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Combat-related Blast Exposure and Traumatic Brain Injury Influence Brain Glucose Metabolism during REM Sleep in Military Veterans

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Abstract

Traumatic Brain Injury (TBI), a signature wound of Operations Enduring and Iraqi Freedom, can result from blunt head trauma or exposure to a blast/explosion. While TBI affects sleep, the neurobiological underpinnings between TBI and sleep are largely unknown. To examine the neurobiological underpinnings of this relationship in military veterans, [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG PET) was used to compare mTBI-related changes in relative cerebral metabolic rate of glucose (rCMRglc) during wakefulness, Rapid Eye Movement (REM) sleep, and non-REM (NREM) sleep, after adjusting for the effects of posttraumatic stress (PTS). Fourteen Veterans with a history of Blast Exposure and/or mTBI (B/mTBI) (age 27.5 ± 3.9) and eleven Veterans with no history (No B/mTBI) (age 27.7 ± 3.8) completed FDG PET studies during wakefulness, REM sleep, and NREM sleep. Whole-brain analyses were conducted using Statistical Parametric Mapping (SPM8). Between group comparisons revealed that B/mTBI was associated with significantly lower rCMRglc during wakefulness and REM sleep in the amygdala, hippocampus, parahippocampal gyrus, thalamus, insula, uncus, culmen, visual association cortices, and midline medial frontal cortices. These results suggest alterations in neurobiological networks during Wakefulness and REM sleep subsequent to B/mTBI exposure, may contribute to chronic sleep disturbances, and differ in individuals with acute symptoms.

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1. Introduction

During Operation Enduring Freedom and Operation Iraqi Freedom (OEF/OIF), blasts from explosions have accounted for 60% of casualties related to combat exposure.[1] As cited by Warden,[2] these injuries are responsible for nearly two thirds of medical evacuations in war zones. One type of casualty, Traumatic Brain Injury (TBI), is a leading cause of death, impairments, and disability, among military veterans of OEF/OIF. [2-4] Since the onset of the Afghanistan and Iraq Wars, surveys indicate that between 15% and 23% of OEF/OIF military service men and women have sustained TBI. [2,5-7] Further, statistics released by Walter Reed Medical Center indicate that of those injured by exposure to blast, 60% lead to TBI.[2] Nevertheless, the majority of TBI's that have been sustained fall into the mild category (mTBI).[2,6,7]

Exposure to events that could lead to mTBI and prolonged stress characterize military deployment and can lead to both chronic symptoms of posttraumatic stress[8,9] and physiological distress (i.e., postconcussive symptoms).[3] Prior research has attempted to elucidate the sequelae of varying severity of TBI.[10] mTBI is diagnosed when there is a period of 30 minutes or less of loss of consciousness (LOC), a Glasgow Coma Scale of 13 or greater, and less than a 24 hour time frame of posttraumatic amnesia.[11,12] A primary focus of empirical research in the past has been with individuals sustaining mTBI who had lost consciousness momentarily, if at all, and the onset of posttraumatic stress disorder (PTSD).[11] In a sample of 46 patients who sustained TBI's of heterogeneous severity, 27% that remained conscious throughout the traumatic event were diagnosed with PTSD.[10] For individuals with more severe TBI (LOC > 12 hours), only 3% were diagnosed with PTSD. [10] It has been postulated that individuals who have suffered a mTBI have a greater risk of developing PTSD as the amount of time spent unconscious is limited or nonexistent.[8,11] Further, it is suggested that PTSD is more prevalent when memories of the traumatic event are encoded in the brain, allowing those memories to be encoded and subsequently reexperienced.[5,13,14] The effects of PTSD following mTBI may also linger, resulting in long term morbidity. Recently, researchers reported that nearly 1/3 of US Army Special Operations Forces personnel who were exposed to a previous blast or combination blast-blunt mTBI met the criteria for clinical PTSD. [15] While the association between mTBI and psychological distress remains an area for further exploration, so too does the relationship between mTBI and subsequent physiological disturbances.

Typical symptoms of mTBI manifest as concussive states (i.e., headache, sensitivity to light and noise, mood changes, fatigue, cognitive deficits, and shifts in sleep patterns).[16] For a majority of those who sustained a mTBI, vast improvements are seen within the first 6 months following injury.[3] While improvements in neurological functioning (i.e., less frequent or severe headaches, improved motor coordination, etc.) can be seen upwards of 2

years or more, chronic symptoms, including sleep disturbances, are frequently identified in those who have sustained a mTBI.[3,17]

Sleep disturbances are reported by 30 to 70% of patients with head injury,[18] and include symptoms of insomnia, hypersomnia, nightmares, and irregular sleep/wake patterns. Sleep-wake disturbances (SWD) that occur after a mTBI have been shown to impede cognitive and neurological functioning.[3,19] It was observed that nearly 75% of individuals who were hospitalized as a result of mTBI developed SWD at or within 6 months of the injury.[20] Further, interrupted sleep and daytime fatigue and sleepiness have been reported in populations of military personnel subsequent to mTBI exposure.[21,22] Posttraumatic hypersomnia is seen in a majority of mTBI patients,[20] and may result from alterations in brain regions involved in maintaining wakefulness (i.e., brainstem reticular formation and posterior hypothalamus) are impacted.[18] Similarly, insomnia may arise from alterations to brain areas involved in sleep initiation and maintenance, such as the anterior hypothalamus and ventromedial prefrontal cortex. In closed head mTBI, where coup-contrecoup injuries yield trauma at the sphenoid ridges at the base of the skull, damage to the inferior frontal region, suprachiasmatic nucleus, anterior temporal area, and the basal forebrain may also lead to insomnia and circadian changes.[18]

Polysomnography (PSG) is the gold standard to objectively measure sleep/wake disturbances, and abnormalities on PSG have been reported in individuals with a history of sustaining mTBI.[21,22] However, PSG measures may not capture the alterations in brain regions and mechanisms that contribute to sleep/wake disturbances. For instance, brain glucose metabolism during sleep has been shown to differ in patients with depression and insomnia compared to healthy sleepers, even when PSG characteristics did not differ among groups.[23-26] Furthermore, studies have shown that persistent activation of brain glucose metabolism in the thalamocortical network during non- rapid-eye movement (NREM) is associated with subjective sleep complaints.[24,27]

1.1. Objective

Blast–related mTBI can lead to persistent neurobiological alterations. [28-30] In a recent study, Peskind and colleagues[31] found regional brain hypometabolism of the infratentorial region (cerebellum, vermis, pons) and medial temporal area in blast exposed OIF military veterans with chronic post-concussive symptoms compared to a control group with no history of head trauma. However, it is unclear whether prior blast exposure or past mTBI can be associated with chronic cerebral metabolic changes, even in the absence of current post-concussive symptoms. Here, we used [18F]-fluorodeoxyglucose positron emission tomography ([18F]-FDG PET) to examine the potential impact of prior blast or mild TBI exposure on brain glucose metabolism during wakefulness, REM sleep, and NREM sleep in a sample of combat-exposed veterans with and without a history of blast exposure or mTBI, and after adjusting for the effects of posttraumatic stress symptom severity.[8,9] We hypothesized that blast exposure and/or mTBI (B/mTBI) would be associated with alterations in relative cerebral metabolic rate of glucose (rCMRglc) during both wakefulness and sleep, which may reflect long-term neural effects of B/mTBI exposure.

2. Methods

2.1. Participants

PET imaging data were collected from two research studies that were reviewed and approved by the Institutional Review Board at the University of Pittsburgh and Human Research Protection Office of the Department of Defense. Of the collected data from 71 OEF/OIF Military veterans who completed FDG PET studies during wakefulness, due to subsequent exclusion, being withdrawn, or withdrawing from the studies, 67 veterans continued to complete FDG PET studies during REM sleep and 59 completed during NREM sleep. Veterans included in the initial sample of 71 were mainly Caucasian (90%, n=64). Only veterans who completed all three scans (wakefulness, REM, and NREM) and whose FDG PET studies met the threshold of PET quality were included in the current study (n=25, 100% Caucasian). Of these 25 veterans, 14 endorsed a history of blast exposure and/or mTBI (B/mTBI group) (age 27.5 ± 3.9) and 11 denied a history of blast exposure and/or mTBI (control group) (age 27.7 ± 3.8). Of the participants in the B/mTBI group, only one reported experiencing blunt force trauma in addition to exposure to blast. All participants provide written informed consent.

2.2. Design

Eligible participants were all medication-free, and free of medical and psychiatric comorbidity other than PTSD. Participants completed an extensive diagnostic evaluation, along with a physical examination and urine drug screen to verify stable medical health and the absence of recent or current substance use. The Structured Clinical Interview for DSM-IV Axis I disorders (SCID)[32] was administered to assess for comorbid Axis I disorders. None of the participants met the criteria for comorbid Axis I disorders, other than PTSD. Current PTSD severity and status was assessed using the Clinician Administered PTSD Scale (CAPS), the gold standard PTSD diagnostic instrument. [33] Additionally, participants completed the *Combat Exposure Scale* (CES)[34],a 7-item self-report instrument that indicates the level of combat exposure based on the frequency of seven combat situations. They also completed the *Pittsburgh Sleep Quality Index* (PSQI)[35] , an 18-item self-report measure that assesses seven components of sleep quality (i.e., subjective sleep quality, sleep latency, duration, efficiency, disturbances, use of sleep medication, and daytime dysfunction). As symptoms of depression are commonly comorbid with PTSD, despite participants not meeting diagnostic criteria for a comorbid mood disorder, the Beck Depression Inventory (BDI) [36], a 21-item self-report measure that assesses the severity of depressive symptoms, was also completed.

Participants in the B/mTBI group were identified based on information gathered from the *Life Events Checklist* (LEC), on the CAPS, the *Military Acute Concussion Evaluation* (MACE)[37], or during the physical examination and medical review. The B/mTBI group included Veterans who reported that they had directly been exposed to an explosive blast, and/or reported a history of blast, mTBI and concussive symptoms while deployed. The average time since the self-reported last blast exposure or mTBI was 42.6 ± 26.9 months (range: 15 to 86 months). Veterans in the control group did not report any exposure to blast or mTBI before, during, or after deployment.

2.3. Procedures

All participants underwent a brain magnetic resonance (MR) scan on a Siemens 3T Trio scanner. The following axial series was oriented to the anterior commissure-posterior commissure line: fast spin-echo T2-weighted images (TE/TR=104/4660ms, FOV 18x24cm, 46 slices, 3.6mm slices), proton density-weighted images (TE/TR=23/4050ms, FOV 18x24cm, 46 slices, 3.6mm slices) and fast fluid-attenuated inversion recovery images (TE/TR/TI=90/9160/2500ms, FOV 21.2x25.6cm, 48 slices, 3mm slices). A volumetric MPRAGE sequence was acquired in the sagittal plane (TE/TR=2.98/2300ms, flip angle=9°, FOV 24x25.6cm, 160 slices, 1.2mm slices). MR data was registered with PET data using Automated Image Registration.

After completing a one-night sleep screening study at the University of Pittsburgh Neuroscience Clinical & Translational Research Center (N-CTRC; RR024153), all participants returned to the sleep laboratory for four consecutive PSG sleep studies. The first night served as a screening sleep study to rule out the presence of sleep apnea or periodic leg movement disorder. The second night served as an adaptation night. The waking PET scan was conducted the following morning, two to four hours after the participant's habitual rise time. The NREM PET study was conducted on Night 3. Night 4 served as a recovery night, and the REM PET study was conducted on Night 5. All procedures were performed in the same order for all participants.

Prior to each PET study, two intravenous catheters were placed, one in each arm, with normal saline infused at the minimal rate to keep the vein open. The radioligand was injected through one catheter, and the other catheter was used to sample glucose and radioactivity. These PET procedures were originally described by Nofzinger and colleagues.[38]

For the wake PET scan (2-4 hours post-waking), participants lay supine with their eyes closed while their wakefulness was continuously monitored with PSG. After 20 minutes of PSG-monitored wakefulness, the intravenous bolus of approximately 5milliCurie of [18F]-FDG was injected.

For the REM sleep PET scan, [18F]-FDG was injected at the onset of the 2nd REM sleep period. For the NREM sleep PET scan, [18F]-FDG was injected 10 minutes after the detection of sleep onset. PSG was continuously monitored during the uptake period for 20 minutes, after which participants were awakened, and transported from the N-CTRC sleep laboratory to the University of Pittsburgh PET Center for a 10-15 minute transmission scan and a 60-minute emission scan. PET studies were conducted on a Siemens/CTI ECAT HR+ PET scanner with a Neuro-insert (CTI PET Systems, Knoxville, TN) in 3D mode. PET images were reconstructed using standard commercial software as 63 2.4-mm transaxial slices. The estimated full-width half-maximum resolution of reconstructed images was 6 mm in the transverse plane.

2.4. Statistical Analysis

Relative cerebral metabolic rate of glucose (rCMRglc) was assessed during wakefulness, NREM sleep, and REM sleep according to previously validated methodology for FDG PET

imaging.[38-40] Image analyses were conducted using Statistical Parametric Mapping (SPM8).[41] Whole-brain interactions were conducted to compare group (B/mTBI vs. Control) by state (Wake vs. REM and Wake vs. NREM sleep) changes in rCMRglc in wakefulness and REM sleep or NREM sleep, using current PTSD severity as measured by the CAPS (past month) as a covariate. Post-hoc between-group differences were then examined separately using independent samples t-tests. Given the exploratory nature of the study, the uncorrected significance threshold at the cluster level was set at 0.05 for all statistical analyses. Effect sizes were extracted using contrast estimates and 90% confidence intervals (90% CI). [42]

Mean rCMRglc values for each significant cluster were extracted using the MATLAB toolbox rex (web.mit.edu/swg/rex/ rex.pdf). The mean extracted rCMRglc values were then correlated with the CES, CAPS, and PSQI. Pearson correlation coefficients were utilized as all variables were checked for normal distribution, and non-normal variables were transformed prior to statistical analyses, when needed.

3. Results

3.1. Clinical, demographic, and sleep measures

Only veterans who completed all three scans (wakefulness, REM, and NREM) and whose FDG PET studies met the threshold of PET quality were included in the current study (n=25, 100% Caucasian). Clinical, demographic, and sleep parameters of the two groups are provided in Table 1. Current PTSD severity and status was also assessed using the CAPS. Eleven of the 14 veterans in the B/mTBI group met diagnostic criteria for PTSD (mean CAPS score = 45.29±18.32), while eight of the 11 veterans from the control group met diagnostic criteria for PTSD (mean CAPS score = 43.64 ± 19.69). Independent samples t-tests revealed no significant differences between B/mTBI and control groups on measures of combat exposure or PTSD severity.

As shown in Table 1, none of the objective measures differed between the two groups. Polysomnographic profiles did not suggest gross disruption of sleep.

3.2. PET analyses

No Significant Group x State interactions were found for either wakefulness vs. REM or wakefulness vs. NREM sleep analyses. Between group comparisons revealed that the B/mTBI group showed lower rCMRglc during both wakefulness and REM sleep. During wakefulness, the B/mTBI group showed lower rCMRglc compared to the control group in two clusters (Figure 1). The first cluster (MNI coordinates of voxel of maximal significance: *x, y, z* = 16, 8, -16; *k* = 4943, *Z*=3.76, *p* = 0.006, contrast estimate = 8.04 [90% CI = 5.11-10.96]) was lateralized to the right hemisphere, and included the olfactory gyrus, caudate, putamen, amygdala, hippocampus, parahippocampal gyrus, and extended centrally into the pons. This cluster also extended into temporal and visual cortices, including the right fusiform, lingual, angular, and rectus gyrus, and inferior and superior temporal gyrus. The second cluster significance (x, y, z = -2, 32, 10; *k* = 2621, *Z*=2.91, *p* =.034, contrast estimate = 9.95 [90% CI = 4.93-14.97]) included midline medial regions such as the

cingulate gyrus, and extended to the left medial frontal gyrus, middle frontal gyrus, and superior frontal gyrus. No brain regions showed increased rCMRglc in the B/mTBI group compared to the control group during wakefulness.

The B/mTBI group also showed a significant decrease in rCMRglc during REM sleep compared to the control group in one cluster that encompassed 3585 contiguous voxels (Figure2) (x, y, z, = -8, -12, -8; Z=3.43, p =0.01, contrast estimate = 5.52 [90% CI = 3.26-7.79]). This area was restricted to the left hemisphere, and from the brainstem, extended into the thalamus, putamen and caudate, insula, uncus, parahippocampal gyrus, middle temporal gyrus, subcallosal gyrus, fusiform gyrus, lentiform nucleus, and the precentral gyrus. No brain regions showed increased rCMRglc in the B/mTBI group compared to the control group during REM sleep.

No significant Group X State interactions were revealed from wakefulness to NREM sleep. Post-hoc comparisons also failed to reveal significant group differences during NREM sleep.

Figure 3 depicts the extracted mean values of rCMRglc in the above mentioned significant clusters between groups during both wakefulness and REM sleep. As shown in Table 2, mean rCMRglc in these clusters were not significantly correlated with CES scores, CAPS total scores, or PSQI scores.

4. Discussion

To the best of our knowledge, this is the first study to use [18F]-FDG PET to explore the potential long-term neurobiological effects of prior blast exposure/mTBI on wakefulness, REM sleep, and NREM sleep in the absence of concurrent post-concussive symptoms, and after adjusting for PTSD symptom severity. The primary finding of this study is the detectable decrease in rCMRglc during both wakefulness and REM sleep in OEF/OIF veterans with prior B/mTBI exposure compared to those with no history of B/mTBI. Hypometabolism was detected in the right basal ganglia, amygdala, hippocampus, parahippocampal gyrus, culmen, visual association cortices, and midline medial frontal cortices. These brain regions may be especially susceptible to long-term impacts of blast exposure or mTBI. Hypometabolism in these limbic regions may constitute a risk factor for chronic concussive symptoms following re-exposure to blast and/or mTBI, or to chronic maladaptive stress responses such as PTSD following these events.

The lack of significant correlations between the extracted mean values of rCMRglc within the significant clusters and clinical variables of interest suggests that the observed hypometabolism in wakefulness and REM sleep may reflect long-term neural effects of B/mTBI exposure, beyond the effects of concurrent PTSD symptoms, combat exposure severity, and subjective or objective sleep quality. Functional impairments (i.e., slower processing speed, attention and concentration difficulties, etc.) are often observed among individuals with concussive symptoms, PTSD, and poor sleep quality. In this study, however, participants were free from active concussive symptoms. These hypometabolic profiles observed here may be associated with subtle, cognitive impairments. Thus, future

studies of rCMRglc during wakefulness and REM sleep in B/mTBI exposed veterans should explore potential significant relationships between decreased rCMRglc and combat exposure, PTSD severity, and sleep quality independent of self-report measures, by examining components of other cognitive, psychological, and physiological functioning (i.e., neuropsychological testing, fMRI, etc.). Indeed, biomechanical studies suggest that structures located around the middle axis of the brain are at increased vulnerability to acceleration-deceleration forces ubiquitous to mTBI injuries [43-45] Further, electrophysiological, [46,47] and diffusion tensor imaging [48,49] studies also suggest common areas of vulnerability, including the corticospinal tract, which has direct connections to the thalamus and basal nuclei.

Chronically reduced rCMRglc is associated with several neurodegenerative disorders, albeit with very different metabolic patterns. [50-52] Altered cerebral metabolism is thought to be a hallmark of mild mTBI and has been documented across several different time points post-injury in different populations with vastly different outcomes. [53-59] However, these studies have typically involved samples with blunt brain injuries. Whether the observed neurometabolic changes confer heightened vulnerability to chronic concussive symptoms following subsequent B/mTBI is unknown. Further, whether those participants showing reduced rCMRglc are necessarily more vulnerable to other neuropathologies or behavioral deficits is unknown. Prospective and longitudinal studies are necessary to elucidate the neural impacts of blast and mTBI on neurobiological correlates underlying cognitive, affective, neuromotor, and behavioral post-concussive symptoms and impairment.

These types of aforementioned studies may be difficult, however, due to the diffuse injury conditions typically seen in mTBI.[60] As such, the neural substrates implicated in prior studies explicitly focusing on sleep disorders or mTBI may not be the same as those evidenced in studies examining the neurobiological sequelae of blast injury. Brain injuries related to blast exposure serve to increase the complexity of the resulting neurotrauma, as there is a widely distributed pattern of white matter degradation compared to the more localized, focal injury observed in blunt force trauma. [61-63] This disruption of white matter integrity throughout a number of fiber tracks throughout both cortical and subcortical structure has been shown to be present in patients diagnosed with mTBI during wakefulness. [64] Just as alterations are seen during wakefulness following mTBI, altered structural integrity and functionality of brain regions are likely to exist during REM sleep.

In the current study, Veterans with B/mTBI exposure also demonstrated a decrease in rCMRglc during REM sleep compared to those without B/mTBI exposure. A pattern of hypometabolism was seen in a more restricted brainstem, thalamus, basal ganglia, amygdala, hippocampus and parahippocampal gyrus, insula, and uncus. These structures have typically shown increased activation during REM sleep relative to wakefulness in healthy subjects, as well as in individuals with PTSD.[65] The decrease in rCMRglc in these limbic and paralimbic structures during REM sleep in the B/mTBI group compared to the control group may reflect an inherent functional difference in the neurobiological impacts of B/mTBI on REM sleep, independent of the effects of PTSD. Limbic structures like the amygdala and hippocampus have been shown to be the most densely packed with cholinergic axons and 5-HT1A receptor sites, followed by regions of the paralimbic cortex.[65,66] The diffuse axonal

injury shown to follow B/mTBI may indeed alter connections throughout the brain, especially those in deep subcortical structures which are densely packed with cholinergic axons and 5-HT1A receptor sites and known to be implicated during REM sleep. REM sleep, a state of cholinergic and monoaminergic balance, may therefore be sensitive to B/mTBI exposure. In turn, changes in REM sleep that facilitate the restorative effects of REM sleep on emotional and cognitive functioning may be altered.

There were no differences in rCMRglc during NREM sleep between Veterans with B/mTBI exposure and those without B/mTBI exposure. NREM sleep is characterized an overall decrease in cerebral blood flow and glucose metabolism by as much as 30 to 40%. [27] Neuroimaging studies have shown that relative to wakefulness, NREM is associated with relative persistence of neural activity in limbic regions concurrent with overall reductions of glucose metabolism and blood flow in prefrontal and paralimbic structures. [27 ,67] This disengagement between limbic structures from paralimbic/prefrontal regions may facilitate the endogenous restorative effects of NREM sleep. [27, 67, 68] Thus, NREM is a state of reduced neuronal activity, which may not unmask injury-related impacts that are apparent during more active states, including wakefulness and REM sleep. However, replications in larger samples are required to ascertain that blast/mTBI exposure does not yield detectable cerebral metabolic changes during NREM sleep.

Finally, the results of the current study also suggest possible alterations in neurobiological networks involved in threat responses and memory during both wakefulness and REM sleep subsequent to B/mTBI exposure. Indeed, there has been extensive research conducted examining these neurobiological networks in both animal and human models. [68] Coordinated engagement of the amygdala, hippocampus, prefrontal cortices, periaqueductal gray, and the bed nucleus of the stria terminalis serve to not only detect threat, but also mediate anxiety, encode memories, extinguish fear, and coordinate physiological responses to perceived threat. [70-76] As the findings of the current study demonstrate alterations in rCMRglc in the right basal ganglia, amygdala, hippocampus, parahippocampal gyrus, culmen, visual association cortices, and midline medial frontal cortices subsequent to B/mTBI exposure, these alterations may dysregulate the a number of the key neural substrate involved in threat detection and memory processing. Future studies should include other functional neuroimaging methods and analytical techniques such as fMRI and DTI or high definition fiber tracking (HDTF), as well as exposure to potentially threatening stimuli and memories to probe and assess the integrity these circuits across the sleep/wake cycle.

Because of the limited sample size, racial composition, and cross-sectional design of the present study, speculations in terms of the generalizability and the temporal course of alterations in rCMRglc in veterans exposed to blast or mTBI is limited. However, these findings suggest that B/mTBI exposure may have long-lasting neural effects that are detectable during both wakefulness and REM sleep. Germain et al.[40,68] have postulated that REM sleep subsequent to trauma could very well be critical to recovery and psychological resilience. Additionally, due to the overlap of symptom presentation in both mTBI and PTSD following a traumatic event (i.e., blast), alterations observed in the neurobiological correlates responsible for arousal and sleep circuitry in mTBI may partially overlap with those observed in PTSD. However, the two groups in the current study scored similarly on

PTSD suggesting that the reported differences are related to B/mTBI exposure and not PTSD per se. Studies have demonstrated that neural substrate (i.e., amygdala, hippocampus, medial prefrontal cortex) activity governing arousal and threat response is in fact exaggerated in anxiety disorders, such as PTSD. [77-79] As such, the present findings revealing decreased rCMRglc in these structures suggest that REM sleep, as well as wakefulness, may be compromised following exposure to mTBI, independent of the effects of PTSD symptomology.[40]

Future research should continue to focus on the neurobiological sequelae of blast exposure, relative to other types of mTBI and after adjusting for PTSD, during wakefulness, REM sleep, and NREM sleep. More specifically, a larger sample of groups of Veterans with blunt, blast, and no mTBI should be compared to a group with PTSD with no mTBI. Given that this sample is 100% Caucasian, the sample of convenience assembled for this exploratory study is indeed not an accurate representation of the demographics of the US military. Because the exploratory analyses reported here included PET scans and data only from Veterans who successfully completed all three PET scans, it is possible that non-Caucasian participants are more likely to experience stage shifts during the FDG uptake periods. Thus, future studies specifically designed to test a priori hypothesis regarding the effects of mTBI/blast exposure on brain glucose metabolism should dedicate efforts to enroll a racially and ethnically diverse sample that is representative of the US military. Additionally, the generalizability of the results of the present study is limited as the sample size in this analysis did not yield sufficient power to be able to conduct sensitivity analyses of the potential impact of military occupational specialty (MOS) (i.e., infantry, artillery, mechanic, etc.) on rCMRglc in combat veterans with and without B/mTBI exposure. Indeed, certain MOS' have a higher likelihood of encountering scenarios that could lead to B/mTBI exposure, or PTSD. Therefore, future studies with a larger sample size allowing for the analysis of the effects of MOS on rCMRglc in combat veterans with and without B/mTBI exposure, and with or without PTSD, may further elucidate the unique neurobiological sequelae of blast exposure during both wakefulness and sleep. Exploring the neurobiological impacts of brain injury on sleep may ultimately guide the personalization of diagnosis and treatment efforts that accelerate recovery from nighttime and daytime consequences of mTBI.

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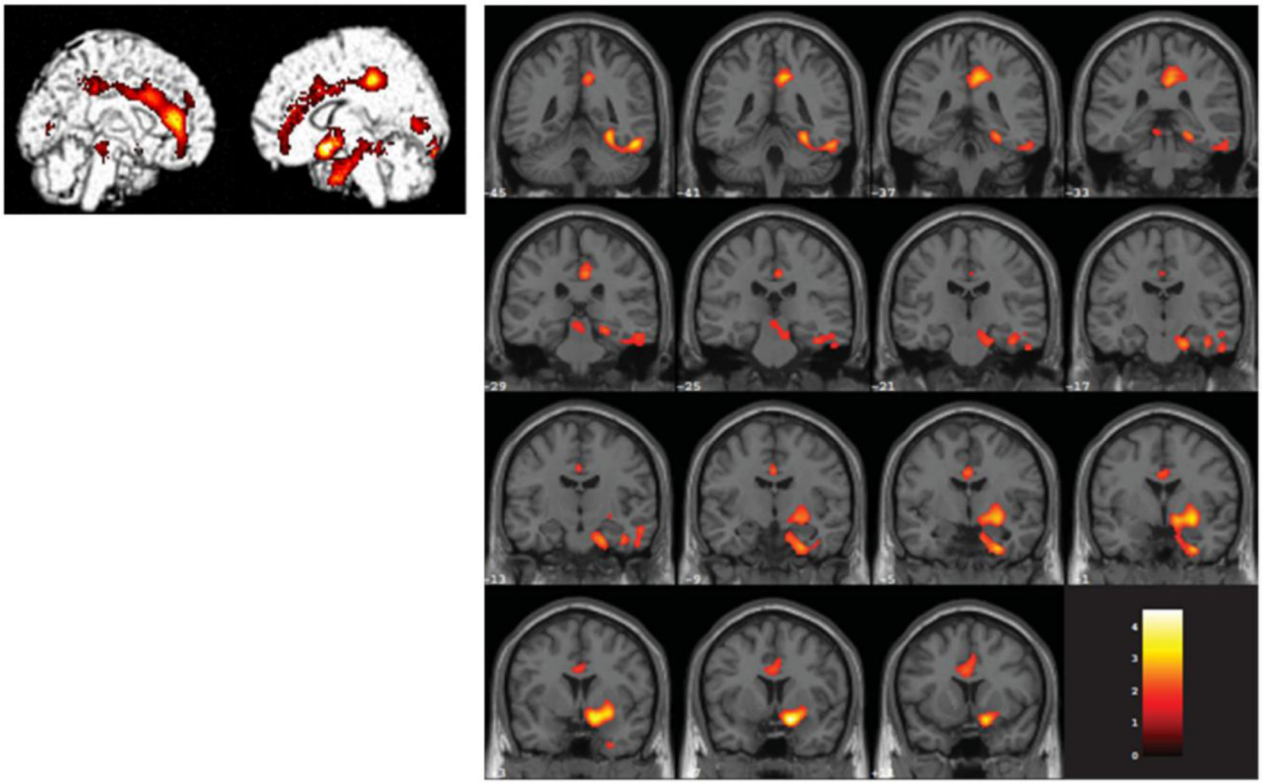

Figure 1.

Areas of the brains where blast/TBI exposed veterans showed lower rCMRglc relative to veterans who did not report blast ormTBI exposure. (la:above) Render images depicting 2 clusters of significance in medial frontal region, and in paralimbic/limbic and temporal and occipital cortices. (1b: right). Coronal section (4mm thickness) depicting the same contrast. Colors correspond to degree of PET scan activation, as measured by relative regional cerebral metabolic rate of glucose metabolism(rCMRglc), with yellow colors indicating higher activation than red colors.

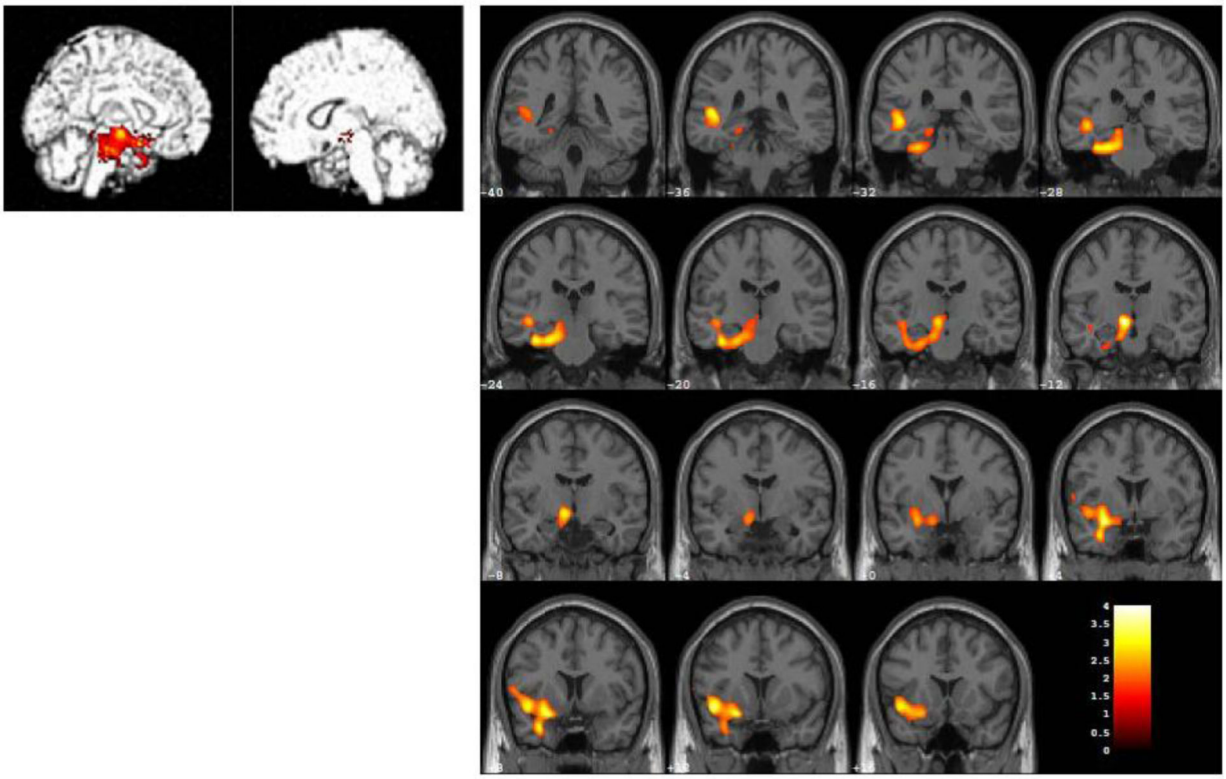

Figure 2.

Areas of the brains where blast/TBI exposed veterans showed lowerrCMRglc relative to veterans who did not report blast or mTBI exposure. (2a:above) Render images depicting one cluster of significance in the brainsteam, basal ganglia, amygdala, hippocampus, insula and uncus, and extending into middle temporal gyrus. (2b: right) Coronal section (4mm thickness) depicting these brains regions for the same contrast. Colors correspond to degree of PET scan activation, as measured by relative regional cerebral metabolic rate of glucose metabolism (rCMRglc), with yellow colors indicating higher activation than red colors.

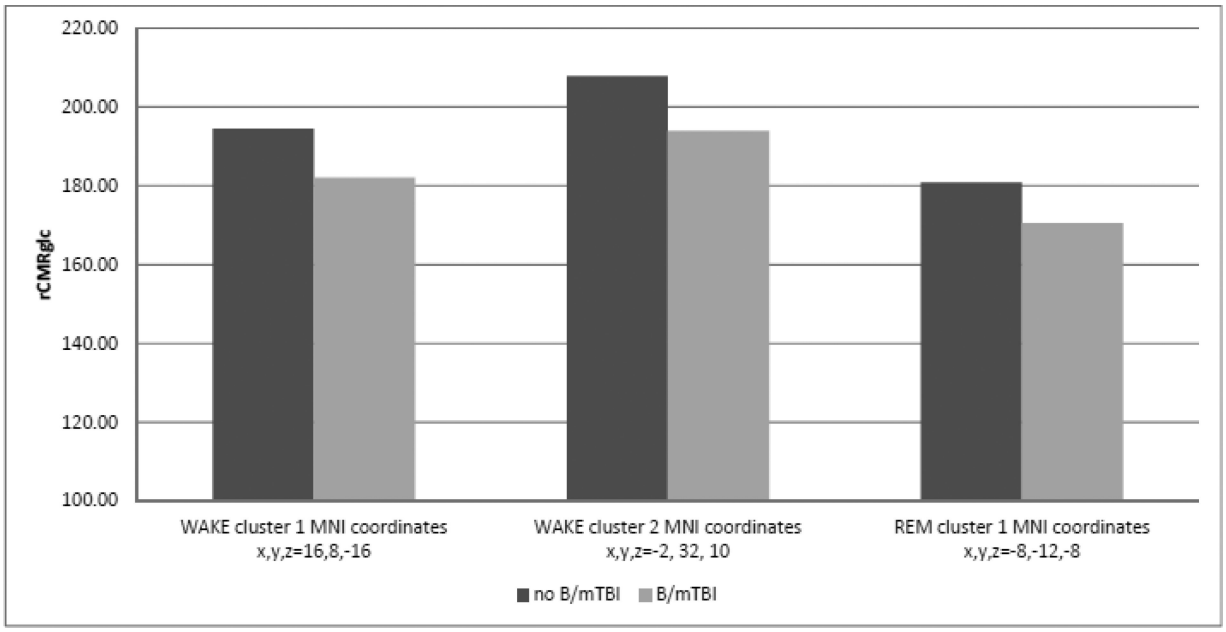

Figure 3.

Detectable in rCMR in regions of interest between veterans with blast and/or mTBI exposure and veterans with no blast and/or mTBI exposure during wakefulness and REM sleep.

Table 1

Demographic, clinical, and sleep measures in veterans with and without blast and or mTBI exposure

Measure	B/mTBI (n=14)	No B/mTBI (n=ll)	*t*(df),*p*
Age	27.52 ± 3.91	28.08 ±4.33	f(23)=.31,*p* = .68
% Men (n)	85.71% (12)	81.82% (9)	χ^2(1,*N*=25) = 0.070.*p* = .79
% Army (n)	71.43% (10)	72.73% (8)	χ^2(2,*N*=25)=0.063,.*p*=.97
% PTSD (n)	78.57% (11)	72.73% (8)	χ^2 (1,*N*=25) = 0.115, *p* = .73
% Caucasian (n)	100% (14)	100% (11)	
Elapsed months since B/mTBI exposure	42.64 ± 26.88		
Combat Exposure Scale	23.43 ± 9.83	18.36 ±11.30	*t*(23)=−1.20,*p* = .24
CAPS total	45.29 ±18.32	43.64 ±19.69	*t*(23) = −.22,*p* = .82
Pittsburgh Sleep Quality Index	7.36 ±3.08	6.73 ±2.72	*t*(23) = −.53.*p* = .60
Beck Depression Inventory	7.36 ±5.36	7.09 ± 3.45	*t*(23)=−.14.*p*.89
Wake time After Sleep Onset	24.64 ±18.00	17.45 ±6.55	*t*(23)=−1.26 *p* = .22
Sleep Latency	19.67 ±18.04	31.15 ±18.39	*t*(23)= 1.56, *p* = .13
Sleep Efficiency	89.28 ±7.91	88.99 ±4.31	*t*(23) = −.11,*p* = .92
Total Sleep Time	390.98 ± 68.71	394.06±40.52	*t*(23) =.13, *p* = .90
Latency to REM Sleep (min)	69.45 ±31.84	66.73 ± 30.54	*t*(23) = −.22,*p* = .83
% of Total Sleep Time in REM Sleep	26.21 ± 6.44	25.28 ± 6.44	*t*(23) =−.35. *p* = .73
REM Duration (mm)	104.14 ±35.42	99.80 = 28.80	*t*(23) = − .33, *p* = .75

Table 2

Bivariate correlations between rCMRglc clusters of significant group differences and combat exposure, PTSD severity, and sleep quality in veterans with and without blast and/ormTBI exposure (N=14 and N = l 1, respectively).

Variable	Combat Exposure Scale	CAPS Total Score: PTSD Severity	Pittsburgh Sleep Quality Index: Sleep Quality
B/mTBI exposure			
Wake cluster 1	.35	−.07	.48
Wake cluster 2	.15	.02	.04
REM cluster l[a]	−.10	.20	.10
Xo B/mTBI exposure			
Wake cluster 1	−.13	.50	−.18
Wake cluster 2	.14	.31	.06
REM cluster l[a]	.013	−.14	.29

[a] Ln-trans formed.