are potentially sensitive measures of sleep and wake anomalies in TBI. Stocker and colleagues (2014) used [^{18}F]-fluorodeoxyglucose positron emission tomography to compare glucose metabolism during wakefulness, REM sleep, and NREM sleep in Veterans with a history of blast exposure without current concussive symptoms, relative to Veterans without a history of blast exposure. After controlling for PTSD symptoms, results revealed hypometabolism in limbic regions and visual cortices during wake and REM sleep in blast-exposed Veterans, despite similar PSG profiles and PSQI scores as the non-blast exposed group. Such findings suggest that there might be metabolic dysregulation during REM sleep and wake indicative of functional impairments in chronic blast-induced TBI—beyond stress or sleep symptoms—that would otherwise go undetected using standard sleep measures.

Conclusion

There are numerous possible refractory and protracted sleep disturbances in TBI, including hypsomnia, hypersomnia, and circadian dysrhythmia. Prior work has established a direct association between disturbed sleep and TBI beyond co-occurring psychological symptoms (Baumann et al., 2007). The mTBI population, which accounts for the majority of the TBI population, might be most affected by the sleep disturbances, compared to moderate and severe TBI. It is unclear how sleep disturbance severity interacts with the type and severity of brain injury as well as time post-injury. Further, the effects of head injury on sleep disturbance are cumulative, which is particularly problematic for returning Veterans with repetitive blast-induced mTBI. However, as in the PTSD literature, the inconsistent reports of the prevalence of SWDs in TBI might arise from sleep discrepancies between objective and subjectively measured sleep in TBI, suggesting sleep state misperceptions. More research is necessary to understand how objective and subjective measures can best characterize the incidence and persistence of SWDs across the spectrum of TBI severity. Further longitudinal studies and meta-analytic reviews with standardized sleep measurement criterion are also needed to delineate the complex temporal relationship between TBI and SWDs.

Pathophysiology of mTBI and relation to sleep

The prevalence of both sleep and arousal related complaints following TBI appear to be directly attributable to damage to sleep-regulation centers and arousal networks in the brain. Although these networks are mutually inhibitory, they are nonetheless distinct and it is important to investigate sleep and arousal related dysfunction both together and separately in the context of brain injury. In order to parse apart the factors underlying the complex relationship between sleep and TBI we briefly review the pathophysiology of mTBI in relation to sleep and arousal networks.

There are two types of traumatic brain damage; primary and secondary. Primary traumatic brain injury occurs at the moment of physical trauma and refers to the immediate mechanical load on the brain during rapid acceleration, deceleration, direct impact, penetration, and/or blast wave (Maas, Stocchetti, & Bullock, 2008). Primary damage affects the brain on both the tissue and cellular levels. Diffuse axonal injury, the most common form of primary tissue injury, results from rapid rotational acceleration of the brain that causes dynamic shearing of white matter tracts as well as tensile and compression strain (Johnson, Stewart, & Smith, 2013; Kan, Ling, & Lu, 2012). Other types of primary damage can include focal contusions, hematomas, and edema (Kan et al., 2012). Diffuse axonal injury is also of particular interest as it is common across the TBI severity spectrum (Johnson et al., 2013).

Following the impact of the trauma, primary injuries can induce a cascade of secondary complications, which are associated with a myriad of biochemical processes including excitotoxicity, inflammation, free radical generation, oxidative stress, lipid peroxidation, hyperglycolysis, hyperglycemia, gene activation, neurotransmitter release, and calcium mediated damage (Johnson et al., 2013; Kan et al., 2012). Secondary damage can induce dysfunction at the mitochondrial level (Johnson et al., 2013; Kan et al., 2012; Maas et al.,

2008). While the frontal lobes are the most susceptible to TBI-related injury (Dombovy, 2011; Marquez de la Plata et al., 2011), cortico-spinal strain and shear can inflict injury upon more distant, subcortical brain regions (Baumann, 2012). One of the most commonly affected areas following a TBI is the corpus callosum (Morey et al., 2013). Some have speculated that damage to the callosal fibers, which may aid in synchronization of interhemispheric connectivity during REM and NREM sleep (Bertini et al., 2004; Buchmann et al., 2011; Nielsen, Montplaisir, & Lassonde, 1992) and regulate the modulation of timing of REM sleep (Nielsen et al., 1992), contributes to disrupted sleep-wake processes.

Sleep promoting regions of the brain are still under investigation, however, the preoptic area including the ventrolateral (VLPO) and median (MNPO) preoptic areas have been shown to contain sleep-promoting neurons (Gong et al., 2004; D. McGinty et al., 2004; Sherin, Shiromani, McCarley, & Saper, 1996). The neurons in these regions are active during (NREM) sleep and are inactive during wakefulness (Suntsova, Szymusiak, Alam, Guzman-Marin, & McGinty, 2002; Szymusiak, Alam, Steininger, & McGinty, 1998; Takahashi, Lin, & Sakai, 2009). Lesion studies of the VLPO and MNPO have demonstrated a marked reduction in overall quantity and quality of sleep (Lu, Greco, Shiromani, & Saper, 2000; D. J. McGinty & Serman, 1968). The VLPO and MNPO are thought to promote sleep by inhibiting arousal regions during sleep. Their nuclei release the inhibitory neurotransmitter gamma-aminobutyric acid and the inhibitory neuropeptide galanin and innervate brain areas that function in arousal including the locus coeruleus, dorsal raphe, and the hypothalamic orexin/hypocretin neurons (Gaus, Strecker, Tate, Parker, & Saper, 2002; Saper, Fuller, Pedersen, Lu, & Scammell, 2010; Saper, Scammell, & Lu, 2005; Sherin, Elmquist, Torrealba, & Saper, 1998). This inhibitory interaction functions similarly to a flip-flop switch (Saper et al., 2001), by which a transition from wakefulness to sleep and vice versa is produced when the system is pushed into one direction or the other. However with neuronal loss or damage on either side of the switch, the result may be less stability in the inhibitory mechanisms of the switch, thus resulting in more transitions between sleep and wakefulness (i.e., frequent awakenings) (Chou et al., 2003). For example, some have suggested that age-related cell loss in the VLPO results in sleep fragmentation and increased daytime sleepiness due to weakening of the flip-flop switch (Saper, Cano, & Scammell, 2005).

It has been postulated that fatigue-related symptoms following TBI might have specific neurobiological underpinnings (Belmont, Agar, Hugeron, Gallais, & Azouvi, 2006). The wake promoting neurotransmitter hypocretin (orexin) is produced by a distinct set of neurons in the posterior hypothalamus (Baumann, 2012) and plays a crucial role in sustaining arousal, and preventing flip-flop between sleep-wake transition states (Saper, Scammell, et al., 2005) and fatigue-related symptoms following TBI may be due to damage to the system sustaining arousal via the “flip-flop” switch (Belmont et al., 2006). Low cerebrospinal fluid (CSF) hypocretin (orexin) has been reported in patients following TBI (Baumann et al., 2009; Baumann et al., 2005). While hypocretin (orexin) levels recovered in some patients at 6 months post-TBI, some patients showed only a partial recovery. Moreover, the reported low levels of CSF hypocretin at 6 months post injury were associated with excessive daytime sleepiness (Baumann et al., 2007).

As mentioned earlier, a growing body of evidence suggests dysregulation of BDNF in TBI and PTSD (for a review see Kaplan et al., 2010). There is evidence that upregulation of BDNF reduces the impact of secondary injury following TBI (Kaplan et al., 2010). However, there might be decreases in BDNF with increased time since injury, resulting from tissue loss over the first year post-injury (Schober, Block, Requena, Hale, & Lane, 2012). Previous work suggests a causal link between BDNF expression during wakefulness and subsequent slow-wave activity (SWA) during sleep (Faraguna et al., 2008). SWA is a sensitive marker for sleep need and NREM sleep intensity, as evidenced by increased SWA following prolonged daytime activity (Faraguna et al., 2008). Further, exogenous application of BDNF to one hemisphere in awake rats is associated with increased SWA during NREM in sleep the BDNF-injected hemisphere relative to the contralateral hemisphere and vehicle injection group (Faraguna et al., 2008). Given the foregoing findings, it is possible that downregulation of BDNF in chronic TBI or PTSD (or an interaction of the two) could decrease NREM sleep intensity and/or drive for sleep initiation.

Conclusion

Despite a multitude of secondary complications associated with TBI, it appears that SWDs may be linked to the neuronal injury itself, while psychiatric co-morbidities such as depression may serve as additional risk factors for post-traumatic SWDs (Baumann et al., 2007; Kempf et al., 2010). Incongruent findings between studies and wide ranges of SWD incidences reported in the literature may be due to heterogeneous methodologies including variability of: measures and methods used to obtain the data, sample size, and proportion of TBI severity groups within mixed samples (Baumann et al., 2007). Inconsistent findings and reported discrepancies in prevalence of mild and severe TBI, particularly by studies using subjective (self-report) sleep measures, may also be due to varying levels of anxiety, depression, or patient's self-insight, as patients with mTBI may have increased awareness of post-injury health complications and may be more likely to report sleep disturbance as an injury-related problem (Tham et al., 2012). Moreover, studies that collapse data from the mixed severity samples may lack sensitivity to detect the differences in sleep disturbance presentation between mild, moderate, and severe TBI. Finally, mixed findings of sleep disturbances in TBI may reflect the differential neuronal injury profiles resulting from variable sources of insult (i.e., blast, motor vehicle accident, etc). Overall, research suggests that sleep and arousal deficits are clearly present in individuals with TBI regardless of severity, and there are likely neurobiological underpinnings to these difficulties that need to be investigated further in order to elucidate the mechanism of recovery and to improve outcomes in TBI.

Impact of sleep on cognition in TBI

In individuals with TBI, cognitive deficits are among the most frequently reported symptoms regardless of severity of the injury (Senathi-Raja, Ponsford, & Schonberger, 2010; Heidi Terrio, Nelson, Betthauser, Harwood, & Brenner, 2011). In mTBI, decrements in performance are found in processing speed, working memory, attention, memory, and executive functioning immediately post-injury (Frencham, Fox, & Maybery, 2005), but problems often decrease with time after injury (Brenner et al., 2010). Despite the evidence that performance on cognitive measures improves over time after mTBI, subjective

complaints remain (Senathi-Raja et al., 2010; Heidi Terrio et al., 2009) raising the possibility that traditionally used objective measures may not be able to capture the subtle difficulties experienced by individuals with mTBI (Brenner, 2011). Additionally, it has been postulated that although cognitive performance among individuals with mTBI may not be substantially different than those without TBI, they may require more functional resources to complete tasks, such as requiring larger areas of their cortex for task completion (Van Boven et al., 2009).

Sleep difficulties in those with mTBI may further impact their cognitive functioning and may contribute to the variability in cognitive performance, which may also explain the reported discrepancies in the literature discussed earlier in this review. Individuals with TBI are particularly vulnerable to sleep difficulties, and some evidence suggests that those with mTBI may be at even greater risk for sleep disturbances compared to more severe TBI, due to greater self-insight and therefore may present with increased vulnerability to sleep deficits associated with psychological and emotional factors (Bloomfield, Espie, & Evans, 2010). Indeed, at least one study examining whether sleep difficulties exacerbate deficits in sustained attention following TBI found that when individuals with TBI were separated into good and poor sleepers, based on both subjective and objective measures of sleep, poor sleepers performed significantly worse on measures of sustained attention (Bloomfield et al., 2010). A large proportion of individuals coming from the OEF/OIF/OND combat arenas present with both PTSD and mTBI and approximately 40% of PTSD-mTBI Veterans report severe sleep disturbances (Wallace et al., 2011) as well as cognitive problems (Schiehser et al., 2011; Spencer, Drag, Walker, & Bieliauskas, 2010). Therefore, the examination of the relation between their cognitive difficulties and sleep problems is particularly important. Kark and colleagues (2013) examined the relationship between sleep, PTSD symptom severity, daily cognition, and quality of life in OEF/OIF/OND Veterans with exposure to blast and current cognitive complaints. Veterans with PTSD had worse sleep on both subjective and objective measures of sleep quality and poor sleep was related to worse self-reported daily cognition, poorer community integration, and reduced satisfaction with life.

Conclusion

Cognitive deficits, namely attention, concentration, and executive dysfunction, are the primary complaints of individuals with TBI. There is evidence that these deficits may be exacerbated by poor sleep, however few studies have examined the association between poor sleep following TBI and cognition. It is also unclear how severity, type, and number of brain injuries might contribute to objective and subjective cognitive impairments differently. Future work is needed to not only understand how poor sleep perpetuates poor cognition, but also how cognitive impairment might effect sleep (e.g., elevated stress related to adverse functional consequences of executive dysfunction).

Sleep interventions in TBI

Studies of pharmacologic treatment in TBI have mostly focused on treatment of fatigue and daytime somnolence associated with moderate to severe TBI. One study examined individualized treatment of patients with TBI that involved either pharmacologic or behavioral treatment and found that effective treatment optimized recovery and outcomes for

adults with chronic TBI. Notably, the authors did not specify the modality of treatments used (Wiseman-Hakes et al., 2013).

There is a paucity of studies examining the efficacy of treatments aimed at alleviating sleep difficulties and fatigue in individuals with TBI. One single-case experimental design study found that CBT-I reduced nocturnal sleep difficulties in one individual with TBI (Ouellet & Morin, 2007). A recent study examining the impact of sleep interventions in a small group of moderate to severe TBI (n=10) and 2 mTBI patients, found that individualized sleep interventions that included sleep hygiene recommendations, pharmacological interventions and/or treatments for sleep apnea, was associated with improvements in insomnia severity, depression symptoms, speed of cognitive processing, and language functions (Wiseman-Hakes et al., 2013). As with other individuals with sleep difficulties, long term use of pharmacologic agents for sleep is not generally recommended and is particularly not recommended for individuals with TBI due to side effects such as impaired daytime alertness and cognitive function that could prove an additional burden (Flanagan, Greenwald, & Wieber, 2007; Larson & Zollman, 2010). Further careful consideration is required for treatment of sleep in comorbid TBI and PTSD, since some traditionally prescribed PTSD medications may further exacerbate the TBI- and/or treatment-related cognitive problems. One study examined the effect of melatonin on sleep and daytime alertness in comparison to amitriptyline. This study found no improvement in sleep quality with either treatment, but found that melatonin had a greater effect on daytime alertness than amitriptyline (Kemp, Biswas, Neumann, & Coughlan, 2004). Another study recently reported that relaxation treatment in OEF/OIF/OND Veterans with mTBI was an acceptable milieu by both patient and provider, although the Veterans preferred a combination of relaxation and pharmacologic treatment (Epstein, Babcock-Parziale, Haynes, & Herb, 2012).

There is emerging evidence for the therapeutic utility of novel non-invasive neuromodulation interventions, such as low-level laser therapy (LLLT) in sleep disorders. Therapeutic effects of LLLT using red light-emitting diodes (LED) on sleep were demonstrated in healthy adults (Zhao, Tian, Nie, Xu, & Liu, 2012) and patients with insomnia (Xu, Wang, Ta, & Li, 2001; Xu, Wu, Wang, Shang, & Li, 2002). We are aware of one pilot study reporting improved sleep and PTSD symptoms following the red/near infra-red LED treatment in patients with chronic moderate TBI and comorbid PTSD (Bogdanova et al., 2014). The study results suggest that sleep structure (ACT recordings) can be changed by transcranial LED treatment in patients with chronic TBI, as sleep efficiency increased one week post-LED treatment and was maintained at 2-month follow-up. LED is a non-invasive, portable and relatively inexpensive neuromodulation treatment with potential to reduce multi-symptoms in patients with TBI and associated comorbidities, such as sleep disturbance and PTSD. More research and randomized controlled studies are needed to investigate specific LED effects on sleep and other neuropsychiatric symptoms in this population.

Treatment with bright light to improve daytime function and alertness has been suggested in TBI, but there were no published studies evidencing its efficacy (Ponsford et al., 2012). A recent study evaluated efficacy of short wavelength (blue) light therapy on fatigue in patients with TBI who self-reported fatigue and/or sleep disturbance (Sinclair, Ponsford, Taffe, Lockley, & Rajaratnam, 2014). Researchers reported that the high-intensity blue light

therapy resulted in reduced fatigue and daytime sleepiness during the treatment phase, with a trend toward baseline levels 4 weeks after the treatment. The authors concluded that the light therapy appears to be effective in alleviating fatigue and daytime sleepiness following TBI.

Taken together these and other preliminary findings suggest that novel photobiomodulation therapeutic approaches have the potential to reduce sleep disturbance in patients with TBI and associated neuropsychiatric symptoms.

Conclusion

Sleep disturbance presents significant problems for the returning Veterans with TBI and associated neuropsychiatric comorbidities, such as PTSD and depression. Given that sleep plays an important role in the physiologic processes underlying neural recovery (Parcell, Ponsford, Redman, & Rajaratnam, 2008), it is critical to identify and treat sleep disorders in patients with TBI early in order to promote and facilitate their recovery. As we discussed earlier, pharmacologic management has been the main treatment option for sleep disorders for patients with insomnia and other neurologic and neuropsychiatric disorders. There is limited evidence for treatments specifically aimed at alleviating sleep disturbance in TBI or TBI with PTSD. Recent studies suggest that novel neuromodulation treatments, such as LED or light therapy, can improve sleep in TBI, and may potentially provide a safe and non-invasive non-pharmacological treatment for patients with TBI and associated neuropsychiatric comorbidities.

CHALLENGES AND FUTURE DIRECTIONS

There is currently a need for research to identify best practices for treatment of patients with mTBI and associated comorbidities, such as PTSD and sleep disturbance (Report of VA Consensus Conference, 2010). An interdisciplinary team approach can provide the necessary resources for diagnosis and treatment of multiple comorbidities in this population (Institute of Medicine, 2011). Future efforts should focus on the development of new treatment protocols and multi-modal treatment programs that could be individually tailored to better serve the patient's individual needs.

One of the challenges in treatment planning for returning Veterans with TBI, PTSD, and sleep difficulties is determining the optimal timing for treatment of each of the multiple health issues. The argument in favor of early treatment of cognitive dysfunction may be based on the premise that TBI-related cognitive deficits may diminish treatment response to PTSD interventions, such as cognitive-behavioral treatment or exposure therapy (Bogdanova & Verfaellie, 2012). Alternatively, PTSD treatment may become a priority for patients with more severe PTSD symptomatology, since problems with impulse control and emotion regulation may affect patient's ability to engage in cognitive treatment (Bryant & Hopwood, 2006). Moreover, there is a possibility that PTSD interventions may also help to improve sleep but in most cases sleep problems remain at clinical levels (Belleville, Guay, & Marchand, 2011; Galovski, Monson, Bruce, & Resick, 2009; Zayfert & DeViva, 2004) even after successful PTSD treatment. However, if sleep problems do indeed stand in the way of successful recovery from PTSD and mTBI, then sleep may become the principal target of

treatment, possibly preceding the start of intervention targeting the primary symptoms for each condition. Future clinical trials may provide a much needed evidence base.

Another key issue to consider is treatment accessibility. Providing treatment to patients in rural locations might be possible utilizing web-based treatment paradigms. Though limited, there is emerging evidence that web-based CBT with automated support may be effective in improving the sleep and associated daytime functioning of adults with insomnia (Espie et al., 2012). Tele-health protocols specifically targeting sleep difficulties in Veterans with multiple comorbidities should be developed and implemented. Three recent research reports demonstrate that up to eight weekly sessions of telephone-delivered CBT-I (Arnedt et al., 2013) or five weeks of computerized CBT-I (Vincent & Walsh, 2013) or six weeks of unsupported, internet-delivered self-help CBT-I (Lancee, van den Bout, van Straten, & Spoormaker, 2012) can improve sleep in adults with chronic insomnia. It would be also important to evaluate whether such protocols can be utilized in treating active duty military personnel. For example, one recent study reported efficacy of a behavioral intervention for insomnia in OEF/OIF/OND Veterans that involved one in-person and three telephone sessions as well as electronic delivery components (Epstein et al., 2013). The authors reported large effect sizes for pre- to post-treatment decrease in insomnia severity and sleep improvements were maintained at 3-months post-treatment.

Further research is needed to develop treatment programs that would optimize outcome and increase adherence to the treatment, which presents significant challenge for Veterans with mTBI/PTSD and their providers (Sayer et al., 2009). PTSD symptoms, such as emotional dysregulation and avoidance may significantly limit and disrupt the treatment of sleep or cognitive problems. Web-based treatment programs, as well as integrated programs implemented in primary care clinical settings, might be easier for Veterans to handle. Randomized clinical trials are needed to evaluate efficacy of such programs in Veteran population.

While there is currently much interest in potential biomarkers for the diagnosis and prognosis of outcome in TBI, this area is still under development. Research is needed to develop methods for identification of predictors and moderators of natural recovery and treatment outcomes in Veterans with TBI and multiple comorbidities, such as sleep problems and PTSD, so that treatment programs can be optimized to fit the patient's needs. Future research efforts can elucidate the neural bases of sleep interventions and the mechanisms of change underlying the efficacy of sleep treatments, and inform the future treatment programs development.

SUMMARY

TBI and PTSD are currently in the spotlight as problems impacting the current wave of Veterans returning from the OEF/OIF/OND combat arenas. However, neither condition is specific to this group of Veterans as both have been endemic to combat and non-combat Veterans through generations. More recently, sleep has gained the attention of researchers and clinicians from a variety of disciplines, being recognized as bi-directionally related to multiple psychological and medical conditions, as well as mortality. While sleep problems

have been shown to impact quality of life and functional status on many levels, including psychological, cognitive, and physical functioning, it is also understood that sleep can be disrupted by multiple physical and psychological conditions.

Sleep is among the primary symptoms of PTSD and TBI, and one of the mediating factors affecting the level of severity and treatment outcome of both conditions. Despite its high prevalence, few treatments and rehabilitation protocols target sleep as a primary symptom; although in many cases even after the resolution of mTBI or PTSD, poor sleep remains at clinical levels (Belanger, Morin, Langlois, & Ladouceur, 2004; Clum, Nishith, & Resick, 2001; Kramer, Booth, Han, & Williams, 2003; Wittmann, Schredl, & Kramer, 2007) and continues to impact daily functioning and quality of life (Belanger, Morin, Langlois, & Ladouceur, 2004; Clum, Nishith, & Resick, 2001; Kramer, Booth, Han, & Williams, 2003; Wittmann, Schredl, & Kramer, 2007).

One of the key problems in sleep research is that sleep is not a stable state, and sleep need and drive vary significantly between individuals, especially those with neurologic and neuropsychiatric disorders. As a result, the research on sleep, which is limited by the nature of the sleep state and sleep measurement (i.e., objective vs. subjective reporting; inter-individual and within-individual differences), has resulted in many inconsistencies among studies and a lack of consensus on a variety of sleep-related issues, including treatment recommendations. Future research efforts should target the development of sleep-focused interventions and multi-modal treatment programs adjustable to the specific needs of patients with multiple comorbidities, such as TBI, PTSD, depression, and sleep disturbance.

Research suggests that sleep is necessary for the consolidation of memories and is important for cognitive, psychological, and physical functioning, which leads to the main point presented in this review: *evaluation and treatment of sleep problems in TBI and PTSD should become an integral part of clinical management of these disorders*. Although the treatment of sleep problems has long been rooted in pharmacology, more recently developed non-pharmacologic interventions have proven effective in treating sleep, and may become efficient clinical tools to improve daily functioning, treatment outcome, and quality of life in individuals with TBI and PTSD.

Acknowledgements

We would like to acknowledge Shana DeLuca, B.S., and Megan Yee, M.A., for assistance with manuscript preparation.

Role of funding sources

This work was supported by the Rehabilitation Research and Development Service of the Department of Veterans Affairs (VA) grants D6996W and I21RX001773-01 to YB, the National Institutes of Health and Boston University Clinical and Translational Science Institute grant UL1-RR025771 to YB, the VA Translation Research Center for TBI and Stress Disorders (TRACTS) [YB], and the VA Psychology Research Service [YB and KSG].

Abbreviations

ACTH	Adrenocorticotrophic hormone
BDNF	Brain-derived neurotrophic factor

CRSD	Circadian rhythm sleep disorders
CBT-I	Cognitive Behavioral Therapy for Insomnia
CAR	Cortisol awakening response
CSF	Cerebrospinal Fluid
HPA	Hypothalamic-Pituitary-Adrenal axis
IRT	Imagery Rehearsal Therapy
LED	Light emitting diodes
LLLT	Low-level laser therapy
MNPO	Median preoptic area
OSA	Obstructive sleep apnea
OEF/OIF/OND	Operations Enduring Freedom and Iraqi Freedom and Operation New Dawn
PSG	Polysomnography
PTSD	Post-Traumatic Stress Disorder
REM	Rapid eye movement
NREM	Non-rapid eye movement
SWDs	Sleep-wake disturbances
SWA	Slow wave activity
SWS	Slow wave sleep
TBI	Traumatic brain injury
TST	Total sleep time
VLPO	Ventrolateral preoptic area

REFERENCES

- American Academy of Sleep Medicine. International Classification of Sleep Disorders – Third Edition (ICSD-3). 3rd ed.. Darien, IL: American Academy of Sleep Medicine; 2014.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth ed. 5th ed.. Arlington, VA: American Psychiatric Publishing; 2013.
- Armed Forces Health Surveillance Center (AFHSC). Incident diagnoses of common symptoms (“sequelae”) following traumatic brain injury, active component, U.S. Armed Forces, 2000–2012. Medical Surveillance Monthly Report. 2013; 20(6):9–13.
- Arnedt JT, Cuddihy L, Swanson LM, Pickett S, Aikens J, Chervin RD. Randomized controlled trial of telephone-delivered cognitive behavioral therapy for chronic insomnia. *Sleep*. 2013; 36(3):353–362. [PubMed: 23450712]

- Ayalon L, Borodkin K, Dishon L, Kanety H, Dagan Y. Circadian rhythm sleep disorders following mild traumatic brain injury. *Neurology*. 2007; 68(14):1136–1140. [PubMed: 17404196]
- Babson K, Feldner M, Badour C, Trainor C, Blumenthal H, Sachs-Ericsson N, Schmidt N. Posttraumatic stress and sleep: differential relations across types of symptoms and sleep problems. *J Anxiety Disord*. 2011; 25(5):706–713. [PubMed: 21482065]
- Babson KA, Feldner MT. Temporal relations between sleep problems and both traumatic event exposure and PTSD: a critical review of the empirical literature. *J Anxiety Disord*. 2010; 24(1):1–15. [PubMed: 19716676]
- Backhaus J, Junghanns K, Hohagen F. Sleep disturbances are correlated with decreased morning awakening salivary cortisol. *Psychoneuroendocrinology*. 2004; 29(9):1184–1191. [PubMed: 15219642]
- Baddeley JL, Gros DF. Cognitive behavioral therapy for insomnia as a preparatory treatment for exposure therapy for posttraumatic stress disorder. *Am J Psychother*. 2013; 67(2):203–214. [PubMed: 23909060]
- Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, Riemann D. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *J Affect Disord*. 2011; 135(1–3):10–19. [PubMed: 21300408]
- Bailey SL, Heitkemper MM. Circadian rhythmicity of cortisol and body temperature: morningness-eveningness effects. *Chronobiol Int*. 2001; 18(2):249–261. [PubMed: 11379665]
- Bajor LA, Ticlea AN, Osser DN. The Psychopharmacology Algorithm Project at the Harvard South Shore Program: an update on posttraumatic stress disorder. *Harv Rev Psychiatry*. 2011; 19(5):240–258. [PubMed: 21916826]
- Baumann CR. Traumatic brain injury and disturbed sleep and wakefulness. *Neuromolecular Med*. 2012; 14(3):205–212. [PubMed: 22441999]
- Baumann CR, Bassetti CL, Valko PO, Haybaeck J, Keller M, Clark E, Scammell TE. Loss of hypocretin (orexin) neurons with traumatic brain injury. *Ann Neurol*. 2009; 66(4):555–559. [PubMed: 19847903]
- Baumann CR, Stocker R, Imhof HG, Trentz O, Hersberger M, Mignot E, Bassetti CL. Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology*. 2005; 65(1):147–149. [PubMed: 16009905]
- Baumann CR, Werth E, Stocker R, Ludwig S, Bassetti CL. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain*. 2007; 130(Pt 7):1873–1883. [PubMed: 17584779]
- Beetar JT, Guilmette TJ, Sparadeo FR. Sleep and pain complaints in symptomatic traumatic brain injury and neurologic populations. *Arch Phys Med Rehabil*. 1996; 77(12):1298–1302. [PubMed: 8976315]
- Belanger L, Morin CM, Langlois F, Ladouceur R. Insomnia and generalized anxiety disorder: effects of cognitive behavior therapy for gad on insomnia symptoms. *J Anxiety Disord*. 2004; 18(4):561–571. [PubMed: 15149714]
- Belleville G, Guay S, Marchand A. Persistence of sleep disturbances following cognitive-behavior therapy for posttraumatic stress disorder. *J Psychosom Res*. 2011; 70(4):318–327. [PubMed: 21414451]
- Belmont A, Agar N, Hugeron C, Gallais B, Azouvi P. Fatigue and traumatic brain injury. *Ann Readapt Med Phys*. 2006; 49(6):283–288. [PubMed: 16716438]
- Bennion KA, Mickley Steinmetz KR, Kensinger EA, Payne JD. Sleep and Cortisol Interact to Support Memory Consolidation. *Cereb Cortex*. 2013
- Bertini M, De Gennaro L, Ferrara M, Curcio G, Romei V, Fratello F, Rossini PM. Reduction of transcallosal inhibition upon awakening from REM sleep in humans as assessed by transcranial magnetic stimulation. *Sleep*. 2004; 27(5):875–882. [PubMed: 15453545]
- Blechert J, Michael T, Vriends N, Margraf J, Wilhelm FH. Fear conditioning in posttraumatic stress disorder: evidence for delayed extinction of autonomic, experiential, and behavioural responses. *Behav Res Ther*. 2007; 45(9):2019–2033. [PubMed: 17442266]

- Bloomfield ILM, Espie CA, Evans JJ. Do sleep difficulties exacerbate deficits in sustained attention following traumatic brain injury? *J Int Neuropsychol Soc.* 2010; 16(1):17–25. [PubMed: 19796442]
- Bogdanova Y, Martin PI, Ho MD, Krengel MH, Ho VT, Yee MK, Naeser MA. LED therapy improves sleep and cognition in chronic moderate TBI: pilot case studies. Abstract. *Archives of Physical Medicine and Rehabilitation.* 2014; 95(10):e77.
- Bogdanova Y, Verfaellie M. Cognitive sequelae of blast-induced traumatic brain injury: recovery and rehabilitation. *Neuropsychol Rev.* 2012; 22(1):4–20. [PubMed: 22350691]
- Boynton L, Bentley J, Strachan E, Barbato A, Raskind M. Preliminary findings concerning the use of prazosin for the treatment of posttraumatic nightmares in a refugee population. *J Psychiatr Pract.* 2009; 15(6):454–459. [PubMed: 19934720]
- Bramoweth AD, Germain A. Deployment-related insomnia in military personnel and veterans. *Curr Psychiatry Rep.* 2013; 15(10):401–401. [PubMed: 24005883]
- Bremner JD. Neuroimaging in posttraumatic stress disorder and other stress-related disorders. *Neuroimaging Clin N Am.* 2007; 17(4):523–538. [PubMed: 17983968]
- Bremner JD, Randall P, Scott TM, Capelli S, Delaney R, McCarthy G, Charney DS. Deficits in short-term memory in adult survivors of childhood abuse. *Psychiatry Res.* 1995; 59(1–2):97–9107. [PubMed: 8771224]
- Brenner LA. Neuropsychological and neuroimaging findings in traumatic brain injury and post-traumatic stress disorder. *Dialogues Clin Neurosci.* 2011; 13(3):311–323. [PubMed: 22034217]
- Brenner LA, Terrio H, Homaifar BY, Gutierrez PM, Staves PJ, Harwood JEF, Warden D. Neuropsychological test performance in soldiers with blast-related mild TBI. *Neuropsychology.* 2010; 24(2):160–167. [PubMed: 20230110]
- Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. *Arch Gen Psychiatry.* 2004; 61(5):508–516. [PubMed: 15123496]
- Brownlow JA, Brown TS, Mellman TA. Relationships of posttraumatic stress symptoms and sleep measures to cognitive performance in young-adult African Americans. *J Trauma Stress.* 2014; 27(2):217–223. [PubMed: 24740871]
- Bryan CJ. Repetitive traumatic brain injury (or concussion) increases severity of sleep disturbance among deployed military personnel. *Sleep.* 2013; 36(6):941–946. [PubMed: 23729938]
- Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC. Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. *Sleep.* 2010; 33(1):69–74. [PubMed: 20120622]
- Bryant RA, Hopwood S. Commentary on “Trauma to the Psyche and Soma”. *Cognitive and Behavioral Practice.* 2006; 13:17–23.
- Buchmann A, Kurth S, Ringli M, Geiger A, Jenni OG, Huber R. Anatomical markers of sleep slow wave activity derived from structural magnetic resonance images. *J Sleep Res.* 2011; 20(4):506–513. [PubMed: 21435064]
- Bushnik T, Englander J, Wright J. Patterns of fatigue and its correlates over the first 2 years after traumatic brain injury. *J Head Trauma Rehabil.* 2008; 23(1):25–32. [PubMed: 18219232]
- Buyse DJ, Angst J, Gamma A, Ajdacic V, Eich D, Rossler W. Prevalence, course, and comorbidity of insomnia and depression in young adults. *Sleep.* 2008; 31(4):473–480. [PubMed: 18457234]
- Calhoun PS, Wiley M, Dennis MF, Means MK, Edinger J, Beckham JC. Objective evidence of sleep disturbance in women with posttraumatic stress disorder. *J Trauma Stress.* 2007; 20(6):1009–1018. [PubMed: 18157880]
- Capaldi VF 2nd, Guerrero ML, Killgore WD. Sleep disruptions among returning combat veterans from Iraq and Afghanistan. *Mil Med.* 2011; 176(8):879–888. [PubMed: 21882777]
- Carlson KF, Kehle SM, Meis LA, Greer N, Macdonald R, Rutks I, Wilt TJ. Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: a systematic review of the evidence. *J Head Trauma Rehabil.* 2011; 26(2):103–115. [PubMed: 20631631]
- Casement MD, Swanson LM. A meta-analysis of imagery rehearsal for post-trauma nightmares: effects on nightmare frequency, sleep quality, and posttraumatic stress. *Clin Psychol Rev.* 2012; 32(6):566–574. [PubMed: 22819998]

- Cassidy JD, Carroll LJ, Peloso PM, Borg J, von Holst H, Holm L, Coronado VG. Incidence, risk factors and prevention of mild traumatic brain injury: results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *J Rehabil Med*. 2004; (43 Suppl):28–60.
- Castriotta RJ, Wilde MC, Lai JM, Atanasov S, Masel BE, Kuna ST. Prevalence and consequences of sleep disorders in traumatic brain injury. *J Clin Sleep Med*. 2007; 3(4):349–356. [PubMed: 17694722]
- Chao LL, Mohlenhoff BS, Weiner MW, Neylan TC. Associations between subjective sleep quality and brain volume in Gulf War veterans. *Sleep*. 2014; 37(3):445–452. [PubMed: 24587566]
- Chen MJ, Ivy AS, Russo-Neustadt AA. Nitric oxide synthesis is required for exercise-induced increases in hippocampal BDNF and phosphatidylinositol 3' kinase expression. *Brain Res Bull*. 2006; 68(4):257–268. [PubMed: 16377431]
- Chiu H-Y, Lo W-C, Chiang Y-H, Tsai P-S. The effects of sleep on the relationship between brain injury severity and recovery of cognitive function: a prospective study. *Int J Nurs Stud*. 2014; 51(6):892–899. [PubMed: 24246095]
- Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J. Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *J Neurosci*. 2003; 23(33):10691–10702. [PubMed: 14627654]
- Clinchot DM, Bogner J, Mysiw WJ, Fugate L, Corrigan J. Defining sleep disturbance after brain injury. *Am J Phys Med Rehabil*. 1998; 77(4):291–295. [PubMed: 9715917]
- Clow A, Thorn L, Evans P, Hucklebridge F. The awakening cortisol response: methodological issues and significance. *Stress*. 2004; 7(1):29–37. [PubMed: 15204030]
- Clum GA, Nishith P, Resick PA. Trauma-related sleep disturbance and self-reported physical health symptoms in treatment-seeking female rape victims. *J Nerv Ment Dis*. 2001; 189(9):618–622. [PubMed: 11580006]
- Cohen DJ, Begley A, Alman JJ, Cashmere DJ, Pietrone RN, Seres RJ, Germain A. Quantitative electroencephalography during rapid eye movement (REM) and non-REM sleep in combat-exposed veterans with and without post-traumatic stress disorder. *J Sleep Res*. 2013; 22(1):76–82. [PubMed: 22845675]
- Collen J, Orr N, Lettieri CJ, Carter K, Holley AB. Sleep disturbances among soldiers with combat-related traumatic brain injury. *Chest*. 2012; 142(3):622–630. [PubMed: 22459784]
- Cook JM, Harb GC, Gehrman PR, Cary MS, Gamble GM, Forbes D, Ross RJ. Imagery rehearsal for posttraumatic nightmares: a randomized controlled trial. *J Trauma Stress*. 2010; 23(5):553–563. [PubMed: 20839311]
- Dagan Y, Eisenstein M. Circadian rhythm sleep disorders: toward a more precise definition and diagnosis. *Chronobiol Int*. 1999; 16(2):213–222. [PubMed: 10219492]
- Dagan Y, Zinger Y, Lavie P. Actigraphic sleep monitoring in posttraumatic stress disorder (PTSD) patients. *J Psychosom Res*. 1997; 42(6):577–581. [PubMed: 9226605]
- Davis JL, Wright DC. Exposure, relaxation, and rescripting treatment for trauma-related nightmares. *J Trauma Dissociation*. 2006; 7(1):5–18. [PubMed: 16618692]
- de Kloet CS, Vermetten E, Geuze E, Kavelaars A, Heijnen CJ, Westenberg HGM. Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *J Psychiatr Res*. 2006; 40(6):550–567. [PubMed: 16214171]
- Dell'Osso L, Carmassi C, Del Debbio A, Catena Dell'Osso M, Bianchi C, da Pozzo E, Piccinni A. Brain-derived neurotrophic factor plasma levels in patients suffering from post-traumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33(5):899–902. [PubMed: 19409951]
- Deppermann S, Storchak H, Fallgatter AJ, Ehrlis AC. Stress-induced neuroplasticity: (mal)adaptation to adverse life events in patients with PTSD--a critical overview. *Neuroscience*. 2014; 283:166–177. [PubMed: 25193848]
- Dikmen S, McLean A, Temkin N. Neuropsychological and psychosocial consequences of minor head injury. *J Neurol Neurosurg Psychiatry*. 1986; 49(11):1227–1232. [PubMed: 3794728]
- DOD (Department of Defense). DOD/VA Code Proposal Final. 2009. Retrieved from <http://www.cdc.gov/nchs/data/icd/Sep08TBI.pdf>.

- Dombovy ML. Patient management problem-preferred responses. *Continuum (Minneapolis, Minn)*. 2011; 17(3):688–694.
- Drake CL, Roehrs T, Roth T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety*. 2003; 18(4):163–176. [PubMed: 14661186]
- Edinger J, Means MK. Cognitive-behavioral therapy for primary insomnia. *Clin Psychol Rev*. 2005; 25(5):539–558. [PubMed: 15951083]
- Edinger J, Wohlgemuth WK, Radtke RA, Marsh GR, Quillian RE. Cognitive behavioral therapy for treatment of chronic primary insomnia: a randomized controlled trial. *JAMA*. 2001; 285(14):1856–1864. [PubMed: 11308399]
- Englander J, Hall K, Stimpson T, Chaffin S. Mild traumatic brain injury in an insured population: subjective complaints and return to employment. *Brain Inj*. 1992; 6(2):161–166. [PubMed: 1571720]
- Epstein DR, Babcock-Parziale JL, Haynes PL, Herb CA. Insomnia treatment acceptability and preferences of male Iraq and Afghanistan combat veterans and their healthcare providers. *J Rehabil Res Dev*. 2012; 49(6):867–878. [PubMed: 23299258]
- Epstein DR, Babcock-Parziale JL, Herb CA, Goren K, Bushnell ML. Feasibility test of preference-based insomnia treatment for Iraq and Afghanistan war veterans. *Rehabil Nurs*. 2013; 38(3):120–132. [PubMed: 23319338]
- Espie CA, Kyle SD, Williams C, Ong JC, Douglas NJ, Hames P, Brown JSL. A randomized, placebo-controlled trial of online cognitive behavioral therapy for chronic insomnia disorder delivered via an automated media-rich web application. *Sleep*. 2012; 35(6):769–781. [PubMed: 22654196]
- Faestel PM, Littell CT, Vitiello MV, Forsberg CW, Littman AJ. Perceived insufficient rest or sleep among veterans: Behavioral Risk Factor Surveillance System 2009. *J Clin Sleep Med*. 2013; 9(6):577–584. [PubMed: 23772191]
- Faraguna U, Vyazovskiy VV, Nelson AB, Tononi G, Cirelli C. A causal role for brain-derived neurotrophic factor in the homeostatic regulation of sleep. *J Neurosci*. 2008; 28(15):4088–4095. [PubMed: 18400908]
- Farrell-Carnahan L, Franke L, Graham C, McNamee S. Subjective sleep disturbance in veterans receiving care in the Veterans Affairs Polytrauma System following blast-related mild traumatic brain injury. *Mil Med*. 2013; 178(9):951–956. [PubMed: 24005542]
- Fichtenberg NL, Millis SR, Mann NR, Zafonte RD, Millard AE. Factors associated with insomnia among post-acute traumatic brain injury survivors. *Brain Inj*. 2000; 14(7):659–667. [PubMed: 10914647]
- Flanagan SR, Greenwald B, Wieber S. Pharmacological treatment of insomnia for individuals with brain injury. *J Head Trauma Rehabil*. 2007; 22(1):67–70. [PubMed: 17235234]
- Fogelberg DJ, Hoffman JM, Dikmen S, Temkin NR, Bell KR. Association of sleep and co-occurring psychological conditions at 1 year after traumatic brain injury. *Arch Phys Med Rehabil*. 2012; 93(8):1313–1318. [PubMed: 22840828]
- Frencham KAR, Fox AM, Maybery MT. Neuropsychological studies of mild traumatic brain injury: a meta-analytic review of research since 1995. *J Clin Exp Neuropsychol*. 2005; 27(3):334–351. [PubMed: 15969356]
- Fries E, Dettenborn L, Kirschbaum C. The cortisol awakening response (CAR): facts and future directions. *Int J Psychophysiol*. 2009; 72(1):67–73. [PubMed: 18854200]
- Galovski TE, Monson C, Bruce SE, Resick PA. Does cognitive-behavioral therapy for PTSD improve perceived health and sleep impairment? *J Trauma Stress*. 2009; 22(3):197–204. [PubMed: 19466746]
- Galuszko-Wielniak M, Jakuszkowiak-Wojten K, Wiglusz MS, Cubala WJ, Landowski J. The efficacy of Cognitive-Behavioural Therapy (CBT) as related to sleep quality and hyperarousal level in the treatment of primary insomnia. *Psychiatr Danub*. 2012; 24(Suppl 1):51–55. [PubMed: 22447086]
- Gamaldo C, Shaikh A, McArthur J. The sleep-immunity relationship. *Neurol Clin*. 2012; 30(4):1313–1343. [PubMed: 23099140]
- Gaus SE, Strecker RE, Tate BA, Parker RA, Saper CB. Ventrolateral preoptic nucleus contains sleep-active, galaninergic neurons in multiple mammalian species. *Neuroscience*. 2002; 115(1):285–294. [PubMed: 12401341]

- Gehrman P, Seelig AD, Jacobson IG, Boyko EJ, Hooper TI, Gackstetter GD, Smith TC. Predeployment Sleep Duration and Insomnia Symptoms as Risk Factors for New-Onset Mental Health Disorders Following Military Deployment. *Sleep*. 2013; 36(7):1009–1018. [PubMed: 23814337]
- Gerhart JI, Hall BJ, Russ EU, Canetti D, Hobfoll SE. Sleep disturbances predict later trauma-related distress: cross-panel investigation amidst violent turmoil. *Health Psychol*. 2014; 33(4):365–372. [PubMed: 23668851]
- Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. *Sleep Med Rev*. 2008; 12(3):185–195. [PubMed: 17997114]
- Germain A, Hall M, Shear M, Nofzinger EA, Buysse DJ. Ecological study of sleep disruption in PTSD: a pilot study. *Ann N Y Acad Sci*. 2006; 1071:438–441. [PubMed: 16891594]
- Germain A, James J, Insana S, Herringa RJ, Mammen O, Price J, Nofzinger E. A window into the invisible wound of war: functional neuroimaging of REM sleep in returning combat veterans with PTSD. *Psychiatry Res*. 2013; 211(2):176–179. [PubMed: 23149024]
- Germain A, Richardson R, Moul DE, Mammen O, Haas G, Forman SD, Nofzinger EA. Placebo-controlled comparison of prazosin and cognitive-behavioral treatments for sleep disturbances in US Military Veterans. *J Psychosom Res*. 2012; 72(2):89–96. [PubMed: 22281448]
- Germain A, Shear M, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: a pilot study. *Behav Res Ther*. 2007; 45(3):627–632. [PubMed: 16777060]
- Ghadami MR, Khaledi-Paveh B, Nasouri M, Khazaie H. PTSD-related paradoxical insomnia: an actigraphic study among veterans with chronic PTSD. *J Inj Violence Res*. 2014
- Gillin JC, Byerley WF. Drug therapy: The diagnosis and management of insomnia. *N Engl J Med*. 1990; 322(4):239–248. [PubMed: 2242104]
- Gong H, McGinty D, Guzman-Marin R, Chew K-T, Stewart D, Szymusiak R. Activation of c-fos in GABAergic neurones in the preoptic area during sleep and in response to sleep deprivation. *J Physiol*. 2004; 556(Pt 3):935–946. [PubMed: 14966298]
- Gourley SL, Kedves AT, Olausson P, Taylor JR. A history of corticosterone exposure regulates fear extinction and cortical NR2B, GluR2/3, and BDNF. *Neuropsychopharmacology*. 2009; 34(3):707–716. [PubMed: 18719621]
- Gujar N, Yoo S-S, Hu P, Walker MP. Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *J Neurosci*. 2011; 31(12):4466–4474. [PubMed: 21430147]
- Habukawa M, Uchimura N, Maeda M, Kotorii N, Maeda H. Sleep findings in young adult patients with posttraumatic stress disorder. *Biol Psychiatry*. 2007; 62(10):1179–1182. [PubMed: 17543289]
- Harb GC, Phelps AJ, Forbes D, Ross RJ, Gehrman PR, Cook JM. A critical review of the evidence base of imagery rehearsal for posttraumatic nightmares: pointing the way for future research. *J Trauma Stress*. 2013; 26(5):570–579. [PubMed: 24114887]
- Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med*. 2004; 351(1):13–22. [PubMed: 15229303]
- Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med*. 2008; 358(5):453–463. [PubMed: 18234750]
- Hu P, Stylos-Allan M, Walker MP. Sleep facilitates consolidation of emotional declarative memory. *Psychol Sci*. 2006; 17(10):891–898. [PubMed: 17100790]
- Huber R, Tononi G, Cirelli C. Exploratory behavior, cortical BDNF expression, and sleep homeostasis. *Sleep*. 2007; 30(2):129–139. [PubMed: 17326538]
- Hucklebridge F, Hussain T, Evans P, Clow A. The diurnal patterns of the adrenal steroids cortisol and dehydroepiandrosterone (DHEA) in relation to awakening. *Psychoneuroendocrinology*. 2005; 30(1):51–57. [PubMed: 15358442]
- Hughes KC, Shin LM. Functional neuroimaging studies of post-traumatic stress disorder. *Expert Rev Neurother*. 2011; 11(2):275–285. [PubMed: 21306214]
- Institute of Medicine. Cognitive Rehabilitation Therapy for Traumatic Brain Injury: Evaluating the Evidence. Washington, DC: The National Academies Press; 2011.

- Jackson ML, Sztendur EM, Diamond NT, Byles JE, Bruck D. Sleep difficulties and the development of depression and anxiety: a longitudinal study of young Australian women. *Arch Womens Ment Health*. 2014; 17(3):189–198. [PubMed: 24647705]
- Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol*. 2013; 246:35–43. [PubMed: 22285252]
- Kan EM, Ling E-A, Lu J. Microenvironment changes in mild traumatic brain injury. *Brain Res Bull*. 2012; 87(4–5):359–372. [PubMed: 22289840]
- Kaplan GB, Vasterling JJ, Vedak PC. Brain-derived neurotrophic factor in traumatic brain injury, post-traumatic stress disorder, and their comorbid conditions: role in pathogenesis and treatment. *Behav Pharmacol*. 2010; 21(5–6):427–437. [PubMed: 20679891]
- Kark S, Stavitsky K, Deluca S, Lafleche G, Bogdanova Y. Poor sleep quality is related to PTSD, cognitive difficulties, and quality of life in OEF/OIF veterans with blast exposure. Abstract. *Journal of International Neuropsychological Society*. 2013; 19:i-122.
- Karlin BE, Trockel M, Taylor CB, Gimeno J, Manber R. National dissemination of cognitive behavioral therapy for insomnia in veterans: therapist- and patient-level outcomes. *J Consult Clin Psychol*. 2013; 81(5):912–917. [PubMed: 23586730]
- Kaufman Y, Tzischinsky O, Epstein R, Etzioni A, Lavie P, Pillar G. Long-term sleep disturbances in adolescents after minor head injury. *Pediatr Neurol*. 2001; 24(2):129–134. [PubMed: 11275462]
- Kellner R, Neidhardt J, Krakow B, Pathak D. Changes in chronic nightmares after one session of desensitization or rehearsal instructions. *Am J Psychiatry*. 1992; 149(5):659–663. [PubMed: 1349459]
- Kellner R, Singh G, Irigoyen-Rascon F. Rehearsal in the treatment of recurring nightmares in posttraumatic stress disorders and panic disorder: Case histories. *Annals of Clinical Psychiatry*. 1991; 3(1):67–71.
- Kemp S, Biswas R, Neumann V, Coughlan A. The value of melatonin for sleep disorders occurring post-head injury: a pilot RCT. *Brain Inj*. 2004; 18(9):911–919. [PubMed: 15223743]
- Kempf J, Werth E, Kaiser PR, Bassetti CL, Baumann CR. Sleep-wake disturbances 3 years after traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2010; 81(12):1402–1405. [PubMed: 20884672]
- Khawaja I, Hashmi A, Aftab M, Westermeyer J, Hurwitz T. Actigraphy in post traumatic stress disorder. *Pak J Med Sci*. 2014; 30(2):438–442. [PubMed: 24772158]
- Klein E, Koren D, Arnon I, Lavie P. Sleep complaints are not corroborated by objective sleep measures in post-traumatic stress disorder: a 1-year prospective study in survivors of motor vehicle crashes. *J Sleep Res*. 2003; 12(1):35–41. [PubMed: 12603785]
- Kobayashi I, Huntley E, Lavela J, Mellman T. Subjectively and objectively measured sleep with and without posttraumatic stress disorder and trauma exposure. *Sleep*. 2012; 35(7):957–965. [PubMed: 22754042]
- Kobayashi I, Mellman T. Gender differences in sleep during the aftermath of trauma and the development of posttraumatic stress disorder. *Behav Sleep Med*. 2012; 10(3):180–190. [PubMed: 22742436]
- Koffel E, Polusny MA, Arbisi PA, Erbes CR. Pre-deployment daytime and nighttime sleep complaints as predictors of post-deployment PTSD and depression in National Guard troops. *J Anxiety Disord*. 2013; 27(5):512–519. [PubMed: 23939336]
- Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Prince H. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. *JAMA*. 2001; 286(5):537–545. [PubMed: 11476655]
- Krakow B, Zadra A. Clinical management of chronic nightmares: imagery rehearsal therapy. *Behav Sleep Med*. 2006; 4(1):45–70. [PubMed: 16390284]
- Kramer TL, Booth BM, Han X, Williams DK. Service utilization and outcomes in medically ill veterans with posttraumatic stress and depressive disorders. *J Trauma Stress*. 2003; 16(3):211–219. [PubMed: 12816332]
- Krystal AD, Erman M, Zammit GK, Soubrane C, Roth T. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with

chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep*. 2008; 31(1):79–90. [PubMed: 18220081]

Kudielka BM, Buchtal J, Uhde A, Wust S. Circadian cortisol profiles and psychological self-reports in shift workers with and without recent change in the shift rotation system. *Biol Psychol*. 2007; 74(1):92–9103. [PubMed: 17101207]

Kudielka BM, Federenko IS, Hellhammer DH, Wust S. Morningness and eveningness: the free cortisol rise after awakening in “early birds” and “night owls”. *Biol Psychol*. 2006; 72(2):141–146. [PubMed: 16236420]

Kumari M, Badrick E, Ferrie J, Perski A, Marmot M, Chandola T. Self-reported sleep duration and sleep disturbance are independently associated with cortisol secretion in the Whitehall II study. *J Clin Endocrinol Metab*. 2009; 94(12):4801–4809. [PubMed: 19850688]

Lancee J, van den Bout J, van Straten A, Spoormaker VI. Internet-delivered or mailed self-help treatment for insomnia?: a randomized waiting-list controlled trial. *Behav Res Ther*. 2012; 50(1):22–29. [PubMed: 22055281]

Lang KP, Veazey-Morris K, Andrasik F. Exploring the role of insomnia in the relation between PTSD and pain in veterans with polytrauma injuries. *J Head Trauma Rehabil*. 2014; 29(1):44–53. [PubMed: 23835878]

Larson EB, Zollman FS. The effect of sleep medications on cognitive recovery from traumatic brain injury. *J Head Trauma Rehabil*. 2010; 25(1):61–67. [PubMed: 20051895]

Lew HL, Otis JD, Tun C, Kerns RD, Clark ME, Cifu DX. Prevalence of chronic pain, posttraumatic stress disorder, and persistent postconcussive symptoms in OIF/OEF veterans: polytrauma clinical triad. *J Rehabil Res Dev*. 2009; 46(6):697–702. [PubMed: 20104399]

Lewis V, Creamer M, Failla S. Is poor sleep in veterans a function of post-traumatic stress disorder? *Mil Med*. 2009; 174(9):948–951. [PubMed: 19780370]

Li Y, Sato Y, Yamaguchi N. Potential biochemical pathways for the relationship between sleep duration and mortality. *Sleep Med*. 2013; 14(1):98–9104. [PubMed: 23127582]

Liberzon I, Sripada CS. The functional neuroanatomy of PTSD: a critical review. *Prog Brain Res*. 2008; 167:151–169. [PubMed: 18037013]

Lofaso F, Coste A, Gilain L, Harf A, Guilleminault C, Goldenberg F. Sleep fragmentation as a risk factor for hypertension in middle-aged nonapneic snorers. *Chest*. 1996; 109(4):896–900. [PubMed: 8635367]

Long ME, Hammons ME, Davis JL, Frueh BC, Khan MM, Elhai JD, Teng EJ. Imagery rescripting and exposure group treatment of posttraumatic nightmares in Veterans with PTSD. *J Anxiety Disord*. 2011; 25(4):531–535. [PubMed: 21354767]

Lu J, Greco MA, Shiromani P, Saper CB. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J Neurosci*. 2000; 20(10):3830–3842. [PubMed: 10804223]

Maas AI, Stocchetti N, Bullock R. Moderate and severe traumatic brain injury in adults. *Lancet Neurol*. 2008; 7(8):728–741. [PubMed: 18635021]

Macera CA, Aralis HJ, Rauh MJ, MacGregor AJ. Do sleep problems mediate the relationship between traumatic brain injury and development of mental health symptoms after deployment? *Sleep*. 2013; 36(1):83–90. [PubMed: 23288974]

Maguen S, Lau KM, Madden E, Seal K. Relationship of screen-based symptoms for mild traumatic brain injury and mental health problems in Iraq and Afghanistan veterans: Distinct or overlapping symptoms? *J Rehabil Res Dev*. 2012; 49(7):1115–1126. [PubMed: 23341283]

Mahmood O, Rapport LJ, Hanks RA, Fichtenberg NL. Neuropsychological performance and sleep disturbance following traumatic brain injury. *J Head Trauma Rehabil*. 2004; 19(5):378–390. [PubMed: 15597029]

Margolies SO, Rybarczyk B, Vrana SR, Leszczyszyn DJ, Lynch J. Efficacy of a cognitive-behavioral treatment for insomnia and nightmares in Afghanistan and Iraq veterans with PTSD. *J Clin Psychol*. 2013; 69(10):1026–1042. [PubMed: 23629959]

Marquez de la Plata CD, Garces J, Shokri Kojori E, Grinnan J, Krishnan K, Pidikiti R, Diaz-Arrastia R. Deficits in functional connectivity of hippocampal and frontal lobe circuits after traumatic axonal injury. *Arch Neurol*. 2011; 68(1):74–84. [PubMed: 21220676]

- Marshall KR, Holland SL, Meyer KS, Martin EM, Wilmore M, Grimes JB. Mild traumatic brain injury screening, diagnosis, and treatment. *Mil Med.* 2012; 177(8 Suppl):67–75. [PubMed: 22953443]
- Marx BP, Doron-Lamarca S, Proctor SP, Vasterling JJ. The influence of pre-deployment neurocognitive functioning on post-deployment PTSD symptom outcomes among Iraq-deployed Army soldiers. *J Int Neuropsychol Soc.* 2009; 15(6):840–852. [PubMed: 19891817]
- Masson F, Maurette P, Salmi LR, Dartigues JF, Vecsey J, Destailats JM, Erny P. Prevalence of impairments 5 years after a head injury, and their relationship with disabilities and outcome. *Brain Inj.* 1996; 10(7):487–497. [PubMed: 8806009]
- Mathias JL, Alvaro PK. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: a meta-analysis. *Sleep Med.* 2012; 13(7):898–905. [PubMed: 22705246]
- Matthews EE, Arnedt JT, McCarthy MS, Cuddihy LJ, Aloia MS. Adherence to cognitive behavioral therapy for insomnia: a systematic review. *Sleep Med Rev.* 2013; 17(6):453–464. [PubMed: 23602124]
- McGinty D, Gong H, Suntsova N, Alam MN, Methippara M, Guzman-Marin R, Szymusiak R. Sleep-promoting functions of the hypothalamic median preoptic nucleus: inhibition of arousal systems. *Arch Ital Biol.* 2004; 142(4):501–509. [PubMed: 15493551]
- McGinty DJ, Stermann MB. Sleep suppression after basal forebrain lesions in the cat. *Science.* 1968; 160(3833):1253–1255. [PubMed: 5689683]
- McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. *Mil Med.* 2010; 175(10):759–762. [PubMed: 20968266]
- Mellman T, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry.* 2002; 159(10):1696–1701. [PubMed: 12359675]
- Mellman T, Kobayashi I, Lavela J, Wilson B, Hall Brown T. A relationship between REM sleep measures and the duration of posttraumatic stress disorder in a young adult urban minority population. *Sleep.* 2014; 37(8):1321–1326. [PubMed: 25083012]
- Mellman T, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. *Am J Psychiatry.* 1995; 152(1):110–115. [PubMed: 7802100]
- Middleboe T, Andersen HS, Birket-Smith M, Friis ML. Minor head injury: impact on general health after 1 year. A prospective follow-up study. *Acta Neurol Scand.* 1992; 85(1):5–9. [PubMed: 1546534]
- Milad MR, Orr SP, Lasko NB, Chang Y, Rauch SL, Pitman RK. Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *J Psychiatr Res.* 2008; 42(7):515–520. [PubMed: 18313695]
- Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM). Definition of mild traumatic brain injury. *Journal of Head Trauma Rehabilitation.* 1993:86–87.
- Mitchell MD, Gehrman P, Perlis M, Umscheid CA. Comparative effectiveness of cognitive behavioral therapy for insomnia: a systematic review. *BMC Fam Pract.* 2012; 13:40–40. [PubMed: 22631616]
- Moore BA, Krakow B. Imagery rehearsal therapy for acute posttraumatic nightmares among combat soldiers in Iraq. *Am J Psychiatry.* 2007; 164(4):683–684. [PubMed: 17403990]
- Morey RA, Haswell CC, Selgrade ES, Massoglia D, Liu C, Weiner J, McCarthy G. Effects of chronic mild traumatic brain injury on white matter integrity in Iraq and Afghanistan war veterans. *Hum Brain Mapp.* 2013; 34(11):2986–2999. [PubMed: 22706988]
- Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, Zak R. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. *Sleep.* 2007; 30(12):1705–1711. [PubMed: 18246980]
- Morin CM, Bootzin RR, Buysse DJ, Edinger J, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). *Sleep.* 2006; 29(11):1398–1414. [PubMed: 17162986]
- Mustafa M, Erokwu N, Ebose I, Strohl K. Sleep problems and the risk for sleep disorders in an outpatient veteran population. *Sleep Breath.* 2005; 9(2):57–63. [PubMed: 15875229]

- Mysliwiec V, Gill J, Lee H, Baxter T, Pierce R, Barr TL, Roth BJ. Sleep disorders in US military personnel: a high rate of comorbid insomnia and obstructive sleep apnea. *Chest*. 2013; 144(2): 549–557. [PubMed: 23681455]
- Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. *Sleep*. 2013; 36(2):167–174. [PubMed: 23372263]
- Nakamura Y, Lipschitz DL, Landward R, Kuhn R, West G. Two sessions of sleep-focused mind-body bridging improve self-reported symptoms of sleep and PTSD in veterans: A pilot randomized controlled trial. *J Psychosom Res*. 2011; 70(4):335–345. [PubMed: 21414453]
- Nappi CM, Drummond SPA, Hall JMH. Treating nightmares and insomnia in posttraumatic stress disorder: a review of current evidence. *Neuropharmacology*. 2012; 62(2):576–585. [PubMed: 21396945]
- Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Delucchi KL, Schoenfeld FB. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. *Am J Psychiatry*. 1998; 155(7):929–933. [PubMed: 9659859]
- Nielsen T, Montplaisir J, Lassonde M. Sleep architecture in agenesis of the corpus callosum: laboratory assessment of four cases. *J Sleep Res*. 1992; 1(3):197–200. [PubMed: 10607051]
- Nishida M, Pearsall J, Buckner RL, Walker MP. REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cereb Cortex*. 2009; 19(5):1158–1166. [PubMed: 18832332]
- Ohayon MM. [Prevalence and comorbidity of sleep disorders in general population]. *Rev Prat*. 2007; 57(14):1521–1528. [PubMed: 18018450]
- Olf M, Guzelcan Y, de Vries G-J, Assies J, Gersons BPR. HPA- and HPT-axis alterations in chronic posttraumatic stress disorder. *Psychoneuroendocrinology*. 2006; 31(10):1220–1230. [PubMed: 17081699]
- Orff HJ, Ayalon L, Drummond SPA. Traumatic brain injury and sleep disturbance: a review of current research. *J Head Trauma Rehabil*. 2009; 24(3):155–165. [PubMed: 19461363]
- Orr, N.; Carter, K.; Collen, JF.; Hoffman, M.; Holley, ABL.; Lettieri, CJ. Prevalence of Sleep Disorders Among Soldiers With Combat-Related Posttraumatic Stress Disorder; Paper presented at the Chest, Honolulu, Hawaii. 2010. http://chestjournal.chestpubs.org/cgi/content/meeting_abstract/138/4_MeetingAbstracts/704A
- Orr SP, Metzger LJ, Lasko NB, Macklin ML, Peri T, Pitman RK. De novo conditioning in trauma-exposed individuals with and without posttraumatic stress disorder. *J Abnorm Psychol*. 2000; 109(2):290–298. [PubMed: 10895567]
- Ouellet M-C, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. *J Head Trauma Rehabil*. 2006; 21(3):199–212. [PubMed: 16717498]
- Ouellet M-C, Morin CM. Efficacy of cognitive-behavioral therapy for insomnia associated with traumatic brain injury: a single-case experimental design. *Arch Phys Med Rehabil*. 2007; 88(12): 1581–1592. [PubMed: 18047872]
- Pace-Schott EF, Milad MR, Orr SP, Rauch SL, Stickgold R, Pitman RK. Sleep promotes generalization of extinction of conditioned fear. *Sleep*. 2009; 32(1):19–26. [PubMed: 19189775]
- Pace-Schott EF, Verga PW, Bennett TS, Spencer RMC. Sleep promotes consolidation and generalization of extinction learning in simulated exposure therapy for spider fear. *J Psychiatr Res*. 2012; 46(8):1036–1044. [PubMed: 22578824]
- Parcell DL, Ponsford JL, Rajaratnam SM, Redman JR. Self-reported changes to nighttime sleep after traumatic brain injury. *Arch Phys Med Rehabil*. 2006; 87(2):278–285. [PubMed: 16442985]
- Parcell DL, Ponsford JL, Redman JR, Rajaratnam SM. Poor sleep quality and changes in objectively recorded sleep after traumatic brain injury: a preliminary study. *Arch Phys Med Rehabil*. 2008; 89(5):843–850. [PubMed: 18452730]
- Patel R, Spreng RN, Shin LM, Girard TA. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev*. 2012; 36(9):2130–2142. [PubMed: 22766141]
- Payne JD, Chambers AM, Kensinger EA. Sleep promotes lasting changes in selective memory for emotional scenes. *Front Integr Neurosci*. 2012; 6:108–108. [PubMed: 23181013]

- Payne JD, Kensinger EA. Sleep leads to changes in the emotional memory trace: evidence from FMRI. *J Cogn Neurosci*. 2011; 23(6):1285–1297. [PubMed: 20521852]
- Peppard PE, Szklo-Coxe M, Hla KM, Young T. Longitudinal association of sleep-related breathing disorder and depression. *Arch Intern Med*. 2006; 166(16):1709–1715. [PubMed: 16983048]
- Pervanidou P, Chrousos GP. Neuroendocrinology of post-traumatic stress disorder. *Prog Brain Res*. 2010; 182:149–160. [PubMed: 20541663]
- Pietrzak RH, Goldstein MB, Malley JC, Rivers AJ, Johnson DC, Southwick SM. Risk and protective factors associated with suicidal ideation in veterans of Operations Enduring Freedom and Iraqi Freedom. *J Affect Disord*. 2010; 123(1–3):102–107. [PubMed: 19819559]
- Pigeon WR, Britton PC, Ilgen MA, Chapman B, Conner KR. Sleep disturbance preceding suicide among veterans. *Am J Public Health*. 2012; 102(Suppl 1):93–97.
- Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J Clin Psychiatry*. 2012; 73(9):1160–1167.
- Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep-what a nightmare! *Sleep Med Rev*. 2000; 4(2):183–200. [PubMed: 12531165]
- Ponsford JL, Parcell DL, Sinclair KL, Roper M, Rajaratnam SMW. Changes in sleep patterns following traumatic brain injury: a controlled study. *Neurorehabil Neural Repair*. 2013; 27(7):613–621. [PubMed: 23549523]
- Ponsford JL, Ziino C, Parcell DL, Shekleton JA, Roper M, Redman JR, Rajaratnam SMW. Fatigue and sleep disturbance following traumatic brain injury--their nature, causes, and potential treatments. *J Head Trauma Rehabil*. 2012; 27(3):224–233. [PubMed: 22573041]
- Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, von Auer K, Jobst S, Kirschbaum C. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life Sci*. 1997; 61(26):2539–2549. [PubMed: 9416776]
- Quinto C, Gellido C, Chokroverty S, Masdeu J. Posttraumatic delayed sleep phase syndrome. *Neurology*. 2000; 54(1):250–252. [PubMed: 10636163]
- Ragsdale KA, Neer SM, Beidel DC, Frueh BC, Stout JW. Posttraumatic stress disorder in OEF/OIF veterans with and without traumatic brain injury. *J Anxiety Disord*. 2013; 27(4):420–426. [PubMed: 23746495]
- Randler C, Schaal S. Morningness-eveningness, habitual sleep-wake variables and cortisol level. *Biol Psychol*. 2010; 85(1):14–18. [PubMed: 20450953]
- Rao V, McCann U, Han D, Bergey A, Smith MT. Does acute TBI-related sleep disturbance predict subsequent neuropsychiatric disturbances? *Brain Inj*. 2014; 28(1):20–26. [PubMed: 24328797]
- Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, McFall ME. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with post-traumatic stress disorder. *Biol Psychiatry*. 2007; 61(8):928–934. [PubMed: 17069768]
- Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, McFall MM. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. *Am J Psychiatry*. 2003; 160(2):371–373. [PubMed: 12562588]
- Raskind MA, Peterson K, Williams T, Hoff DJ, Hart K, Holmes H, Peskind ER. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. *Am J Psychiatry*. 2013; 170(9):1003–1010. [PubMed: 23846759]
- Raskind MA, Thompson C, Petrie EC, Dobie DJ, Rein RJ, Hoff DJ, Peskind ER. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. *J Clin Psychiatry*. 2002; 63(7):565–568. [PubMed: 12143911]
- Rasmusson AM, Shi L, Duman R. Downregulation of BDNF mRNA in the hippocampal dentate gyrus after re-exposure to cues previously associated with footshock. *Neuropsychopharmacology*. 2002; 27(2):133–142. [PubMed: 12093587]
- Report of VA Consensus Conference. Practice Recommendations for Treatment of Veterans with Comorbid TBI, Pain, and PTSD. 2010
- Ribeiro JD, Pease JL, Gutierrez PM, Silva C, Bernert RA, Rudd MD, Joiner TE. Sleep problems outperform depression and hopelessness as cross-sectional and longitudinal predictors of suicidal

- ideation and behavior in young adults in the military. *J Affect Disord.* 2012; 136(3):743–750. [PubMed: 22032872]
- Richey SM, Krystal AD. Pharmacological advances in the treatment of insomnia. *Curr Pharm Des.* 2011; 17(15):1471–1475. [PubMed: 21476952]
- Rodenbeck A, Huether G, Ruther E, Hajak G. Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neurosci Lett.* 2002; 324(2):159–163. [PubMed: 11988351]
- Rosenberg RP. Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. *Ann Clin Psychiatry.* 2006; 18(1):49–56. [PubMed: 16517453]
- Ross RJ, Gresch PJ, Ball WA, Sanford LD, Morrison AR. REM sleep inhibition by desipramine: evidence for an alpha-1 adrenergic mechanism. *Brain Res.* 1995; 701(1–2):129–134. [PubMed: 8925274]
- Rowe RK, Harrison JL, O'Hara BF, Lifshitz J. Diffuse brain injury does not affect chronic sleep patterns in the mouse. *Brain Inj.* 2014; 28(4):504–510. [PubMed: 24702469]
- Samuelson KW, Neylan TC, Metzler TJ, Lenoci M, Rothlind J, Henn-Haase C, Marmar CR. Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology.* 2006; 20(6):716–726. [PubMed: 17100516]
- Sanchez-Ortuno MM, Edinger J. Cognitive-behavioral therapy for the management of insomnia comorbid with mental disorders. *Curr Psychiatry Rep.* 2012; 14(5):519–528. [PubMed: 22865156]
- Saper CB, Cano G, Scammell TE. Homeostatic, circadian, and emotional regulation of sleep. *J Comp Neurol.* 2005; 493(1):92–98. [PubMed: 16254994]
- Saper CB, Chou TC, Scammell TE. The sleep switch: hypothalamic control of sleep and wakefulness. *Trends Neurosci.* 2001; 24(12):726–731. [PubMed: 11718878]
- Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. *Neuron.* 2010; 68(6):1023–1042. [PubMed: 21172606]
- Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature.* 2005; 437(7063):1257–1263. [PubMed: 16251950]
- Sayer NA, Rettmann NA, Carlson KF, Bernardy N, Sigford BJ, Hamblen JL, Friedman MJ. Veterans with history of mild traumatic brain injury and posttraumatic stress disorder: challenges from provider perspective. *J Rehabil Res Dev.* 2009; 46(6):703–716. [PubMed: 20104400]
- Schiehser DM, Delis DC, Filoteo JV, Delano-Wood L, Han SD, Jak AJ, Bondi MW. Are self-reported symptoms of executive dysfunction associated with objective executive function performance following mild to moderate traumatic brain injury? *J Clin Exp Neuropsychol.* 2011; 33(6):704–714. [PubMed: 21958432]
- Schober ME, Block B, Requena DF, Hale MA, Lane RH. Developmental traumatic brain injury decreased brain derived neurotrophic factor expression late after injury. *Metab Brain Dis.* 2012; 27(2):167–173. [PubMed: 22527999]
- Schoenfeld FB, Deviva JC, Manber R. Treatment of sleep disturbances in posttraumatic stress disorder: a review. *J Rehabil Res Dev.* 2012; 49(5):729–752. [PubMed: 23015583]
- Schreiber S, Barkai G, Gur-Hartman T, Peles E, Tov N, Dolberg OT, Pick CG. Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects. *Sleep Med.* 2008; 9(5):481–487. [PubMed: 17638592]
- Seelig AD, Jacobson IG, Smith B, Hooper TI, Boyko EJ, Gackstetter GD, Smith TC. Sleep patterns before, during, and after deployment to Iraq and Afghanistan. *Sleep.* 2010; 33(12):1615–1622. [PubMed: 21120123]
- Senathi-Raja D, Ponsford J, Schonberger M. Impact of age on long-term cognitive function after traumatic brain injury. *Neuropsychology.* 2010; 24(3):336–344. [PubMed: 20438211]
- Shekleton JA, Parcell DL, Redman JR, Phipps-Nelson J, Ponsford JL, Rajaratnam SMW. Sleep disturbance and melatonin levels following traumatic brain injury. *Neurology.* 2010; 74(21):1732–1738. [PubMed: 20498441]
- Sherin JE, Elmquist JK, Torrealba F, Saper CB. Innervation of histaminergic tuberomammillary neurons by GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus of the rat. *J Neurosci.* 1998; 18(12):4705–4721. [PubMed: 9614245]

- Sherin JE, Shiromani PJ, McCarley RW, Saper CB. Activation of ventrolateral preoptic neurons during sleep. *Science*. 1996; 271(5246):216–219. [PubMed: 8539624]
- Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SMW. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair*. 2014; 28(4): 303–313. [PubMed: 24213962]
- Spencer RJ, Drag LL, Walker SJ, Bieliauskas LA. Self-reported cognitive symptoms following mild traumatic brain injury are poorly associated with neuropsychological performance in OIF/OEF veterans. *J Rehabil Res Dev*. 2010; 47(6):521–530. [PubMed: 20848365]
- Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? *Sleep Med Rev*. 2008; 12(3):169–184. [PubMed: 18424196]
- Steele DL, Rajaratnam SMW, Redman JR, Ponsford JL. The effect of traumatic brain injury on the timing of sleep. *Chronobiol Int*. 2005; 22(1):89–105. [PubMed: 15865324]
- Stickgold R, Hobson JA, Fosse R, Fosse M. Sleep, learning, and dreams: off-line memory reprocessing. *Science*. 2001; 294(5544):1052–1057. [PubMed: 11691983]
- Stickgold R, Walker MP. Sleep and memory: the ongoing debate. *Sleep*. 2005; 28(10):1225–1227. [PubMed: 16295206]
- Stickgold R, Walker MP. Sleep-dependent memory consolidation and reconsolidation. *Sleep Med*. 2007; 8(4):331–343. [PubMed: 17470412]
- Stocker RPI, Cieply MA, Paul B, Khan H, Henry L, Kontos AP, Germain A. Combat-related blast exposure and traumatic brain injury influence brain glucose metabolism during REM sleep in military veterans. *Neuroimage*. 2014; 99:207–214. [PubMed: 24893322]
- Straus LD, Drummond SPA, Nappi CM, Jenkins MM, Norman SB. Sleep variability in military-related PTSD: a comparison to primary insomnia and healthy controls. *J Trauma Stress*. 2015; 28(1):8–16. [PubMed: 25630526]
- Stulemeijer M, van der Werf S, Bleijenberg G, Biert J, Brauer J, Vos PE. Recovery from mild traumatic brain injury: a focus on fatigue. *J Neurol*. 2006; 253(8):1041–1047. [PubMed: 16708266]
- Suntsova N, Szymusiak R, Alam MN, Guzman-Marin R, McGinty D. Sleep-waking discharge patterns of median preoptic nucleus neurons in rats. *J Physiol*. 2002; 543(Pt 2):665–677. [PubMed: 12205198]
- Swinkels CM, Ulmer CS, Beckham JC, Buse N, Calhoun PS. The Association of Sleep Duration, Mental Health, and Health Risk Behaviors among U.S. Afghanistan/Iraq Era Veterans. *Sleep*. 2013; 36(7):1019–1025. [PubMed: 23814338]
- Szklo-Coxe M, Young T, Peppard PE, Finn LA, Benca RM. Prospective associations of insomnia markers and symptoms with depression. *Am J Epidemiol*. 2010; 171(6):709–720. [PubMed: 20167581]
- Szymusiak R, Alam N, Steininger TL, McGinty D. Sleep-waking discharge patterns of ventrolateral preoptic/anterior hypothalamic neurons in rats. *Brain Res*. 1998; 803(1–2):178–188. [PubMed: 9729371]
- Takahashi K, Lin JS, Sakai K. Characterization and mapping of sleep-waking specific neurons in the basal forebrain and preoptic hypothalamus in mice. *Neuroscience*. 2009; 161(1):269–292. [PubMed: 19285545]
- Talbot LS, Maguen S, Metzler TJ, Schmitz M, McCaslin SE, Richards A, Neylan TC. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. *Sleep*. 2014; 37(2):327–341. [PubMed: 24497661]
- Taylor F, Raskind MA. The alpha1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. *J Clin Psychopharmacol*. 2002; 22(1):82–85. [PubMed: 11799347]
- Terrio H, Brenner LA, Ivins BJ, Cho JM, Helmick K, Schwab K, Warden D. Traumatic brain injury screening: preliminary findings in a US Army Brigade Combat Team. *J Head Trauma Rehabil*. 2009; 24(1):14–23. [PubMed: 19158592]
- Terrio H, Nelson LA, Betthausen LM, Harwood JE, Brenner LA. Postdeployment traumatic brain injury screening questions: Sensitivity, specificity, and predictive values in returning soldiers. *Rehabil Psychol*. 2011; 56(1):26–31. [PubMed: 21401283]

- Tham SW, Palermo TM, Vavilala MS, Wang J, Jaffe KM, Koepsell TD, Rivara FP. The longitudinal course, risk factors, and impact of sleep disturbances in children with traumatic brain injury. *J Neurotrauma*. 2012; 29(1):154–161. [PubMed: 22029569]
- Ulmer CS, Edinger J, Calhoun PS. A multi-component cognitive-behavioral intervention for sleep disturbance in veterans with PTSD: a pilot study. *J Clin Sleep Med*. 2011; 7(1):57–68. [PubMed: 21344046]
- Van Boven RW, Harrington GS, Hackney DB, Ebel A, Gauger G, Bremner JD, Weiner MW. Advances in neuroimaging of traumatic brain injury and posttraumatic stress disorder. *J Rehabil Res Dev*. 2009; 46(6):717–757. [PubMed: 20104401]
- van Liempt S. Sleep disturbances and PTSD: a perpetual circle? *Eur J Psychotraumatol*. 2012; 3
- van Liempt S, Arends J, Cluitmans PJM, Westenberg HGM, Kahn RS, Vermetten E. Sympathetic activity and hypothalamo-pituitary-adrenal axis activity during sleep in post-traumatic stress disorder: a study assessing polysomnography with simultaneous blood sampling. *Psychoneuroendocrinology*. 2013; 38(1):155–165. [PubMed: 22776420]
- van Liempt S, Vermetten E, Lentjes E, Arends J, Westenberg H. Decreased nocturnal growth hormone secretion and sleep fragmentation in combat-related posttraumatic stress disorder; potential predictors of impaired memory consolidation. *Psychoneuroendocrinology*. 2011; 36(9):1361–1369. [PubMed: 21489700]
- Vandekerckhove M, Cluydts R. The emotional brain and sleep: an intimate relationship. *Sleep Med Rev*. 2010; 14(4):219–226. [PubMed: 20363166]
- Vasterling JJ, Brailey K, Proctor SP, Kane R, Heeren T, Franz M. Neuropsychological outcomes of mild traumatic brain injury, post-traumatic stress disorder and depression in Iraq-deployed US Army soldiers. *Br J Psychiatry*. 2012; 201(3):186–192. [PubMed: 22743844]
- Vasterling JJ, Duke LM, Brailey K, Constans JJ, Allain AN, Sutker PB. Attention, learning, and memory performances and intellectual resources in Vietnam veterans: PTSD and no disorder comparisons. *Neuropsychology*. 2002; 16(1):5–14. [PubMed: 11853357]
- Verma A, Anand V, Verma NP. Sleep disorders in chronic traumatic brain injury. *J Clin Sleep Med*. 2007; 3(4):357–362. [PubMed: 17694723]
- Vgontzas A, Fernandez-Mendoza J. Insomnia with Short Sleep Duration: Nosological, Diagnostic, and Treatment Implications. *Sleep Med Clin*. 2013; 8(3):309–322. [PubMed: 24072989]
- Vgontzas AN, Bixler EO, Lin HM, Prolo P, Mastorakos G, Vela-Bueno A, Chrousos GP. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab*. 2001; 86(8):3787–3794. [PubMed: 11502812]
- Vincent N, Walsh K. Hyperarousal, sleep scheduling, and time awake in bed as mediators of outcome in computerized cognitive-behavioral therapy (cCBT) for insomnia. *Behav Res Ther*. 2013; 51(3):161–166. [PubMed: 23353579]
- Wagner U, Gais S, Born J. Emotional memory formation is enhanced across sleep intervals with high amounts of rapid eye movement sleep. *Learn Mem*. 2001; 8(2):112–119. [PubMed: 11274257]
- Wagner U, Hallschmid M, Rasch B, Born J. Brief sleep after learning keeps emotional memories alive for years. *Biol Psychiatry*. 2006; 60(7):788–790. [PubMed: 16806090]
- Wahbeh H, Oken BS. Salivary cortisol lower in posttraumatic stress disorder. *J Trauma Stress*. 2013; 26(2):241–248. [PubMed: 23529862]
- Walker MP. Sleep, memory and emotion. *Prog Brain Res*. 2010; 185:49–68. [PubMed: 21075233]
- Wallace DM, Shafazand S, Ramos AR, Carvalho DZ, Gardener H, Lorenzo D, Wohlgemuth WK. Insomnia characteristics and clinical correlates in Operation Enduring Freedom/Operation Iraqi Freedom veterans with post-traumatic stress disorder and mild traumatic brain injury: an exploratory study. *Sleep Med*. 2011; 12(9):850–859. [PubMed: 21925943]
- Watson NF, Dikmen S, Machamer J, Doherty M, Temkin N. Hypersomnia following traumatic brain injury. *J Clin Sleep Med*. 2007; 3(4):363–368. [PubMed: 17694724]
- Westermeyer J, Sutherland RJ, Freerks M, Martin K, Thuras P, Johnson D, Hurwitz T. Reliability of sleep log data versus actigraphy in veterans with sleep disturbance and PTSD. *J Anxiety Disord*. 2007; 21(7):966–975. [PubMed: 17291714]
- Wilhelm I, Born J, Kudielka BM, Schlotz W, Wust S. Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology*. 2007; 32(4):358–366. [PubMed: 17408865]

- Williams JM, Kay DB, Rowe M, McCrae CS. Sleep discrepancy, sleep complaint, and poor sleep among older adults. *J Gerontol B Psychol Sci Soc Sci*. 2013; 68(5):712–720. [PubMed: 23804432]
- Wiseman-Hakes C, Murray B, Moineddin R, Rochon E, Cullen N, Gargaro J, Colantonio A. Evaluating the impact of treatment for sleep/wake disorders on recovery of cognition and communication in adults with chronic TBI. *Brain Inj*. 2013; 27(12):1364–1376. [PubMed: 24070180]
- Wittmann L, Schredl M, Kramer M. Dreaming in posttraumatic stress disorder: A critical review of phenomenology, psychophysiology and treatment. *Psychother Psychosom*. 2007; 76(1):25–39. [PubMed: 17170561]
- Woodward SH, Bliwise DL, Friedman MJ, Gusman DF. Subjective versus objective sleep in Vietnam combat veterans hospitalized for PTSD. *J Trauma Stress*. 1996; 9(1):137–143. [PubMed: 8750457]
- Worthington AD, Melia Y. Rehabilitation is compromised by arousal and sleep disorders: results of a survey of rehabilitation centres. *Brain Inj*. 2006; 20(3):327–332. [PubMed: 16537274]
- Woznica AA, Carney CE, Kuo JR, Moss TG. The insomnia and suicide link: toward an enhanced understanding of this relationship. *Sleep Med Rev*. 2014
- Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. *J Clin Psychol*. 2011; 67(12):1240–1258. [PubMed: 22065464]
- Wust S, Federenko I, Hellhammer DH, Kirschbaum C. Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology*. 2000; 25(7):707–720. [PubMed: 10938450]
- Xu C, Wang L, Ta Y, Li Q. Endonasal low energy He-Ne laser treatment of insomnia. *Qian Wei J Med & Pharm*. 2001; 18(5):337–338. [In Chinese].
- Xu C, Wu Z, Wang L, Shang X, Li Q. The effects of endonasal low energy He-Ne laser treatment of insomnia on sleep EEG. *Prac J Med Pharm*. 2002; 19(6):407–408. [In Chinese].
- Yehuda R. Current status of cortisol findings in post-traumatic stress disorder. *Psychiatr Clin North Am*. 2002; 25(2):341–368. [PubMed: 12136504]
- Yoo S-S, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep--a prefrontal amygdala disconnect. *Curr Biol*. 2007; 17(20):877–878.
- Zayfert C, DeViva JC. Residual insomnia following cognitive behavioral therapy for PTSD. *J Trauma Stress*. 2004; 17(1):69–73. [PubMed: 15027796]
- Zhang J, Ma RCW, Kong APS, So WY, Li AM, Lam SP, Wing YK. Relationship of sleep quantity and quality with 24-hour urinary catecholamines and salivary awakening cortisol in healthy middle-aged adults. *Sleep*. 2011; 34(2):225–233. [PubMed: 21286244]
- Zhao J, Tian Y, Nie J, Xu J, Liu D. Red light and the sleep quality and endurance performance of Chinese female basketball players. *J Athl Train*. 2012; 47(6):673–678. [PubMed: 23182016]

Highlights

- Poor sleep may impact recovery and treatment outcome in Veterans with PTSD and TBI
- Sleep difficulties are a risk factor for the development and maintenance of PTSD
- TBI patients can suffer permanent sleep problems regardless of injury severity
- Sleep-focused interventions could augment current TBI and PTSD treatment protocols
- We review physiological mechanisms and treatment of sleep problems in TBI and PTSD