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Short Communication

The Locus Coeruleus and Sleep-Wake Disturbances in Veterans with mTBI

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Abstract

Background: Sleep disturbances after mild traumatic brain injury (mTBI) are common in both civilian and military populations. Consequences of chronic sleep disruption include cognitive, emotional, and physiological problems. We explored the hypothesis that post-mTBI sleep disturbances were related to damage to the locus coeruleus (LC), asleep-relevant structure in the brainstem.

Methods: A magnetic resonance-based imaging protocol (T1-weighted; Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR); and diffusion-weighted) was used to locate and segment the LC in 18 veterans and 19 controls. Fractional anisotropy (FA) and LC volume were calculated for each subject. To establish reliability of our novel LC localization method, LC segmentation of 10 participants were re-generated. Because controls were not given sleep measures, relationships between LCFA and volume and measures of sleep quality were analyzed in the mTBI group only.

Results: The Dice similarity coefficient, assessing voxel-wise overlap between two sets of LC segmentations, ranged from .90-.96, demonstrating good reliability of our localization method. There were no significant differences between groups in either LC volume or FA, but there was a trend toward higher LC volume in controls (p=.079). LC volume was significantly negatively correlated withsleep efficiency (r=-.596, p=.041), breathing comfortably during sleep (r=-.619, p=.031) and hours slept per night (r=-.661, p=.019)in the mTBI group. Although not significant, LC volume was negatively associated with subjective sleep quality, sleep latency and the global score on the Pittsburgh Sleep Quality Index (r=-.403, p=.194; r=-.438, p=.155; r=-.54, p=.07respectively). Reduced LC FA was not significantly associated with any sleep outcomes.

Conclusions: Results suggest that lower LC volume is associated with decreased sleep efficiency, breathing difficulties during sleep, and a decreased number of hoursslept per nightin patients with mTBI.

ABBREVIATIONS

AOC/LOC: Alteration Of Consciousness/Loss Of Consciousness; **ESS:** Epworth Sleepiness Scale; **FA**: Fractional Anisotropy; **Flocs:** FGATIR Locus Coeruleus Segmentation; **FGATIR:** Fast Gray Matter Acquisition T1 Inversion Recovery; **MNI:** Montreal Neurological Institute; **Mnpn**: Medial Preoptic Nucleus; **MRI:** Magnetic Resonance Imaging; **Mtbi:** Mild Traumatic Brain Injury; **PPT**: Pendunculopontine Tegmental Area; **PSQI:** Pittsburgh Sleep Quality Index; **REM**: Rapid Eye Movement; SD: Standard Deviation; **TSE:**Turbo Spin Echo; **VLPO**: Ventrolateralpreoptic Area

INTRODUCTION

Traumatic brain injury (TBI) has become an increasingly important problem among veterans returning from Operation Enduring Freedom/Operation Iraqi Freedom. The Defense and Veterans Brain Injury Center reported that 280,734 soldiers

sustained a TBI between 2000 and 2013, 82.4% of which were classified as mild [1]. While outcomes vary following TBI, core features of post-concussive syndrome, such as dizziness, problems with memory, and sleep disturbance, are often reported [2].Sleep disturbances reported after TBI have been well documented in both civilian and military populations [3-5], and are among the most common complaints in mild TBI (mTBI) patients. Up to 80% of mTBI patients report sleep disturbances[3], which often include sleep architecture abnormalities (e.g., greater sleep onset latency, shorter time in REM), sleep apnea (both obstructive and central) and insomnia [6]. Long term consequences of chronic sleep disruption can lead to declining psychological functioning, contributing to a decreased quality of life and an increase in irritability and depression [7-9]. Sleep is also important for physiological processes, and plays a crucial role in the ability of the brain to clear metabolic waste, such as beta-amyloid, from interstitial space [10].

While emotional disorders, such as anxiety and depression, may contribute to decreased sleep quality after TBI, many mTBI patients with sleep disturbances do not suffer from any co morbid psychological disorders [11]. The prevalence of reported sleep problems following TBI suggests the possibility of a primary neurobiological mechanism. However, this mechanism has not yet been established. The locus Coeruleus (LC), a small grey matter nucleus located within the brainstem, plays a key role in sleep-wake cycles [12,13]. The LC provides nearly all the noradrenergic (NA) innervations to the brain, including areas heavily involved in sleep cycle maintenance, such as the ventrolateralpreoptic area (VLPO) and medial preoptic nucleus (MnPN) of the hypothalamus[12,13]. Lesions to the VLPO have been shown to greatly reduce delta wave power and non-rapid-eye-movement sleep time (NREM), and have caused significant symptoms of insomnia [14]. Lesions to the MnPN are correlated with a reduction in slow wave sleep, and the destruction of noradrenergic afferents to this area is related to increased wakefulness in animal models [15].The LC and VLPO/MnPN share reciprocal inhibitory relationships, in which the LC inhibits these areas during waking and the VLPO/MnPN inhibit the LC during sleep[16]. The LC also shares inhibitory connections with the pendunculopontine tegmental nucleus (PPT), which is important to the regulation of rapid eye movement sleep (REM) [13].

Importantly, the brainstem is particularly susceptible to injury in the course of a TBI [17], and damage to the LC-NA system may help to explain some of the sleep disturbances reported by these patients. However, due to its small size (~1-2mm in diameter) and location within the brainstem, accurate LC visualization is nearly impossible on traditional T1-weightedscans. As a result, very few studies have attempted to localize the LC *in vivo*. Past studies have used neuromelanin imaging sequences to visualize the LC based on its neurochemical components [18 ,19]. Keren et al.,created standardized probabalistic maps of the LC based on a neuromelanin imaging technique which uses the ferromelanin metal-binding properties of LC cells[18]. Other studies have utilized similar neuromelanin imaging techniques to create LC probability maps based on T1 signal hyperintensities [19,20], but there remains no widely used approach for accurate segmentation of the LC.

A novel imaging technique developed by Sudhyadhom et al. (2009), termed Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR), was developed to localize small subcortical structures targeted for deep brain stimulation [21]. This sequence decreaseswhite matter intensity, allowing for smaller grey matter structures to be seen with higher contrast [21]. Due to the low signal intensity imparted by neuromelanin pigmentation within the LC, and the high quality of contrast in FGATIR sequences, this structure becomes hyperintense on FGATIR images and allows for improved LC visualization. Using FGATIR imaging we developed a novel and reliable LC localization method, termed the FGATIR Locus Coeruleus Segmentation (FLoCS) protocol. This protocol was established by combining the population maps created by Keren et al., with manual segmentation using individual pixel intensities and landmark-based estimates on FGATIR images.

In addition to LC localization, the current study assessed differences in volume and diffusivity in the LC between veterans with mTBI and healthy controls using the FLoCS protocol. We hypothesized thatthe LC in the mTBI group would have smaller volume and lower fractional anisotropy (FA), due to neuronal degradationwithin this structure following TBI. We also assessed how structural and morphological differences in the LC were related to sleep quality and daytime sleepiness measures in mTBI. Our hypothesis was that volume and FA within the LC would be negatively correlated with sleep quality and daytime sleepiness scores (where higher sleep scores reflect greater sleep disturbances).We hypothesized that lower FA would be suggestive of a loss of structural connectivity of the LC as a result of mTBI, which may be associated with a disruption to neural sleep circuitry. In addition, we hypothesized that lower LC volume would be correlated with a greater level of daytime sleepiness, a lower subjective sleep quality score, and higher subjective global sleep disturbances throughout the night in mTBI patients.

MATERIALS AND METHODS

Participants

18 veterans with a history of mTBI and 19 healthy controls with no known neurological disorders were recruited from the North Florida/South Georgia Malcom Randall Veteran's Affairs Medical Center and the University of Florida. Written informed consent was obtained from each participant in compliance with the Institutional Review Board guidelines at the University of Florida and the North Florida/South Georgia Veteran's Affairs Medical Center. Mild traumatic brain injury was defined as a loss of consciousness lasting less than 30 minutes, less than 24 hours of post traumatic amnesia (PTA), and no visible abnormalities on a clinical MR scan. All mTBI participants were assessed at least 6 months post-injury. Previous research has shown the prevalence of cardiovascular risk factors in damage to cerebral structures, which could play a role in sleep disturbances, such as obstructive sleep apnea [22]. However, each participant in our study was screened for cardiovascular abnormalities, and participants with any indication of a cardiovascular event were excluded. Also, due to the relatively small proportion of female military personnel deployed in the OEF/OIF campaigns (11.6% female) [23], and thus a relatively small population of female veterans meeting the criteria for the study, we had a male only population sample in our mTBI group. Veterans with mTBI were given a full

neuropsychological battery by a trained psychometrist (JG), as well as an MRI. Controls received an MRI only. See (Table 1) for participant demographic information.

Image acquisition

Scans were collected for each participant on a Philips Achieva 3T scanner (Best, Netherlands) using a 32-channel SENSE head coil. Full details of T1 and diffusion weighted imaging (DWI) acquisition parameters can be found in Ford et al., 2013 (24). For the current study, we analyzed high resolution structural T1-weighted (1 x 1 x 1mm), FGATIR (1 x 1 x 1mm) and DWI (2 x 2 x 2mm) for all participants. 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. For a more in-depth review of FGATIR acquisition parameters, see Sudhyadhom et al., 2009 [21].

Image processing

DWI data were first corrected for eddy current distortions, which consist of stretching, shifting, or shearing of images due to the application of high-powered imaging gradients used in DWI. Next, the images were skull-stripped to remove any non-brain tissues (skull, fat, skin). A diffusion tensor fit was performed in each brain-only voxel (pixel) of DWI data of each participant to calculate diffusivity measures (such as Fractional Anisotropy, FA). Fractional anisotropy is a scalar that describes directionality of diffusion in a given voxel (pixel) of a diffusion-weighted imaging scan. FA values range from 0 to 1, where FA=0 indicates that diffusion is isotropic and particles disperse equidistantly in all directions. FA=1 indicates that all of the particles disperse in a single direction, suggesting that the underlying neuro anatomy (i.e. an axon bundle) is restricting diffusion along a given orientation (along the length of an axon bundle). In our study, diffusion data processing and FA value calculations were performed using the FSL software package FMRIB software Library (www.fmrib.ox.ac.uk/fsl) [25,26].

Table 1: Demographic information.

	mTBI Group	
Age	30.7 (Range: 24-37 years) SE: 1.04 **27.05 (Range: 21-46 years) SE: (1.49)	
Education	14 years (Range: 12-18 years) SE: 0.5	
Gender Male Female	 100% 0%	 **68.4% **31.6%
Ethnicity: Caucasian African American	 73.3% 26.7%	
Mean Time Since Injury	4.3 years	
LOC Events	1.2 (Range: 1-10)	
AOC Events	3.9 (Range: 0-6)	
Combined AOC/LOC Events	5.07 (Range 1-14)	
Sleep Disturbance (>5 PSQI) Mean Range	83% 10.92 5-19	
Mood: PTSD Depression	 92% 42%	
***Data for Control Group*		

Abbreviations: **LOC**: Loss of Consciousness; **AOC:** Alteration of Consciousness

ROI segmentation

We localized the LC in our participants using the FGATIR Locus Coeruleus Segmentation (FLoCS) protocol developed by the authors. First to approximate the location of the LC, we used probabilistic maps developed by Keren and colleagues, provided to us by the Eckert Laboratory [14]. The maps represent two spatial distributions rendered in the Montreal Neurological Institute standard template space (MNI152), which capture the probability of a specific voxel containing the LC tissue based on neuromelanin concentrations. Each distribution represents 1 and 2 standard deviations (SD) of the spatial variance of the LC location across individual participants in the Keren et al study [14].

To improve the quality of registration, first we registered these population templates to each participant's T1-weighted scan using FSL FNIRT [27]. Then in order to register the T1-weighted templates to the FGATIR images, we used linear registration FSL FLIRT [25, 27]. The resulting native space FGATIR LC probabilistic segmentations (1and 2SD) were threshold at 50% to include only thenative-space voxels that spatially overlapped with at least 50% of the standard templatesegmentations. Thesesegmentationswere then manually corrected (by an un-blinded rater) using FGATIR image intensities, and landmark-based approximations (Figure 1) based on Duvernoy's Atlas of the Human Brain **Stem and Cerebellum**[28] . These included:

- Inferior: Middle cerebellar peduncle
- Superior: Inferior colliculus
- Medial: Fourth ventricle
- Lateral: Lateral white matter

To establish reliability measures, LC segmentationsof 10 randomly selected participants were re-traced using this protocol (see Results below). The quality of the registrations between the template (MNI152), T1-weighted, and FGATIR spaces was assessed by registering the Harvard-Oxford thalamus template [29-32] from MNI152 to the individual T1- and FGATIR spaces. The thalamus was chosen as a control grey matter region because of its spatial location away from LC and its ease of localization on the FGATIR images.The location and accuracy of the registration of the thalamic template was verified by a trained neuroanatomist (AB). Manually corrected LC segmentations were then registered to diffusion space for each participant using FSL FLIRT [25, 27], and mean FA values within the LC were calculated for each participant.

Sleep metrics

Each veteran was given the Pittsburgh Sleep Quality Index (PSQI), as well as the Epworth Sleepiness Scale (ESS). The PSQI is a widely used assessment measure for a variety of sleep-related

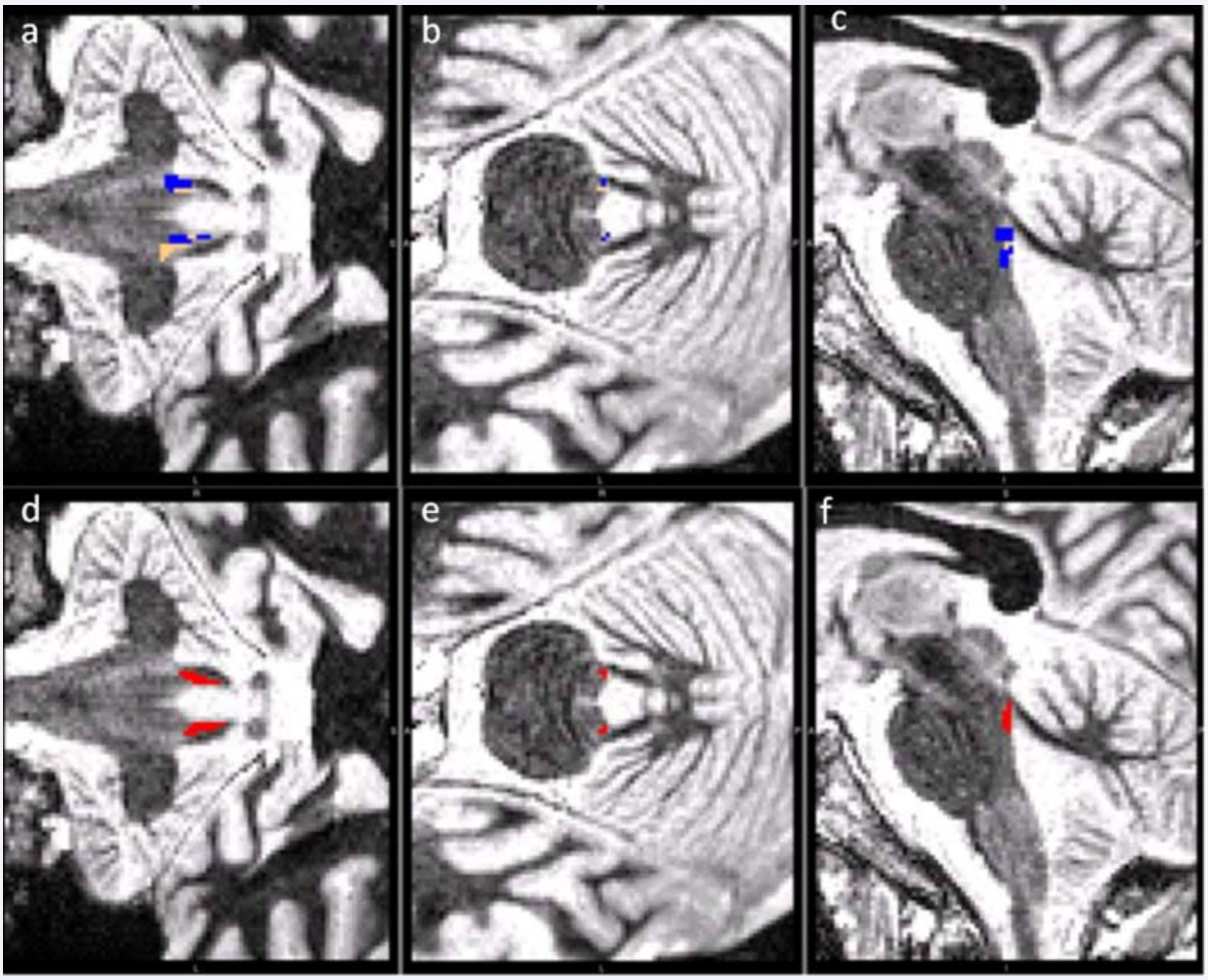

Figure 1 The LC mask in the axial, coronal and sagittal view, overlaid on an FGATIR image. A-C show the 1SD (gold) and 2SD (blue and gold) Eckert LC mask registered to native FGATIR space. D-F shows the manually corrected LC mask based on anatomical landmarks and localization provided by the Eckert masks.

disturbances [33]. The ESS assesses average daytime sleepiness for each participant [34]. In order to explore qualitative differences in sleep and LC metrics, we examined each individual question and component score on the PQSI in relation to LC metrics using the SPSS statistical package. Because controls were not given sleep measures in this study, and due to incomplete sleep data for five veterans, as well as one significant outlier (>3 SD from the mean), these analyses were conducted on the remaining 12 veterans.

RESULTS AND DISCUSSION

The Dice similarity coefficient (DSC) was computed to assess the amount of spatial overlap between two sets of LC masks from 10 randomly selected participants. The DSC for this sample ranged from .90 to .96, indicating 90-96% percent overlap between repeated ROI tracings, and exceeding the acceptability cutoff of 0.7 for reliable cutoff scores. Analysis of thalamic anatomy, to ensure correct ROI registration from MNI to T1- and FGATIR spaces, revealed correct registration and localization of the thalamus in all participants. An independent-samples t-test was used to compare mean FA and volume of the LC between veterans and healthy controls. These analyses revealed no group differences in mean LC FA, but a trend toward higher LC volume in the control group (T=1.832, p=.079).

Co relational analysis examined the relationship of LC volume and mean FA to PSQI sleep data. Spearman rank order correlations were used to compare all variables. PSQI items were entered individually to assess relationships between LC metrics and specific sleep-related disturbances. Relationships were examined between LC volume, FA, the summed frequency of loss of consciousness and alteration of consciousness events for each participant (LOC/AOC frequency), individual PSQI items, Global PSQI sleep scores, and ESS scores.

Analyses revealed that smaller LC volume was correlated with the inability to breathe comfortably during sleep, with higher scores indicating a higher frequency of discomfort with breathing (r=-.619, p=.032). This same relationship was found for hours slept per night, with higher scores indicating fewer hours slept (r=-.661, p=.019),(Table 2)as well as with the sleep efficiency component score (r=-.596, p=.041). The sleep efficiency component score assesses the number of hours slept

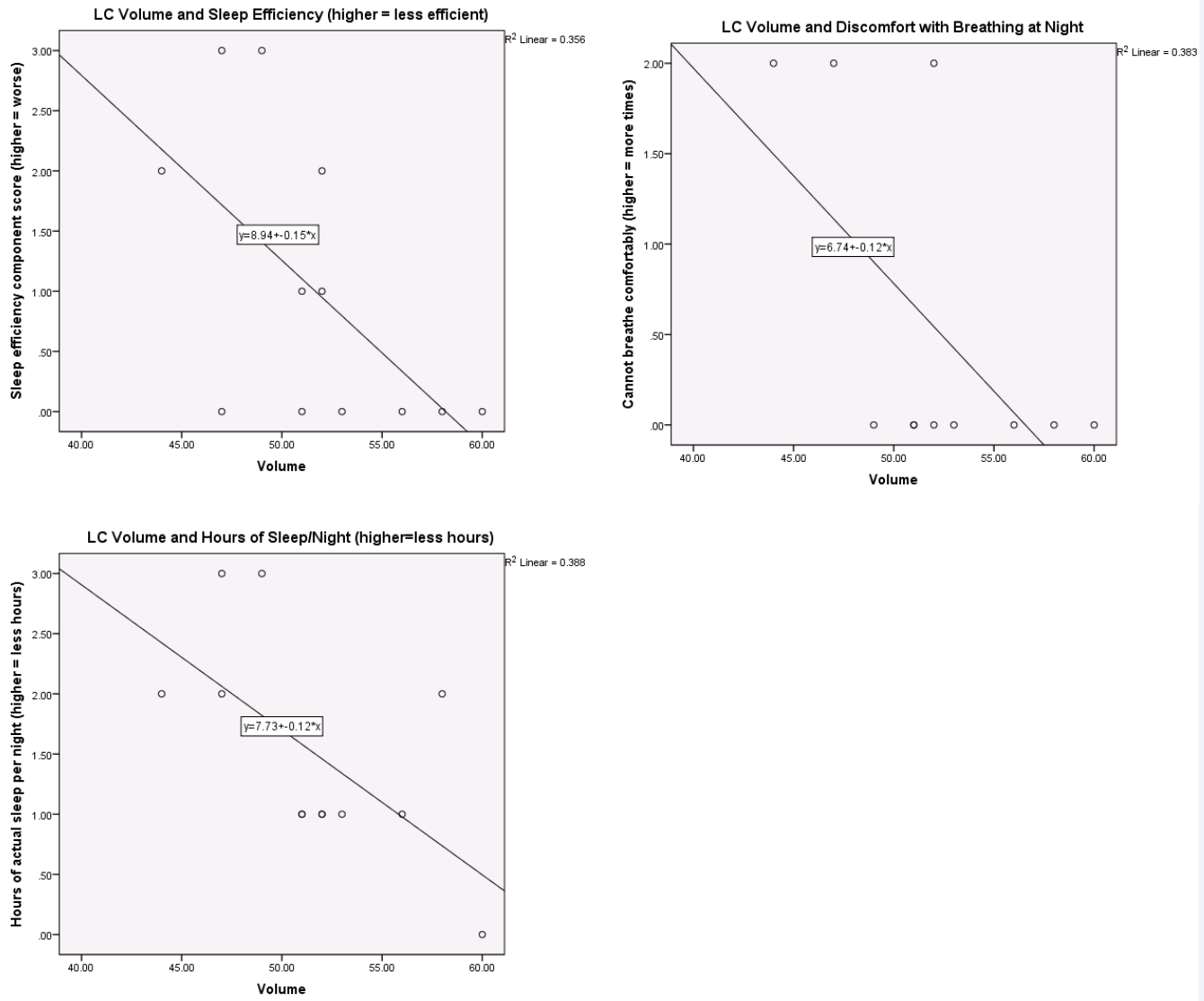

Figure 2 LC Volume and Sleep Outcomes: Significant Correlations (p<.05).

Table 2: Comparison of LC volume and mean FA between healthy controls and veterans with mTBI.

	t	p	Std. Error Difference	Lower CI	Upper CI
FA	.792	.434	.01856	-.023	.052
Volume	1.832	**.079**	2.4958	-.555	9.654

compared to hours spent in bed, with higher scores indicating a greater number of hours spent awake compared to hours slept. Figure 2 shows graphical representations of significant results.

LC volume also showed negative, though non-significant correlations with PSQI subjective sleep quality (r=-.403, p=.194) and sleep latency(r=-.438, p=.155) component scores, as well as the PSQI global sleep score (r=-.54, p=.07). The correlation between LOC/AOC frequency and ESS scores was moderate (r=.496, p=.101), with increased self-reported sleepiness associated with increasing numbers of LOC/AOC events at the individual case level. FA within the LC was not significantly correlated with any outcome variables. Age and education were also not significantly correlated with any outcome variables.

Our findings suggest that decreased volume in the LC was significantly correlated with lower sleep efficiency, a decreased number of hours slept per night and a higher frequency of discomfort with breathing while sleeping. Although the relationship between LC volume and other sleep outcomes did not reach significance, there was a pattern of moderate correlations between lower LC volume and increased difficulties with subjective sleep quality, sleep latency and global sleep scores. These correlations moved in the hypothesized direction,

suggesting that with higher power in our study, we may be able to better show a relationship between abnormalities in the LC and greater sleep disturbances in mTBI patients. Results also indicate that LC volume was a better predictor of sleep outcomes than mean FA within the LC.

Taken together, these findings indicate that lower volume in the LC may be associated with some of the sleep disturbances reported in mTBI patients (Figure2) (discomfort with breathing during sleep, decreased number of hours slept, and sleep efficiency). Previous studies have demonstrated a relationship between decreased signal intensity in the LC and higher frequency of REM sleep disturbances in Parkinson an patients [20]. The current study shows a similar relationship with reduced LC volume and higher levels of sleep disturbances. Our findings also support the current literature on sleep disorders in TBI populations. For instance, discomfort with breathing and coughing or snoring loudly during sleep is suggestive of sleep apnea. Similarly, a decreased number of hours slept per night suggest insomnia in mTBI patients. Each of these behavioral measures had a statistically significant negative correlation with LC volume in our study. Because sleep disturbances are so widely reported after mTBI, along with the high prevalence of brainstem injury in the course of a TBI, disturbance to the LC may help to partially explain sleep-related complaints in symptomatic patients.

LIMITATIONS AND FUTURE DIRECTIONS

The limited sample size in our study limited our ability to fully investigate LC volume and FA differences between mTBI patients and controls, as well as the relationship between these structural measures and behavioral measures of sleep (PSQI and ESS). Some studies suggest that a sample size of at least 54 participants would be needed to reach significance using similar statistical analyses in an mTBI population [35]. A larger sample size would also allow for more robust statistical analyses of the variables. For instance, a hierarchical regression would allow us to control for co morbid psychiatric risk factors involved in sleep disturbances, such as PTSD and depression. In addition, larger neural networks should also be examined to better assess potential structural abnormalities within this LC system. However, the current study provides a proof-of-concept on which to build future research, and provides preliminary data for specific patterns of sleep disturbances as they relate to LC volume.

CONCLUSION

The results presented here provide a reliable protocol for individual mapping of the LC *in vivo*, allowing for future investigation of this structure. Volumetric and morphological data suggest that the LC plays an important role in sleep efficiency, number of hours sleep per night and discomfort with breathing during sleep. Based on the pattern of negative relationships between LC volume loss and increased incidence of sleep disruption, this study provides preliminary evidence to guide future research. A current study underway utilizes the LC segmentation protocol developed here to enable further study of this structure and its pathways. Finding TBI-related disruption in the LC system would be an important first step in developing therapeutic interventions for symptomatic patients.

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REFERENCES

1. DoD TBI Worldwide Numbers since 2000: Defense and Veterans Brain Injury Center (DVBIC); 2013.
2. Petrie EC, Cross DJ, Yarnykh VL, Richards T, Martin NM, Pagulayan K, et al. Neuroimaging, behavioral, and psychological sequelae of repetitive combined blast/impact mild traumatic brain injury in Iraq and Afghanistan war veterans. J Neurotrauma. 2014;31:425-436.
3. Orff HJ, Ayalon L, Drummond SP. Traumatic brain injury and sleep disturbance: a review of current research. J Head Trauma Rehabil. 2009; 24: 155-165.
4. Ouellet MC, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: a preliminary study. Sleep Med. 2006; 7: 486-497.
5. Parcell DL, Ponsford JL, Rajaratnam SM, Redman JR. Self-reported changes to nighttime sleep after traumatic brain injury. Arch Phys Med Rehabil. 2006; 87: 278-285.
6. Castriotta RJ, Murthy JN. Sleep disorders in patients with traumatic brain injury: a review. CNS Drugs. 2011; 25: 175-185.
7. 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;178:951-956.
8. Hou L, Han X, Sheng P, Tong W, Li Z, Xu D, Yu M. Risk factors associated with sleep disturbance following traumatic brain injury: clinical findings and questionnaire based study. PLoS One. 2013; 8: e76087.
9. Rao V, McCann U, Han D, Bergey A, Smith MT. Does acute TBI-related sleep disturbance predict subsequent neuropsychiatric disturbances? Brain Inj. 2014; 28: 20-26.
10. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, O'Donnell J. Sleep drives metabolite clearance from the adult brain. Science. 2013; 342: 373-377.
11. 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: 1873-1883.
12. Chamberlain SR, Robbins TW. Noradrenergic modulation of cognition: therapeutic implications. J Psychopharmacol. 2013; 27: 694-718.
13. Samuels ER, Szabadi E. Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part I: principles of functional organisation. Curr Neuropharmacol. 2008;6:235-253.
14. 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: 3830-3842.

15. Kumar VM, Vetrivelan R, Mallick HN. Noradrenergic afferents and receptors in the medial preoptic area: neuroanatomical and neurochemical links between the regulation of sleep and body temperature. Neurochem Int. 2007; 50: 783-790.

16. Kryger MH, Roth T, Dement WC. Principles and Practice of Sleep Medicine. 5 ed. St. Louis, Missouri: Elsevier; 2011.

17. Bigler ED. Neuroimaging biomarkers in mild traumatic brain injury (mTBI). Neuropsychol Rev. 2013; 23: 169-209.

18. Keren NI, Lozar CT, Harris KC, Morgan PS, Eckert MA. In vivo mapping of the human locus coeruleus. Neuroimage. 2009; 47: 1261-1267.

19. Sasaki M, Shibata E, Tohyama K, Takahashi J, Otsuka K, Tsuchiya K, Takahashi S. Neuromelanin magnetic resonance imaging of locus ceruleus and substantia nigra in Parkinson's disease. Neuroreport. 2006; 17: 1215-1218.

20. Garcia-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, Leu-Semenescu S, Gallea C, Quattrocchi G, et al. The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain. 2013;136:2120-2129.

21. Sudhyadhom A, Haq IU, Foote KD, Okun MS, Bova FJ. A high resolution and high contrast MRI for differentiation of subcortical structures for DBS targeting: the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR). Neuroimage. 2009;47 Suppl 2:44-52.

22. Ciccone MM, Scicchitano P2, Zito A3, Cortese F4, Boninfante B5, Falcone VA6, Quaranta VN7. Correlation between inflammatory markers of atherosclerosis and carotid intima-media thickness in Obstructive Sleep Apnea. Molecules. 2014; 19: 1651-1662.

23. Veteran Population Washington, D.C.: United States Department of Veterans Affairs; 2014 .

24. Ford AA, Triplett W, Sudhyadhom A, Gullett J, McGregor K, Fitzgerald DB, Mareci T. Broca's area and its striatal and thalamic connections: a diffusion-MRI tractography study. Front Neuroanat. 2013; 7: 8.

25. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal. 2001; 5: 143-156.

26. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002; 17: 143-155.

27. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 2002; 17: 825-841.

28. Naidich TP, Duvernoy HM, Delman BN, Sorensen AG, Kollias SS, Haacke EM. Duvernoy's Atlas of the Human Brain Stem and Cerebellum: High-Field MRI: Surface Anatomy, Internal Structure, Vascularization and 3D Sectional Anatomy. Austria: Springer Vienna; 2009.

29. Makris N, Goldstein JM, Kennedy D, Hodge SM, Caviness VS, Faraone SV, et al. Decreased volume of left and total anterior insular lobule in schizophrenia. Schizophr Res. 2006;83:155-171.

30. Frazier JA, Chiu S, Breeze JL, Makris N, Lange N, Kennedy DN, Herbert MR. Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. Am J Psychiatry. 2005; 162: 1256-1265.

31. Desikan RS, Segonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006;31:968-980.

32. Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS Jr, Kennedy DN. Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol Psychiatry. 2007; 61: 935-945.

33. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989; 28: 193-213.

34. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540-545.

35. Christidi F, Bigler ED, McCauley SR, Schnelle KP, Merkley TL, Mors MB, Li X. Diffusion tensor imaging of the perforant pathway zone and its relation to memory function in patients with severe traumatic brain injury. J Neurotrauma. 2011; 28: 711-725.

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