Title

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Journal

The Journal of head trauma rehabilitation, 33(6)

ISSN

0885-9701

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Publication Date

2018-11-01

DOI

10.1097/htr.0000000000000377

Peer reviewed

HHS Public Access

Author manuscript

J Head Trauma Rehabil. Author manuscript; available in PMC 2019 November 01.

Published in final edited form as:

J Head Trauma Rehabil. 2018 ; 33(6): 382–392. doi:10.1097/HTR.0000000000000377.

Fatigue is Associated with Global and Regional Thalamic Morphometry in Veterans with History of Mild Traumatic Brain Injury

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Abstract

Objective—Fatigue is a complex, multidimensional phenomenon that commonly occurs following traumatic brain injury (TBI). The thalamus—a structure vulnerable to both primary and secondary injury in TBI—is thought to play a pivotal role in the manifestation of fatigue. We explored how neuroimaging markers of local and global thalamic morphometry relate to the subjective experience of fatigue post-TBI.

Methods—63 Veterans with history of mild TBI (mTBI) underwent structural magnetic resonance scanning (MRI) and completed questionnaires related to fatigue and psychiatric symptomatology. FMRIB's Software (FSL) was utilized to obtain whole brain and thalamic volume estimates, as well as to perform regional thalamic morphometry analyses.

Results—Independent of age, sex, intracranial volume, PTSD and depressive symptoms, greater levels of self-reported fatigue was significantly associated with decreased right ($p = .026$) and left ($p = .046$) thalamic volumes. Regional morphometry analyses revealed that fatigue was significantly associated with reductions in the anterior and dorsomedial aspects of the right thalamic body ($p < .05$). Similar trends were observed for the left thalamic body ($p < .10$).

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Compliance with Ethical Standards & Disclosures. All procedures involved in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Informed consent was obtained from all patients included in the study. Alexandra Clark, Scott Sorg, Erin Bigler, Kelsey Holiday, Katherine Bangen, Nicole Evangelista, Mark Bondi, Dawn Schiehser, and Lisa Delano-Wood declare no conflicts of interest.

Conclusions—Both global and regional thalamic morphometric changes are associated with the subjective experience of fatigue in Veterans with history of mTBI. These findings support a theory in which disruption of thalamo-cortico-striatal circuitry may result in the manifestation of fatigue in individuals with history of neurotrauma.

Keywords

fatigue; central fatigue; thalamus; thalamic morphometry; thalamic volume; thalamic shape; mild traumatic brain injury; mTBI; Veterans

INTRODUCTION

Central fatigue is a complex, multi-dimensional phenomenon that is common and frequently intractable in the aftermath of traumatic brain injury (TBI). [1–4] It is distinct from more *peripheral* categorizations of fatigue (i.e., disorders of the neuromuscular junction or muscular fatigue) given that it manifests as a result of *central* nervous system damage and/or dysfunction and it has been conceptualized as "the failure to initiate and/or sustain attentional tasks and physical activities requiring self-motivation."[5](p35) Central fatigue (referred to as *fatigue* here within) has components that are both cognitive and physical [5] and, although it overlaps with psychiatric and sleep disturbances, fatigue has been demonstrated to be a distinct or independent construct. [6–8] Importantly, across all severities of TBI (i.e. mild, moderate, or severe), fatigue has been linked to worse outcomes, including increased levels of disability and poorer quality of life. [9–11]

Although the underlying neural network of fatigue remains to be fully characterized, there is a growing body of literature to suggest that thalamus may play a critical role. The thalamus —a subcortical gray matter structure that contains many groups of nuclei—is a critical relay station for a diffuse network of afferent and efferent projections within the brain. [12–14] It processes both motor and sensory information and contributes to high-order cognitive processes including memory and executive functions. [15,16] The thalamus is part of the ascending reticular activating system (ARAS), which ensures adequate levels of arousal needed to carry out various behavioral tasks [17] and is thus positioned to play a critical role in the manifestation of fatigue. In support of this position, structural changes to the thalamus have been linked to greater levels of fatigue across various clinical populations including multiple sclerosis and chronic fatigue syndrome. [18–20]

Within the context of TBI, the thalamus is susceptible to both primary and secondary mechanisms of injury.[21,22] Simulations from finite element head modeling have revealed the thalamus is a region of high shear stress during neurotrauma. [23,24] Furthermore, secondary neuroinflammatory and degenerative processes—which have been demonstrated to persist for many years following neurotrauma—also contribute to thalamic damage following TBI. [16,25–27] Structural magnetic resonance imaging (MRI) methods have been used to examine both global and more nuanced topographic, or regional, alterations of the thalamus post-TBI. Across samples of moderate to severe TBI, global reductions in thalamic volume and regional atrophy in antero-dorsal-medial aspects of the thalamus have been observed post-injury.[28] Moreover, regional changes in thalamic morphometry has been linked to greater

rates of disability [29] and poorer performance on measures of executive control [21,26] in those with history of moderate to severe TBI.

Studies examining both global and regional morphometry in less severe TBI samples (i.e., mild TBI [mTBI]) are relatively limited. Global reductions in thalamic volume [30,31] have been observed and only one study has explored regional morphometry of the thalamus within an mTBI sample. [32] In contrast to the previous studies in moderate to severe TBI samples, regional reductions were limited to the posterolateral portion of the thalamus of the mTBI group relative to orthopedic-injured controls. [32] However, it remains unclear to what degree these alterations in thalamic morphometry may contribute to the subjective experience of fatigue post-mTBI. Therefore, we explored the potential role thalamic integrity may play in the manifestation of fatigue in mTBI. We hypothesized that greater levels of fatigue would be associated with both decreased volume as well as local atrophy in the thalamus in Veterans with history of mTBI.

METHODS

Participants were 63 Operation Enduring Freedom, Operation Iraqi Freedom, and Operation New Dawn (OEF/OIF/OND) Veterans with history of mTBI recruited from posted study advertisements and outpatient clinics at the VA San Diego Healthcare System (VASDHS) in La Jolla, California. The institutional review boards (IRBs) at the VASDHS and University of California, San Diego (UCSD) approved all study procedures. Prior to enrollment in the study, participants provided written and informed consent. TBI history interviews, neuropsychological testing, and study questionnaires were completed at the Veterans Medical Research Foundation located on the VASDHS campus. Brain MRI scans occurred at the UCSD School of Medicine's Center for Functional MRI.

The following exclusionary criteria were applied to the study sample overall: (1) moderate (loss of consciousness [LOC] >30 minutes but < 24 hours, and alteration of consciousness [AOC] > 24 hours or post-traumatic amnesia [PTA] >1 day but < 7 days) or severe (LOC ≥ 24 hours, AOC > 24 hours, or PTA ≥ 7 days) TBI per [33] guidelines; (2) current (within 30 days) alcohol or other substance abuse, (3) current or prior alcohol or substance dependence; (4) current or prior diagnosis of bipolar disorder, schizophrenia, or psychotic disorder as determined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., DSM-IV, American Psychiatric Association, 2000); (5) a positive toxicology screen as measured by the Rapid Response 10-drug Test Panel; (6) prior history of a learning disability; (7) history of any other major neurological (e.g., multiple sclerosis, stroke, seizures) or medical conditions (e.g., chronic fatigue syndrome, diabetes, myocardial infarction) that may affect brain structure or cognition; (8) current suicidal and/or homicidal ideation; (9) involvement in current or pending litigation; (10) any contraindications to MRI scanning (e.g., presence of metal in one's body, or possible pregnancy for females participants); and (11) any gross abnormalities on structural MRI scans.

TBI History Interview and Diagnosis

Each participant underwent a TBI history interview that was conducted by a post-baccalaureate or graduate-level research assistant. TBI history interviews included

assessment of both non-military (i.e., prior to or after discharge from the military) and military-related (i.e., during enlistment in the US armed services) head injuries (see [34] for more comprehensive details). This interview was adapted from the VA Structured Clinical Interview for TBI[35] and involves assessment of any injuries in which participants may have fallen, suffered a blow to the head, or experienced a blast-wave detonation (i.e., overpressure or shock waves resulting from an explosive detonation) within 100 meters (i.e., length of a professional football field). In brief, for each reported injury, participants were queried about: presence and duration of critical injury severity charactertistics (i.e., LOC, AOC, and PTA), the nature of the accident (e.g, fight or motor vechicle accient), the date the injury occurred, the mechanism of injury (i.e., blunt/mechanical or blast-related forces), and the presence and duration of any post-concussive symptoms. Diagnosis of mTBI was based on the VA/DoD guidelines [33] of a loss of consciousness (LOC) < 30 minutes, or alteration of consciousness (AOC) or posttraumatic amnesia (PTA) < 24 hours. The sum of all injuries that met VA/DoD diagnostic criteria for mTBI was calculated to determine the total number of lifetime TBIs each participant experienced. Additionally, injury severity characteristics (i.e., LOC, AOC, PTA) were also utilized to determine the "most significant" or "worst" TBI; this involved direct comparisons of LOC and AOC durations for each injury, and injuries where a LOC was sustained were considered more significant/severe than those that had an AOC only. Finally, the time between participants' most recent and significant TBI and their neuropsychological testing date was calculated."

Assessment of Fatigue

The Modified Fatigue Impact Scale (MFIS) was used to assess current levels of fatigue and its impact on functioning over the past four weeks. The MFIS is a 21-item scale modified from the original 40-item Fatigue Impact Scale [36] that was recently validated for use in Veterans with history of mild or moderate TBI. [37] Items from the MFIS can be summed to generate a total score (ranging from 0 to 84), with higher scores indicating greater effects of fatigue on both cognitive and physical functions.

Psychiatric Symptom Rating Scales and Other Self-Report Questionnaires

Participants completed symptom rating scales that quantified current levels of posttraumatic stress (PTSD Checklist [PCL-M] [38]), depression (Beck-Depression Inventory-II [BDI-II] [39]), and post-concussive symptoms (Neurobehavioral Symptom Inventory [NSI] [40]). For the BDI-II, an affective subscale [1,41] was also generated for use in subsequent analyses given some items overlap with the characterization of fatigue. Exposure to various combat situations and wartime stressors during deployment was assessed using the Combat Exposure Scale ([CES] [42]). Overall sleep quality for the past month was assessed with the Pittsburgh Sleep Quality Index ([PSQI] [43]).

Neuroimaging Data Acquisition

Structural MRI scans were acquired on a 3-Tesla General Electric MR750 system with an eight-channel head coil. A high-resolution T1 anatomical scan was acquired in the sagittal plane with the following parameters: FOV = 24 cm, 256 × 192 matrix, TR = 8.1 ms, TE = 3.192 ms, flip angle = 12°, TI = 550 ms, bandwidth = 31.25 kHz, and 172 1.2 mm slices.

After the images were acquired, they were visually inspected for quality control purposes to ensure there were no artifacts that might affect image processing (e.g., motion).

Neuroimaging Processing & Analyses

Images were processed and analyzed using FMRIB Software Library version 5.0. [44,45] Thalamic segmentation and shape analysis was performed with FMRIB Software Library's Integrated Registration and Segmentation Tool ([FIRST]; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST) which has been demonstrated to have the highest concordance among subcortical structures when compared to manual segmentation methods. [46] FIRST uses a two-stage affine process to register each participant's T1 onto an MNI152 template. In the first step, a whole brain registration was performed. Next, a weighted subcortical mask was applied to the intermediate image, which then underwent another affine registration to ensure optimal registration of subcortical structures. The inverse transformation of the estimated registration was then calculated and applied to the MNI152 template to bring it into native space. A Bayesian Active Appearance Model (AAM), which takes into account both geometric shape (i.e., morphometry) and image intensity, was used to register and segment subcortical structures.[43] After registration, a parameterized surface mesh for each subcortical structure is generated. FSL's *–useReconNative* and *-useRigidAlign* options were used to recreate the mesh in native space and remove pose effects. Registrations and thalamic segmentations were checked with FSL's *slicesdir* command.

Global and Regional Thalamic Morphometry

Thalamic volume estimates were extracted from the FIRST segmentation. Intracranial volume (ICV) estimation occurred through the FMRIB Software Library [44,45] using ENGIMA imaging protocol guidelines (http://enigma.ini.usc.edu). FIRST also enables examination of localized morphometric differences in subcortical structures. A deformable surface mesh model composed of sets of vertices is generated for each subject and allows for the mean shape and any deviations from the mean to be explored. As such, regional morphometry analyses examine any expansions and reductions from the TBI group's mean surface level of the thalamic body. Reduced regional morphometry is associated with negative perpendicular distances from the average surface and expansions represent positive perpendicular distances. [46] In our study, we conducted vertex-wise analyses using general linear modeling (GLM) to explore thalamic morphometry and fatigue associations in the sample. The International Consortium for Brain Mapping Atlas (ICBM) T1 Atlas, [47] which parcellates the thalamus into 11 structurally defined regions of interest (ROIs), was then used to provide additional context about thalamic subnuclei likely involved in the observed regional findings. Prior to overlaying the regional thalamic findings to determine the overlapping ROIs, the ICBM Atlas was registered to MNI-152 space using FSL's FMRIB's Linear Image Registration Tool (FLIRT). ICV was calculated by multiplying the size of the template brain by the inverse of the determinant of the affine matrix.

Statistical Analyses

Hierarchical linear regressions were used to determine whether fatigue was predictive of thalamic volumes above and beyond age, sex, ICV, PCL-M and BDI-II Affective subscale scores using the Statistical Package for the Social Sciences (SPSS) version 21. [48] We entered

age, ICV, and sex into Block 1 of our regression models given their known association with brain volume estimates. The PCL-M and BDI-II Affective subscale were also entered into Block 1 since we were interested in the effects of fatigue—independent of other common psychiatric comorbidities that have been shown across several studies to have some symptom overlap—on thalamic volumes. Multicollinearity of the independent variables was assessed and all variance inflation factor (VIF) values were less than 3. FMIRB's GLM tool (www.fmrib.ox.ac.uk/fsl/fsl/list) was used to explore associations between fatigue and thalamic morphometry while controlling for age, ICV, PCL-M and BDI-II Affective subscale scores. For regional thalamic morphometry analyses, FSL's Randomise tool (www.fmrib.ox.ac.uk/fsl/randomise) was used to test correlation inferences with permutation methods. [49,50] Positive and negative associations for thalamic morphometry and fatigue were explored with 5,000 two-tailed Monte Carlo permutation tests with threshold-cluster free enhancement to correct for multiple comparisons at $p = .05$.

RESULTS

Sample characteristics are presented in Table 1. On average, participants were relatively young (mean age = 31.9), predominantly male (87%), experienced multiple mTBIs (78%), and were many months removed from their most recent injury (mean time = 63.7 months). With respect to their most significant TBI, 58% of these injuries occurred during deployment, 62% involved a LOC versus an AOC, and 67% were due primarily to blunt-force trauma. Of the individuals with a history of multiple TBIs, approximately 18% reported another injury that involved an LOC versus 82% involved an AOC.

Association Between Fatigue and Thalamic Volume

Hierarchical regressions were performed in an effort to determine whether fatigue was predictive of thalamic volume for each hemisphere. Age, ICV, sex, PCL-M total score, and the BDI-II Affective subscale total were entered into Block 1, and the MFIS total score was entered into Block 2 of the models. Results are presented in Table 2. Block 1 explained 28.6% of the variance in right thalamic volume. A significant increase in the amount of variance in right thalamic volume was observed when the MFIS total score was added into Block 2 of the model ($R^2 \Delta = .062$, $F \Delta (1,56) = 5.32$, $p = .025$). Results indicated that lower right thalamic volumes were associated with higher levels of fatigue (see Figure 1). For left thalamic volume, Block 1 explained 30.3% of the variance, which was also increased with the addition of MFIS total score into Block 2 of the model ($R^2 \Delta = .048$, $F \Delta (1,56) = 4.15$, $p = .046$). Results indicated that lower left thalamic volumes were associated with higher levels of fatigue. See Figure 2.

Associations Between Fatigue and Regional Thalamic Morphology

To test for an association between fatigue and regional thalamic morphometry, a series of regression analyses were performed with FSL's GLM and *randomise* tool. Significant negative correlations between fatigue and right thalamic morphometry were found, even after adjusting for age, ICV, sex, PCL-M total score, and the BDI-II Affective subscale total. See Figure 3 for the significant clusters. Results were overlaid onto the ICBM Atlas to provide additional context about the thalamic nuclei that correspond to the atrophied areas.

In particular, reductions in the anterior and dorso-medial aspects of the right thalamus were associated with higher levels of self-reported fatigue (p's < .05). With respect to the left thalamus, there were no significant associations between morphometry and fatigue that survived multiple comparisons (p's > .05). However, when alpha was adjusted to $p < .10$ to explore potential trends, associations between higher levels of fatigue and localized reductions in the anterior, dorsomedial, and reticular aspects of the left thalamus were observed. See Figure 4.

DISCUSSION

Our study provides evidence that the thalamus—a subcortical gray matter nucleus responsible for processing much of our sensory, motor, cognitive and emotional information, and coordinating behavior[51]—is involved in the subjective experience of fatigue following mTBI. In particular, we found that greater levels of fatigue were associated with (1) decreased thalamic volumes and (2) regional reductions in the anterior and dorsomedial aspects of the thalamic body. Importantly, these findings implicate the thalamus as an important structure involved in the underlying neural network of fatigue. Results dovetail with findings from other clinical populations (i.e., multiple sclerosis) demonstrating that the thalamus is involved in the manifestation of fatigue-related symptoms.[18,19,52] Moreover, given careful consideration of important covariates and possible confounds, our results suggest that neurostructural alterations to the thalamus are specifically linked to fatigue post-TBI and not psychiatric symptoms in general.

Chaudhuri and Behan [5] described a model in which disruption and/or dysfunction of the neural circuitry of the thalamo-cortico-striatal loop is thought to result in fatigue. They argue that, when this circuit is functioning normally, there is a positive feedback loop in which: (1) glutamatergic (excitatory) signals from the frontal cortex lead to excitation of the striatum, (2) striatal activation increases the GABAergic (inhibitory) signals of the substantia nigra and globus pallidus, which then (3) decreases the inhibitory signals of the globus pallidus and substantia nigra on the thalamus, resulting in (4) excitatory output from the thalamus to the frontal cortex (see [53] for comprehensive review of this pathway). *Global* thalamic volume loss may thus cause a net change in thalamic activity, and therefore disrupt the behavioral functions associated with these said pathways. Indeed, relative to controls with no history of head-trauma, resting-state functional MRI has revealed decreased thalamic activity [31] and abnormal thalamo-cortical connectivity patterns in mTBI patients. [14,54]

Results from our study revealed that greater levels of fatigue were associated with reduced *regional* thalamic morphometry in the anterior and dorsomedial body of the thalamus. Regarding neuroanatomical connections, the anterior nucleus projects efferent fibers to the oribitofrontal and cingulate cortices, while the dorsomedial nucleus sends fibers to the prefrontal cortex. The thalamo-cortico-striatal projection system is involved in higher-order cognitive processes, including calculating the required effort and reward for engagement in a behavioral task. [55] From a behavioral perspective, fatigue is often described as a difficulty in initiating and sustaining voluntary activities.[4] Thus, regional damage to the anterior and/or dorsomedial nuclei and their frontal projections may dispose an individual to increased levels of fatigue post-TBI. Indeed, prior work from our group has shown greater level of

post-mTBI fatigue was associated with reduced white matter integrity values in the anterior internal capsule—a fiber pathway with connections between the thalamus and the frontal lobe. [56] Moreover, in studies of aging, lower thalamic volume has been shown to be significantly associated with decreased thalamic white matter microstructure,[57,58] especially in regions with fronto-cortico projections.[59]

Our regional thalamic morphometry results dovetail with findings of thalamic atrophy and increased rates of neuronal loss observed in moderate to severe TBI samples [26,29,60] and may be suggestive of a regional vulnerability to injury. While the precise mechanisms underlying thalamic injury are unclear, primary axonal injury may initiate secondary neuroinflammatory processes that contribute to thalamic damage post-injury. [16,26] Indeed, when compared to controls with no history of head trauma, persistent microglial activation —a direct marker of inflammation—was observed in the thalamus of individuals with history of moderate to severe TBI. [27] Importantly, microglial activation within the thalamus correlated with degree of thalamo-cortical tract damage. Given the anterior and dorsomedial body of the thalamus have dense connections with cortical association and projection fibers, these regions may therefore be vulnerable sites of Wallerian and retrograde degeneration post-injury. [27]

Although we chose to focus on the role of both global and regional thalamic morphometry in subjective fatigue post-mTBI, it is important to acknowledge that the underlying network of fatigue is broad and other basal ganglia and limbic structures have been implicated. [4,17,50,51] Therefore, we conducted a series of post-hoc analyses to explore potential associations between fatigue and global volumetric and regional morphometry of the caudate, putamen, nucleus accumbens, and globus pallidus using FSL's FIRST output. Parallel statistical models controlling for age, ICV, sex, PCL-M total score, and the BDI Affective subscale total revealed no significant associations between fatigue and lateralized volumes of the caudate, putamen, nucleus accumbens, and globus pallidus (p's ranged from .12 – .57). No significant associations between fatigue and regional morphometry of lateralized putamen, nucleus accumbens, globus pallidus, and the right caudate (all p's >.05) were observed. However, higher levels of fatigue were significantly associated with localized reductions in the head and medial surface of left caudate (p <. 05). The caudate is part of the ventral striatum, receiving projections from the frontal lobe, and also plays a contributory role in effort-reward valuations. Importantly, studies in TBI and other clinical populations have revealed that structural[18,19,52,61] and functional alterations[62–65] to the caudate have been associated with fatigue. While the mechanisms underlying caudate dysfunction are unclear, it, too, may be susceptible to direct trauma or the same negative neuroinflammatory processes. Alternatively, damage to the frontal or basal ganglia dopaminergic system may negatively alter caudate response.[66]

Increased rates of psychiatric symptoms are also common post-TBI [2,8,67] and, while distinct, there is considerable overlap between the clinical symptoms of depression, PTSD, and fatigue. [8,9,68] Additionally, structural and functional alterations to fronto-limbic and fronto-striatal structures have been linked to increased psychiatric symptom severity post-TBI.[69,70] Our results showed that, independent of PTSD and depressive symptoms, fatigue was associated with both global and regional thalamic morphometry. Importantly, neither PTSD

nor depressive symptoms were significant predictors of thalamic morphometry in our regression models. Moreover, parallel analyses conducted in the putamen, nucleus accumbens, globus pallidus, and caudate revealed no significant associations between volume, morphometry, and psychiatric symptoms. These results therefore suggest that neurostructural alterations to the thalamus (and caudate) are specifically linked to fatigue post-TBI and not psychiatric symptoms in general. Importantly, these findings help assist in clarifying the nature and underlying cause of specific post-concussive symptoms in those with history of mild TBI.

Within the mTBI literature, there is some evidence to suggest that negative brain or behavior consequences differ as a function of type of injury or number of mTBIs, time since injury, or cumulative exposure to blast.[71–74] Notably, 78% of this sample reported experiencing more than one mTBI during their lifetime, with the vast majority of these additional injuries involving an AOC versus an LOC. Moreover, there was considerable variability across the sample in time since their most recent mTBIs and whether they were exposed to blast while on deployment. Teasing apart differential associations between single vs. multiple TBIs within the context of this study is challenging given that only a small proportion of the sample that experienced a single TBI (i.e., only 22%) during their lifetime. However, we conducted a series of secondary analyses in which total number of TBIs, time since most recent TBI, and total number of blast exposures within 100 meters were included as separate covariates in our regression analyses; results revealed that none of these variables were significantly associated with our dependent variables, and all significant fatigue, thalamic volume and morphometry findings held.

To our knowledge, the current study represents the first to directly examine the relationship between fatigue and thalamic morphometry in a sample of Veterans with history of mTBI. Strengths of this study include a relatively large sample of well-characterized Veterans with head trauma histories and investigation of both global and regional thalamic morphometry. However, our study has some weaknesses that should be noted. First, other regions may also be important to investigate in future studies—including projections to and between structures involved in those related to the broader circuit loops described above. Second, as is commonly a limitation in TBI research, our diagnosis of mTBI was based on retrospective self-report and may therefore be subject to recall bias. That said, this bias is mitigated by our comprehensive TBI assessment that takes into account head injuries an individual may have prior to, during, and after their military service. Moreover, to ensure comprehensive and reproducible characterizations, we applied strict VA/DoD diagnostic guidelines[30] to all reported injuries, which will augur for generalizability to other studies that employ the same guidelines. Finally, we collapsed across total number and mechanisms of injury when conducting our analyses; however, future studies are needed in order to tease apart whether or how thalamic morphometry may differ between those with blunt versus blast-related TBI only.

CONCLUSION

In conclusion, fatigue is a common and oftentimes chronic and disabling symptom following TBI. Results from our study align with findings from other clinical populations to show that

the thalamus is a critical structure involved in the manifestation of fatigue. In particular, we found that lower thalamic volumes and reduced regional morphometry in areas containing higher-order nuclei (i.e., antero-dorso-medial aspects of the thalamic body) resulted in greater levels of fatigue in Veterans with mTBI. Future studies should investigate components of fatigue (e.g., physical and cognitive) and integrate multiple MR methods in order to clarify and expand our understanding of thalamic damage and concomitant behavioral consequences in the aftermath of TBI.

Acknowledgments

Sources of Funding: This work was supported Veterans Affairs grants awarded to Drs. Delano-Wood (829-MR-NB-25860), Schiehser (CDA-2-065-10S), and Sorg (CDA-2- CX001508). This work was further supported by grants awarded by the Department of Defense (W81XWH-10-2-0169) to Dr. Delano-Wood and the National Institute Of Neurological Disorders and Stroke of the National Institutes of Health (F31NS09870) to Ms. Clark.

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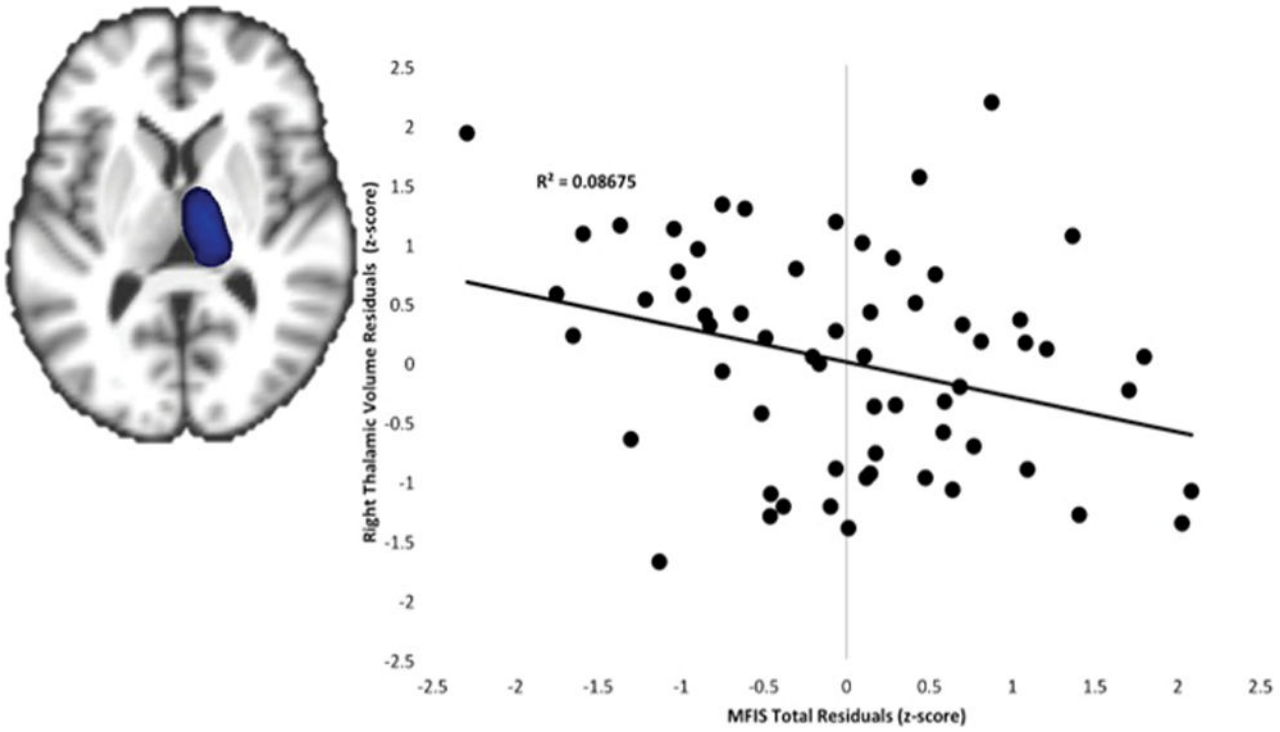

Figure 1.
Partial Regression Plot for Association Between Fatigue and Right Thalamic Volume

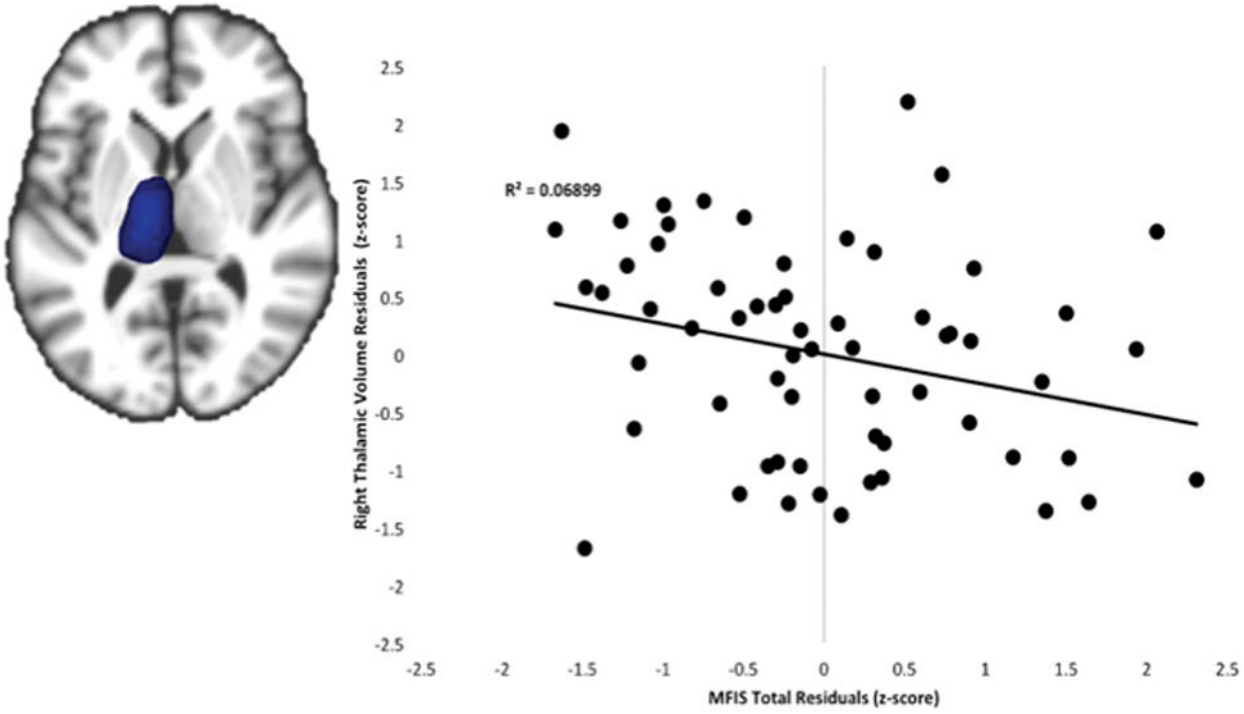

Figure 2.
Partial Regression Plot for Association between Fatigue and Left Thalamic Volume

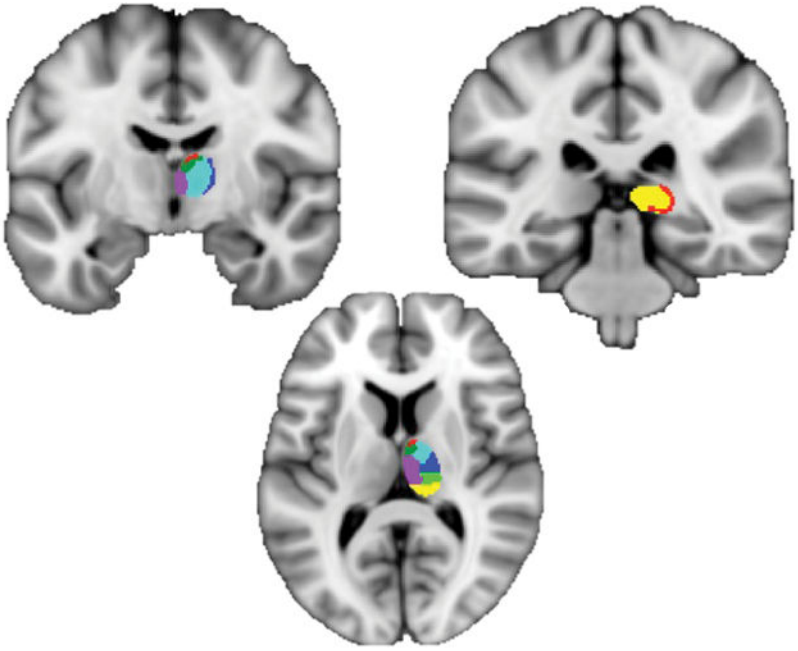

Figure 3.

Regional Atrophy for Right Thalamus

Significant areas of atrophy are depicted in red ($p < .05$). Other colored areas are ICBM T1 Atlas parcellations of thalamus. Dark Green = Anterior Nucleus, Light Green = Lateral Posterior Nucleus, Dark Blue = Ventral Lateral Nucleus, Light Blue = Reticular Nucleus, Purple = Ventral Anterior Nucleus, Yellow = Dorsomedial Nucleus

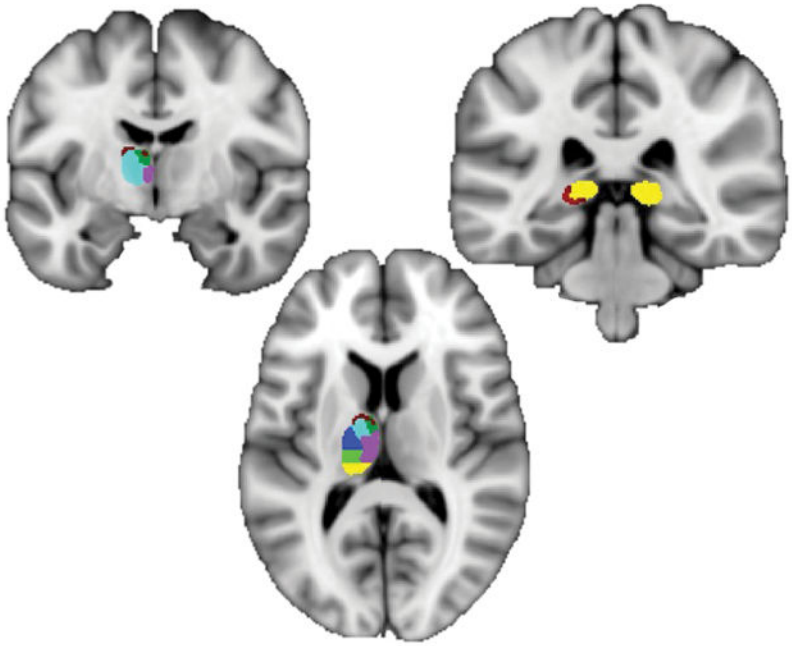

Figure 4.

Regional Atrophy for Left Thalamus

Significant areas of atrophy are depicted in dark red ($p < .01$). Other colored areas are ICBM T1 Atlas parcellations of thalamus. Dark Green = Anterior Nucleus, Light Green = Lateral Posterior Nucleus, Dark Blue = Ventral Lateral Nucleus, Light Blue = Reticular Nucleus, Purple = Ventral Anterior Nucleus, Yellow = Dorsomedial Nucleus

Table 1

Sample Characteristics

	Mean (SD)
Age	31.86 (6.43)
Education	14.19 (1.60)
WRAT-4 Reading Standard Score	101.48 (10.92)
Sex (% Male)	87%
Ethnicity	
Caucasian	44%
African American	8%
Hispanic	35%
Asian	13%
% Of individuals with history of one versus multiple TBIs	22% vs. 78%
Total Number of Lifetime TBIs	2.57 (1.45), *Median* = 2
Time Since Most Recent TBI (months)	63.67 (42.64), *Median* = 58
Time Since Most Significant TBI (months)	70.98 (43.94), *Median* = 67
% With exposed to blast within 100 meters	60%
% With LOC for most Significant Injury	62%
Most Significant TBI Type	
% Blast	19%
% Blunt	67%
% Blast with secondary/tertiary Blunt	14%
Combat Exposure Scale Total	15.75 (11.78)
Modified Fatigue Impact Scale Total	41.16 (19.82)
Post-Traumatic Stress Disorder Checklist Total	43.68 (18.78)
Beck Depression Inventory-II Total	20.77 (12.81)
Beck Depression Inventory-II Affective Subscale Total	9.59 (7.14)
Neurobehavioral Symptom Inventory Total	33.11 (18.18)
Pittsburgh Sleep Quality Index Global Score (n = 57)	10.89 (4.43)

WRAT-4 = Wide Range Achievement Test-4th Edition; TBI = traumatic brain injury; NSI = Neurobehavioral Symptom Inventory; LOC = loss of consciousness

Table 2

Multiple Hierarchical Linear Regression Models for Right Thalamic Volume

	Variable	B	*SE*	β	*p*	F	R^2	Δ R^2
Right Thalamus						4.57	.29	
Block 1	Age	−39.32	13.50	−.333	.005			
	Sex	−529.23	265.80	−.234	.051			
	ICV	1139.69	404.65	.327	.007			
	BDI-II Affective Subscale Total	−10.24	17.52	−.096	.561			
	PCL-M Total	5.42	6.75	.134	.425			
Block 2	Age	−36.18	13.09	−.306	.008	5.32	.35	.062
	Sex	−532.50	256.27	−.235	.042			
	ICV	825.19	413.28	.237	.051			
	BDI-II Affective Subscale Total	2.93	17.83	.027	.870			
	PCL-M Total	12.17	7.13	.301	.093			
	MFIS Total Score	−14.83	6.43	−.387	.025			

Table 3

Multiple Hierarchical Linear Regression Models for Left Thalamic Volume

	Variable	B	*SE*	β	*p*	F	R^2	Δ R^2
Left Thalamus						4.95	.30	
Block 1	Age	−38.87	12.80	−.343	.004			
	Sex	−625.79	252.11	−.288	.016			
	ICV	991.75	383.83	.297	.012			
	BDI-II Affective Subscale Total	−1.98	16.62	−.019	.905			
	PCL-M Total	.620	6.40	.016	.923			
Block 2	Age	−36.21	12.54	−.320	.005	5.04	.35	.048
	Sex	−628.56	245.43	−.290	.013			
	ICV	725.72	395.81	.217	.072			
	BDI-II Affective Subscale Total	9.16	17.08	.090	.594			
	PCL-M Total	6.33	6.83	.163	.358			
	MFIS Total Score	−12.54	6.16	−.341	.046			