Structural vs. Psychiatric Predictors of Sleep Disturbance in Veterans With Mild Traumatic Brain Injury

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Abstract

Background

In Veterans, post-traumatic stress disorder (PTSD) and mild traumatic brain injury (mTBI) are each related to persistent sleep disturbances that are detrimental to overall health and quality of life. Although symptoms of sleep disturbance are similar in PTSD and mTBI, neurobiological mechanisms producing disordered sleep may differ. One key neurobiological substrate of sleep is the ascending noradrenergic system originating in the locus coeruleus (LC).

Methods

An MRI imaging protocol (T1-weighted; Fast Gray Matter Acquisition T1 Inversion Recovery [FGATIR]; and diffusion-weighted) was used to locate and segment the locus coeruleus (LC) in a sample of 12 veterans with mTBI. LC volume was calculated for each participant using a protocol developed in collaboration with the Mareci neuroimaging laboratory at UF. Relationships among LC volume, PTSD severity and subjective sleep quality were analyzed.

Results

PTSD Checklist – Military Version (PCL-M) total score was positively correlated with inability to breathe comfortably during sleep (r=.594, p=.041), having bad dreams (r=.691, p=.013), delayed sleep latency (r=.655, p=.021), sleep disturbances (r=.849, p=<.001), and poor sleep efficiency (r=.576, p=.050) on the Pittsburgh Sleep Quality Index (PSQI). LC volume was negatively correlated with poor sleep efficiency (r=-.596, p=.041) and discomfort with breathing during sleep (r=-.619, r=.032) on the PSQI.

Conclusion

Sleep disturbances after mTBI and PTSD may involve different neural mechanisms. We hypothesize that mTBI is related to damage within neurobiological systems involved in sleep regulation (LC and its projections). Understanding the mechanism whereby comorbid PTSD relates to an exacerbation of sleep problems is important in designing effective treatment programs for symptomatic mTBI patients.
Introduction

Mild traumatic brain injury (mTBI) and post-traumatic Stress Disorder (PTSD) have become important issues among veterans, especially those returning from Operations Enduring Freedom (OEF) and Iraqi Freedom (OIF). Department of Defense (2014) records indicate that from 2000-2013, approximately 294,000 servicemen received diagnoses of TBI. Out of these, 82.5% of them were categorized as mild based on clinical criteria. More specifically, research has found that 15-23% of service members returning from OIF/OEF sustained an mTBI (Farrel-Carnahan, Franke, Graham, & McNamee, 2013). A recent study by Wisco et al. (2014) found the overall lifetime prevalence of PTSD in veterans to be 8.0%. A review of studies by Ramchand et al. (2010) showed that the prevalence of clinically significant Post-traumatic stress disorder symptoms among veterans who served in Iraq and Afghanistan (OEF/OIF) are between 1-60% for those not seeking treatment and between 4.2-50% for those who do seek treatment. Since mTBIs sustained in-theater are often in the course of life threatening events, high levels of comorbid mTBI and PTSD in OEF/OIF veterans are expected (Schneiderman, Braver, & Kang, 2008).

Sleep disturbances are commonly seen in the aftermath of both mTBI and PTSD. As a result of the high prevalence of sleep disturbances, their poorly understood nature and causes, and their potential to significantly harm the health of the patient, they have been gaining importance in the related research. Research has shown that sleep is vital in ensuring metabolic homeostasis and in the clearance of neurodegenerative metabolic waste such as beta-amyloid from the brain (Xie et al., 2012). Additional studies have indicated that large amounts of beta-amyloid are linked to neurodegenerative diseases such as Alzheimer’s disease (Cirrito et al., 2005). Sleep is understood to be a restorative function and chronic sleep disruptions are highly associated with the presence of other symptoms that further negatively impact quality of life, such as depression. (Farrel-Carnahan et al., 2013; Hou et al., 2013).

Sleep disturbances are a core symptom of PTSD and are found in two of the symptom clusters in the DSM-V diagnostic criteria (American Psychiatric Association, 2013). Furthermore, studies have consistently found subjective sleep quality to be the primary concern of veterans with PTSD (Belleville,
Guay, & Marchand, 2009; Ohayon & Shapiro, 2000). A review of PTSD and sleep by Germain (2013) indicates that clinical observations of PTSD patients have been inconsistent but suggest dysregulation in both rapid eye movement (REM) and non-REM (NREM) sleep. These disturbances include insomnia, nightmares, and sleep disordered breathing (SDB) such as sleep apnea. The relationship of sleep disturbances to PTSD have not yet been established, but it has been suggested that altered functioning in neurobiological mechanisms of arousal and fear conditioning in the amygdala and medial prefrontal cortex may provide a common substrate (Cartwright, 1991; Germain, 2013; Goodenough, Witkin, Koulack, & Cohen, 1975; Milad, Rauch, Pitman, & Quirk, 2006; Van Liempt, 2012).

Sleep disturbances have been reported in up to 80% of patients with mTBI (Orff et al., 2009). Even when PTSD is not present, sleep disturbances have been well documented following injury (Orff, Ayalon, & Drummond, 2009; Ouellet, Beaulieu-Bonneau, & Morin, 2006; Parcell, Ponsford, Rajaratnam, & Redman, 2006; Ponsford et al., 2012). The nature of post-mTBI sleep disturbances vary and often include poor sleep efficiency, insomnia, reduced time spent in REM, daytime sleepiness, and sleep-disordered breathing (e.g., sleep apnea) (Castriotta et al., 2007). The frequency of reported sleep disturbances by mTBI patients suggests a primary neurobiological mechanism. However, the etiology of these sleep disturbances has yet to be determined. Advances in technology such as diffusion weighted imaging (DWI) have suggested the involvement of microscopic structural damage to neural connectivity known as diffuse axonal injury (DAI) (Bazarian et al., 2007; Gardner et al., 2012; Shenton et al., 2012). However, Rosenbaum and Lipton (2012) indicate that these structural changes have been difficult to locate in the post-TBI brain due to the amount of inter-subject variability. More recent research has proposed that sleep disturbances are related more specifically to damage to the locus coeruleus (LC) (Sullan et. al, 2014).

The LC, a small structure located within the brainstem, is vital to the sleep-wake cycle (Chamberlain & Robbins, 2013; Samuels & Szabadi, 2008a). The LC is the primary source of ascending noradrenergic (NA) innervation in the brain and projects to other regions that play a key role in sleep-wake cycles, including the ventrolateral preoptic area (VLPO) and medial preoptic nucleus (MnPN).
(Chamberlain & Robbins, 2013; Samuels & Szabadi, 2008b; Schwartz & Roth, 2008). Bigler (2013) identified the brainstem to be prone to injury in TBI. Therefore, in accordance with research by Sullan et al. (2014), evaluating possible trauma-induced abnormalities within the LC may provide further understanding of the nature of sleep disturbances in symptomatic TBI patients.

The prevalence of comorbidity between mTBI and PTSD, especially in OEF/OIF veterans, and the overlap of their symptoms has been debated. According to Bryant (2011), debate exists because PTSD and mTBI “…Both independently and additively, are regarded as being responsible for much impairment following deployments [in OEF/OIF veterans]” (p. 251). This statement can be applied directly to sleep disturbances after PTSD and mTBI. Some studies have found mTBI to be minimally responsible for impairment after controlling for the effects of PTSD and other psychological comorbidities (Hoge et al., 2008; Schneiderman et al. 2008), suggesting that PTSD and associated psychological symptoms are more strongly associated with sleep disturbances after mTBI than the injury itself. However, other studies have contradicted this notion by showing that many mTBI patients with sleep disorders do not suffer from PTSD or other psychological disorders (Baumann, Werth, Stocker, Ludwig, & Bassetti, 2007). To the knowledge of the authors, no study has yet tried to contrast the presentation and etiologies of sleep disturbances among co-occurring PTSD and mTBI.

Aims and Hypotheses

The following study aims to determine if correlations exist among LC volume, measures of PTSD on the PCL-M, and subjective measures of sleep on the PSQI. Based on the notion that mTBI will lead to DAI and contribute to decreased LC volume, we hypothesized that traumatically-induced loss of LC volume would be associated with subjective sleep disturbances (SSD) indicative of insomnia and less comfortable breathing (sleep apnea) on the PSQI. We also hypothesized that the PCL-M would be associated with various categories of subjective sleep disturbances suggestive of nightmares, sleep apnea, and insomnia on the PSQI. Thus we predicted that there would be both similarities and differences between mTBI-induced and PTSD-related subjective sleep disturbances (PSQI items). This is in
concurrence with our hypothesis that the neurobiological mechanisms responsible for sleep disturbances after mTBI (more structural) and PTSD (more psychological) are at least partially separate in nature.

Method

Participants

Our participants were recruited from the North Florida/South Georgia Malcom Randall Veteran’s Affairs Medical Center. In order to be included in the study, patients had to have been deployed in OIF/OEF campaigns and had to have sustained an mTBI at least 6 months prior to evaluation. For the purposes of our study, the ACRM definition of mTBI was used (ACRM, 1993). Accordingly, all participants had loss of consciousness (LOC) lasting less than 30 minutes, posttraumatic amnesia (PTA) lasting less than 24 hours, and lack of abnormalities on a standard clinical magnetic resonance (MR) scan as determined by a physician. Recruitment resulted in a study sample of 18 veterans. However, incomplete sleep questionnaires for 5 participants and one significant outlier on LOC/AOC events (>3 SD from the mean) resulted in a final study population of 12 veterans. Our study participants were male only due to the fact that no female participants met the study criteria. Additional participant demographic information can be found in Table 1.

Instruments

As found in Sullan et al. (2014), the scanner in our study was a Philips Achieva 3T scanner (Best, Netherlands) with a 32-channel SENSE head coil. For additional details regarding T1 acquisition parameters, see Ford et al. (2013). For this study, high-resolution structural T1-weighted (1 x 1 x 1mm) and FGATIR (1 x 1 x 1mm) were analyzed for each participant. FGATIR images were acquired with 160, 1.0 mm axial slices (no gap), FOV = 256 mm × 192 mm, matrix = 320 × 256, TR = 3000ms, TE = 4.39ms, voxel size = 1.0 × 1.0 × 1.0 mm, and time of acquisition = 11 min 14 s. Further details of FGATIR acquisition parameters can be found in Sudhyadhom et al., 2009. Segmentation and volumetric analysis of the LC was conducted using the previously published FGATIR Locus Coeruleus Segmentation (FLoCS) protocol developed within the Bauer and Mareci laboratories at UF. For further details regarding LC segmentation and the image processing protocol, see Sullan et al., 2014.
The measures used for sleep quality and PTSD were the Pittsburgh Sleep Quality Index (PSQI) and the PTSD Checklist – Military Version (PCL-M). Both the PSQI and PCL-M are commonly used metrics of sleep disturbances and PTSD symptom severity (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989; Weathers et al., 1993; Weathers et al., 1994). The data were analyzed using the SPSS statistical package, version 22.

**Procedure**

MRI scans for each participant were acquired during their clinical visit. Each participant then received a full neuropsychological battery and self-report questionnaires administered by a trained psychometrist. This battery included the PSQI and PCL-M. MR images were processed using eddy current correction and skull stripping to enhance brain visualization. The LC was then segmented based on associated anatomical landmarks using the FLoCS protocol, which yields inter-rater reliabilities >.90 for image localization and segmentation (Sullan et al., 2014). Each item on the PSQI was separately analyzed using SPSS in order to examine relationships between our independent variables (LC volume, PCL-M) and our dependent variables (specific qualitative types of sleep disturbances).

**Results**

Due to the nature of the PSQI items (ordinal ranking for frequency and severity measures), we used a Spearman rank order correlation to analyze our data. The Sleep Efficiency component score was determined by comparing hours spent asleep with hours spent awake while in bed, with higher scores indicative of poorer sleep efficiency (more hours awake, less hours asleep). Higher scores on the “cannot breathe comfortably” item indicated a greater frequency of uncomfortable breathing during sleep. Higher scores on the Sleep Latency component score, Sleep Disturbances component score, and PSQI Global Score were indicative of greater time taken to fall asleep, greater frequency of sleep disturbances per week, and worse overall sleep quality, respectively.

The PTSD Checklist – Military Version (PCL-M) total score was positively and significantly correlated with the following items on the PSQI: cannot breathe comfortably during sleep ($r=.594, p < .05$), having bad dreams ($r=.691, p<.05$), Sleep Latency component score ($r=.655, p<.05$), Sleep
Disturbances component score \( (r=.849, p < .001) \), Sleep Efficiency component score \( (r=-.576, p < .05) \), and Global Score \( (r=.761, p < .01) \).

LC volume was negatively and significantly correlated with the Sleep Efficiency component score \( (r=-.596, p < .05) \) and inability to breath comfortably during sleep \( (r=-.619, p < .05) \) on the PSQI. Additional relationships included a positive correlation between PCL-M and the Sleep Efficiency component score \( (r=.576) \) and a negative correlation between LC volume and Global score \( (r=-.550) \). Although not significant, both of these relationships approached significance.

**Discussion**

Data Interpretation

As anticipated, we found a significant amount of overlap and some differences in relationships between measures of PTSD, LC volume, and subjective sleep problems. Previous research has indicated that sleep apnea (suggested by inability to breathe comfortably) and insomnia (suggested by poor sleep efficiency) have both been separately associated with mTBI and PTSD (Castriotta et al., 2007; Germain et al., 2013; Hoge et al., 2008; Schneiderman et al., 2008). However, to our knowledge, no prior study had examined them side-by-side in the same population. Our study results agreed with these previously established findings. Our results also agreed with literature in the field linking PTSD and nightmares (having bad dreams). We found differences in types of SSD associated with LC volume and PCL-M as predicted. For instance, having bad dreams, delayed sleep latency, and a higher frequency of overall sleep disturbances were associated only with heightened scores on the PCL-M, suggestive of PTSD and not with reduced LC volume. Although the PSQI sleep efficiency score was related to both PCL-M scores and LC volumes with equal strength (both correlations \( |.576| \)), the correlation involving LC likely failed to reach significance because of restricted range within the LC variable. Despite this result, our data showed moderate negative correlation trends for LC volume with sleep latency (reduced LC volume, more time to fall asleep) and overall sleep disturbances (reduced LC volume, greater frequency of sleep disturbances). Once again, this was also in the hypothesized direction. Thus, a similar study with greater power may be able to more accurately represent these relationships.
Our overall results indicated a pattern of negative relationships between LC volume and subjective sleep disturbance on the PSQI. Jointly taken with the results of Sullan et al. (2014), these findings suggest that structural damage to the LC may be a viable predictor of the sleep problems documented in mTBI patients. This provides preliminary support for the hypothesis that the etiology of sleep disturbances following mTBI is the result of disruption to a primary neurobiological mechanism. While these mechanisms were not examined for neural systems related to PTSD, future studies may work to examine the differences in PTSD-related networks as they relate to increased disturbances to sleep. Also, because our results demonstrated a pattern of significant positive correlations between the PCL-M and all analyzed PSQI items, we are unable to infer specific information about the etiology of sleep disturbances after PTSD.

**Limitations and Future Directions**

Our small sample size (N=12) was an obvious limitation in our ability to fully examine PCL-M and LC volume relationships with PSQI items. Smaller sample sizes decrease the power of results and limit the ability to use more comprehensive statistical analyses. Also, we lacked a control group for comparison, which would have been useful in examining differences in LC volume between mTBI patients and healthy controls. Our sample was all male, limiting the generalizability of the study.

Using our research as a first step, future research should work to further examine the LC with respect to sleep disturbances following mTBI. Our study focused solely on LC volume, whereas future research may extend to the LC-NA related networks and projections. This could potentially lead to better understanding of the neurobiological mechanisms underlying sleep disturbances from mTBI. Understanding the ways which comorbid PTSD further exacerbates sleep problems is important in designing more targeted therapeutic interventions for the large number of injured veterans. A more highly-powered study that evaluates LC and PSQI sleep data in a matched group of veterans with and without TBI and PTSD (TBI/PTSD; TBI/no PTSD; no TBI/PTSD, noTBI/noPTSD) is needed to better understand the multifactorial etiology of sleep problems in this population.
References


DoD TBI Worldwide Numbers since 2000: Defense and Veterans Brain Injury Center (DVBIC); 2013.


brain injury: a preliminary study. Sleep Med, 7(6), 486-497. doi: 10.1016/j.sleep.2006.03.017


### Tables and Figures

Table 1
Demographic table.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td>30.7</td>
<td>24-37</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>14 years</td>
<td>(12-18 years)</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td>Male</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Ethnicity:</strong></td>
<td>Caucasian</td>
<td>73.3%</td>
</tr>
<tr>
<td></td>
<td>African American</td>
<td>26.7%</td>
</tr>
<tr>
<td><strong>Mean Time Since Inquiry</strong></td>
<td>4.3 years</td>
<td></td>
</tr>
<tr>
<td><strong>LOC Events</strong></td>
<td>Mean</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>(1-10)</td>
</tr>
<tr>
<td><strong>AOC Events</strong></td>
<td>Mean</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>(0-6)</td>
</tr>
<tr>
<td><strong>Combined AOC/LOC Events</strong></td>
<td>Mean</td>
<td>5.07</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>(1-14)</td>
</tr>
<tr>
<td><strong>Sleep Disturbance (&gt;5 PSQI)</strong></td>
<td>Mean</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>10.92 (5-19)</td>
</tr>
<tr>
<td><strong>Psychological Disturbances:</strong></td>
<td>PTSD</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>42%</td>
</tr>
</tbody>
</table>

a. Abbreviations: (LOC) is Loss of Consciousness, (AOC) is Alteration of Consciousness
b. Depression in table acquired through neuropsychological battery.
### Table 2
Significant Correlations.

<table>
<thead>
<tr>
<th>PSQI Items</th>
<th>LC Volume</th>
<th>PCL-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep Latency Component Score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.426</td>
<td>.655</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.167</td>
<td>.021*</td>
</tr>
<tr>
<td>Cannot breathe comfortably:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.619</td>
<td>.594</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.032*</td>
<td>.041*</td>
</tr>
<tr>
<td>Had bad dreams:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.381</td>
<td>.691</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.221</td>
<td>.013*</td>
</tr>
<tr>
<td>Sleep Disturbances Component Score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.424</td>
<td>.849</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.169</td>
<td>.000*</td>
</tr>
<tr>
<td>Global Score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.550</td>
<td>.761</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.064</td>
<td>.004*</td>
</tr>
<tr>
<td>Sleep Efficiency Component Score:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson Correlation</td>
<td>-.596</td>
<td>.576</td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.041*</td>
<td>.050*</td>
</tr>
</tbody>
</table>

a. Asterisk indicates significant relationship (p ≤ .05)
b. Higher scores in Sleep Efficiency Component Score, Global Score, Sleep Disturbances Component Score, Cannot breathe comfortably, Sleep Latency Component Score, and Had bad dreams, are indicative of worse sleep.
Appendix

Acknowledgements

I would like to acknowledge the expertise and assistance of Molly J. Sullan, without whom this thesis could not have been completed. Research was supported in part by Department of Veterans Affairs RR&D CDA-2 # B6698W; State of Florida Brain and Spinal Cord Injury Research Trust Fund; USAMRMC/TATRC Contract #W81XH-11-1-0454 (D. FitzGerald, PI). Mark Eckert and Noam Keren generously provided standardized LC masks for use in developing the FLoCs protocol.