



Subcortical shape and neuropsychological function among U.S. service members with mild traumatic brain injury

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Abstract

In a recent manuscript, our group demonstrated shape differences in the thalamus, nucleus accumbens, and amygdala in a cohort of U.S. Service Members with mild traumatic brain injury (mTBI). Given the significant role these structures play in cognitive function, this study directly examined the relationship between shape metrics and neuropsychological performance. The imaging and neuropsychological data from 135 post-deployed United States Service Members from two groups (mTBI and orthopedic injured) were examined. Two shape features modeling local deformations in thickness (RD) and surface area (JD) were defined vertex-wise on parametric mesh-representations of 7 bilateral subcortical gray matter structures. Linear regression was used to model associations between subcortical morphometry and neuropsychological performance as a function of either TBI status or, among TBI patients, subjective reporting of initial concussion severity (CS). Results demonstrated several significant group-by-cognition relationships with shape metrics across multiple cognitive domains including processing speed, memory, and executive function. Higher processing speed was robustly associated with more dilation of caudate surface area among patients with mTBI who reported more than one CS variables (loss of consciousness (LOC), alteration of consciousness (AOC), and/or post-traumatic amnesia (PTA)). These significant patterns indicate the importance of subcortical structures in cognitive performance and support a growing functional neuroanatomical literature in TBI and other neurologic disorders. However, prospective research will be required before exact directional evolution and progression of shape can be understood and utilized in predicting or tracking cognitive outcomes in this patient population.

Keywords Mild traumatic brain Injury · Subcortical structures · Shape analysis · Service Members · Neuropsychological function · Brain behavior relationships

Introduction

During the past decade, there have been concerted efforts to identify “objective” biomarkers of traumatic brain injury (TBI), especially mild TBI (mTBI) (Koerte et al.

2016; Shenton et al. 2012; Wilde et al. 2015). Advanced neuroimaging techniques have become central to this effort with the goal to improve diagnosis, prognostic accuracy, and develop improved treatment strategies. Regardless, research continues to evolve and requires additional efforts that focus on fully characterizing the range of abnormalities and determining how these biomarkers might be used to accurately predict the heterogeneous clinical and cognitive outcomes observed in individuals with TBI.

TBI is often acknowledged as a “white matter injury” of the brain (Jurick et al. 2016), but this is likely an oversimplification. There can also be extensive volume loss that occurs within gray matter, including subcortical structures,

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that are quantifiable with magnetic resonance imaging (MRI), especially at the severe level of injury (Gale et al. 2005; Lutkenhoff et al. 2013; Primus et al. 1997). Examination of subcortical volumes at the mild end of the TBI severity spectrum typically yields equivocal (i.e., disparate regions of interest (ROI) across studies) or no findings (Bigler et al. 2013; Churchill et al. 2016; Koerte et al. 2016; Shenton et al. 2012; Wilde et al. 2015). However, it is expected that more advanced MRI acquisitions and post-processing techniques (Haacke et al. 2010; Shenton et al. 2012; Van Boven et al. 2009; Wilde et al. 2015) may be better suited for detecting subtler changes after mTBI or concussion.

One such advanced method for quantifying differences in brain structure is shape analysis. These metrics provide unique information that has led to improved diagnosis and pathological understanding of discrete disease (Kim et al. 2015; Quigley et al. 2015; Wade et al. 2015a; Wang et al. 2003) and injury processes (Irimia et al. 2014; Tate et al. 2016). In a recent study by our group, significant shape differences in Service Members with mTBI were noted when compared to post-deployment controls with orthopedic injuries (OI) only (Tate et al. 2016). Though non-significant group differences were demonstrated for gross volumetric data, these advanced shape metrics revealed selective shape features useful in discriminating between the clinical groups even when controlling for several demographic factors such as age, sex, education, and total intracranial volume. Thus, as conceptualized, shape metrics detected subtle differences in subcortical grey matter structures useful in identifying mTBI patients.

It is also possible that shape features could improve our understanding of cognitive and/or behavioral dysfunction in patients with mTBI. In our previous study, the patients with mTBI demonstrated significant differences in shape for the pulvinar of the thalamus, nucleus accumbens, and amygdala (Tate et al. 2016). Each of these structures have well documented associations with cognitive functions, mood, and/or behavior. For example, volume reductions in the thalamus have been demonstrated in other mTBI studies (Grossman and Ingles 2016; Little et al. 2010). Importantly, the thalamus is a structure known to play a critical role in executive function, visual spatial attention or salience, and working memory (Xiong et al. 2016). The pulvinar has been associated with spatial attention, visual processing and memory (Arend et al. 2008; Danziger et al. 2004; Vecera and Rizzo 2003) which are common cognitive complaints in patients with persistent symptoms post injury (Barker-Collo et al. 2015). Interconnected with the thalamus (Kirouac 2015), the nucleus accumbens has notable functional ties to reward, motivation, emotional regulation, depression, and other mood symptoms (Baldo

et al. 2013; Kalivas and Volkow 2005) which are also complaints noted in patients with mTBI. The amygdala also has prominent thalamic and nucleus accumbens connections (Phillips et al. 2003) and is known to be associated with memory (especially emotional memory), emotional regulation and tone (Janak and Tye 2015; Murray et al. 2014). However, our previous investigation did not directly explore behavioral or cognitive relationships with shape features.

The purpose of the current study is to extend our previous group difference findings by directly examining the relationship between shape descriptors of subcortical nuclei (including the thalamus, accumbens, and amygdala) and neuropsychological performance across several cognitive domains. Though this type of shape-functional analysis has seen limited use, there is a growing number of studies that have successfully revealed important relationships between shape and global measures of intelligence (Wade et al. 2015a), general cognitive function (Pujol et al. 2014), and memory (Bergsland et al. 2016; Macfarlane et al. 2015; Machts et al. 2015; Miskowiak et al. 2015). Thus, analyses were conducted to elucidate the relationships between shape measures and seven subcortical structures (e.g., amygdala, hippocampus, globus pallidus, caudate, putamen, thalamus, and nucleus accumbens) with neuropsychological measures across several domains (e.g., attention, processing speed, memory, fluency, executive function). It was expected that measures commonly affected in symptomatic mTBI patients (i.e., processing speed, complex attention, memory (Barker-Collo et al. 2015)) would be associated with distinctive shape metrics in one or more subcortical nuclei (i.e., thalamus) that was shown to be different in our previous study.

Methods

Participants

One hundred thirty-five (118 male, and 17 female) of the original 158 U.S. Service Members described in the previous study (Tate et al. 2016) were used in this study. Briefly, this cohort includes two operationally defined experimental groups including a 'symptomatic mTBI' and 'orthopedic injury (OI)-only control. Recruitment was conducted at a large regional Military Treatment Facility and all research procedures were approved and monitored by the local IRB (protocol #3743378) and the Human Research Protection Office (HRPO; protocol #A-17660-1a and A-17660-1b). Upon completion of the grant requirements and aims, the raw data from this study will be archived in the Federal Interagency

TBI Repository (FITBIR) data systems and at that time will be made available to the public upon request using that system. Demographic data for each of the groups is found in Table 1 and brief description of each group is provided below.

TBI participants

mTBI participants from the Study of Cognitive Rehabilitation Effectiveness (SCORE) treatment trial including 76 (71 male, 5 female) Service Members between the ages of 18 and 55 years who sustained a mTBI during deployment activities 3 to 24 months prior to recruitment. mTBI was diagnosed using the Veteran Affairs (VA)/Department of Defense (DoD) Clinical Practice Guidelines (i.e., loss of consciousness (LOC) < 30 min, alteration of consciousness

(AOC) < 24 h, post-traumatic amnesia (PTA) < 24 h, and no day of injury imaging abnormalities) by trained qualified medical staff using semi-structured interviews. Importantly, mTBI participants were also required to be cognitively symptomatic as defined by a moderate level of endorsement for one or more of the four cognitive symptom questions on the NeuroBehavioral Symptom Inventory (NSI).

Orthopedic injured (OI) only participants

OI-only controls were 59 (47 male, 12 female) Service Members between 18 and 55 years of age who had recently (3 to 24 months) returned from deployment. OI only participants were excluded if they had any self-reported or objective evidence of a previous closed head injury (regardless

Table 1 Demographics by group

	mTBI Group	OI Only group	Total group	Significance
N	76	59	135	
Age	32.85 Years (9.25)	36.95 Years (6.75)	34.92 Years (8.33)	t = 2.8 p = 0.006
Sex (% female)	6.6%	20.3%	12.6%	Chi square = 2.19 p = 0.3
Race	73.7% W 10.5% AA 15.8% Other	65.5% W 31.0% AA 3.5% Other	66.9% W 19.4% AA 13.7% Other	Chi square = 15.4 p < 0.001
Education	60.5% HS 32.6% C 6.9% PG	22.4% HS 53.4% C 24.2% PG	43.8% HS 40.9% C 15.3% PG	Man-Whitney = 4.92 p < 0.001
Time since injury	308.6 Days (176.6) (Median 270 Days)	N/A	N/A	N/A
AOC	69.7%	N/A	N/A	N/A
LOC	42.1%	N/A	N/A	N/A
PTA	7.9%	N/A	N/A	N/A
CS	1 or fewer = 66% 2 or more = 44%	N/A	N/A	N/A
Prior head injury (Subjective reporting)	31.6% No Prior 19.7% 1 Prior 9.2% 2 Prior 13.2% 3 Prior 3.9% 4 Prior 19.8% >5 Prior 2.6% No Data	None reported/Denied	N/A	N/A
Primary method of injury	57.9% Blast 42.1% Other	N/A	N/A	N/A
NSI	35.27 (SD = 2.62)	12.79 (SD = 3.17)	27.3 (SD = 2.63)	t = 10.53 p < 0.001
PCL-M	48.83 (SD = 3.17)	27.98 (SD = 3.69)	41.48 (SD = 2.87)	t = 8.14 p < 0.001

W white, AA African American, O Other Race, HS High School, C College (Associates and/or Bachelor's Degree), PG Post Graduate Degree, AOC Alteration of Consciousness, LOC Loss of Consciousness, PTA Post-Traumatic Amnesia, CS Concussion Severity (see methods for description), NSI Neurobehavioral Symptom Inventory, PCL-M PTSD Check List-Military Version

of severity), and/or a current post-traumatic stress disorder (PTSD) diagnosis (DSM-IV criterion) as identified by the standardized Clinician-Administered PTSD Scale (CAPS) structured interview.

In addition, all participants regardless of group were required to be proficient in English so they could participate fully in cognitive evaluations described below. Regardless of experimental group, participants were excluded if they had any MRI contraindications (i.e., claustrophobia, shrapnel, pregnancy), comorbid neurologic conditions (i.e., seizures, psychosis, bipolar disorder), history of moderate/severe TBI, or had scheduled narcotic prescriptions.

Demographic and clinical variables

For each participant age, sex, education, rank, branch of military service, number of deployments, and years in service were recorded. Additional clinical variables including time since injury (TSI, day of assessment – day of injury), LOC, AOC, PTA, mechanism of injury (blast vs. non-blast), and number of self-reported prior head injuries and blast exposures were also captured in the mTBI group (Table 1). Other demographic variables such as race, branch of service, number of prior deployments, and prior psychiatric diagnoses were not included in these analyses as they were found insignificant in the previous analysis (Tate et al. 2016).

Cognitive assessment and concussion severity self-report

Cognitive assessments were collected concurrently (same week, mode = 1 day) with MRI assessment. See Table S1 for a list and brief description of neuropsychological tests included in this study. This battery of technician-administered cognitive assessments included standard measures from several cognitive domains including attention, processing speed, language, working memory, short/long term memory, and executive function. In addition, the Test of Memory Malingering (TOMM) was also administered to establish effort and/or symptom validity. Notably, there were no TOMM failures (> 5 errors on Trial 2) noted for any participant included in this study.

One limitation of mTBI research is that rating concussion severity (CS) can be complicated in the deployed service member because in theater medical services may not be present to substantiate or diagnose (Brenner et al. 2015). Thus, subject reports for any AOC, LOC, and/or PTA are often used in assisting with classification of injury severity. In this study, self-reported injury variables were used to establish a binary variable that could further refine our understanding of CS in this sample. In the mTBI participants, binary groupings based on these subjective reports of

injury severity symptoms were established as follows: those reporting up to one injury variable and those reporting 2 or more injury variables.

MRI imaging acquisition and post-processing procedures

Each participant underwent multimodal MRI (3 T Siemens Verio) assessment. Only the volumetric T1-weighted sequence was utilized in this study. The scan was acquired using the following sequence parameters: field of view (FOV) = 256 mm, repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, flip angle = 9°, and a slice thickness = 1 mm.

Though the processing procedures are fully described in the previous study (Tate et al. 2016), we offer the following brief description. The raw DICOM data were initially processed using FreeSurfer 5.3 (MGH Martinos Center, Boston, MA). The fully segmented and labeled images from each subject were visually inspected and manually corrected when needed using standardized procedures. For each of the 7 ROIs (thalamus, putamen, pallidum, accumbens, caudate, hippocampus, and amygdala), two shape descriptors (radial distance (RD) and the Jacobian determinant (JD)) were defined for the surfaces of the segmented label map output. RD measures how thick the structure is at a given point defined on its surface using the center of the structure as the standard reference point while JD is a measure of regional surface area dilation.

Statistical procedures

Linear fixed effects regression models were used to model associations of shape with interactions of cognitive measures and diagnosis while covarying for effects of age, sex, total intracranial volume and education level. Age, sex, and intracranial volume were modeled continuously while education was categorical. The form of the model was:

$$Y = \beta_0 + \beta_1(NP * Group) + \beta_2(NP) + \beta_3(Group) + \beta_4(Age) + \beta_5(Sex) + \beta_6(TICV) + \beta_7(Education) + \epsilon$$

where the outcome, Y, took on the locally-defined RD or JD measure. The NP term was raw neuropsychology test scores when available (see Supplemental Table S1 for variable used) because age and education level were included as covariates in the regression model given known associations such covariates have with brain morphometry. The Group term took on one of two identities: (1) To identify differential associations between TBI and OI groups; (2)

To assess the binary mTBI CS variable (0/1 injury variable group; 2/3 injury variables group). For the latter interaction term, OI controls were excluded since none of these factors would be present. Additionally, TSI (modeled continuously) was included in this model as a covariate as TSI was shown to be associated with amygdala shape metrics in our previous study (Tate et al. 2016) as well as TSI associations noted in other TBI studies. Structuring the model in this form allowed us to identify differential associations between brain morphometry and neuropsychological scores by TBI status, TBI CS, and TSI. We did not covary for method of injury, premorbid mental health diagnosis or attention disorder/learning disability because in our previous study on the same cohort (Tate et al. 2016), no significant associations were noted for any of these variables. Shape features were corrected for multiple comparisons within each ROI by applying FDR (0.05) to the set of RD or JD models within each ROI. As a further protection against type I errors, we imposed an arbitrary cluster size (> 5 connected vertices) requirement before reporting any significant findings.

Two additional post-hoc analyses were also undertaken to further explore non-essential and potential confounding variables. In the first, TICV was removed from the model as including it may be over correction given the way the imaging data are processed (i.e., moved to template space). TICV is a common covariate in many models exploring volumetric features of the brain and is often used when employing this method (Wade et al. 2016, 2015b; Wang et al. 2010). This consistency should allow for more direct comparison of studies (including our own (Tate et al. 2016)) using this set of algorithms, but we also recognize that it may be over-correction and therefore include these post-hoc analysis as [supplemental information](#). In the second post-hoc analyses, scores from the PTSD Check List – Military version (PCL-M) were included in the model to control for the possible confounding effects of PTSD diagnosis which often has symptom overlap with mTBI (Vasterling et al. 2009). PCL-M scores were used as a continuous variable as the diagnosis of PTSD using more rigorous methods (i.e., Clinician-Administered PTSD Scale (CAPS)) in the mTBI groups was not available in this sample. The results from both these post-hoc models are described briefly in the [Results](#) section and presented visually as supplemental figures (Figure S2 and S3).

Results

Demographic variables

As noted in the previous study, there were several statistically significant demographic differences between our

groups (see Table 1) including age and education. Along with sex and total intracranial volume (except where indicated), these demographic variables were included as covariates in all analyses reported.

Cognition by diagnosis (Orthopedic Injury (OI) only vs. mTBI) status

We observed several significant interactions between mTBI status and cognitive measures. OI participants showed an inverse association between subregions of the right pallidum RD and total paced auditory serial addition test (PASAT) score whereas this association was positive among mTBI patients (Fig. 1a). This interaction was significant in five clusters on the pallidal surface with mean t-values in each ranging from 3.10 to 3.65 and cluster extents comprising 0.3 to 2% of the region's surface area. An outline of all clusters including their relative sizes and the magnitudes of their constituent t-values is given in Table S2.

In contrast, the radial distance (RD, i.e. thickness) of the right anterolateral thalamus was negatively associated with the total PASAT score among mTBI participants but positively associated with RD among the OI only group (Fig. 1b). The extent of this significant effect covered 2% of the total thalamic surface area (mean [SD] $T = -3.93$ [0.35]).

Time to completion for Trails A was negatively associated with the surface area (modeled by the local JD) of the left posteromedial putamen among OI participants while more modest, positive associations were noted in the mTBI participants (Fig. 1c). The extent of this significant interaction comprised 0.8% of the total surface area of the putamen (mean [SD] $T = 3.82$ [0.15]).

In the post-hoc analyses, removing TICV from the model did not impact the findings appreciably. The location and direction of the findings were consistent between models with minor variability in the number of significant vertices noted. When PCL-M scores were included in the models, no appreciable differences were noted with one exception. The time to completion score for the Trails A and the putamen findings were no longer significant. Again, the direction of the findings remained consistent between models for all analyses including the Trail A time to completion putamen findings (Figure S2 panel c).

Cognition by mTBI self-reported markers of concussion severity

The interactions between the self-reported marker of concussion severity (CS) and cognitive measures for the mTBI participants were conducted separately from

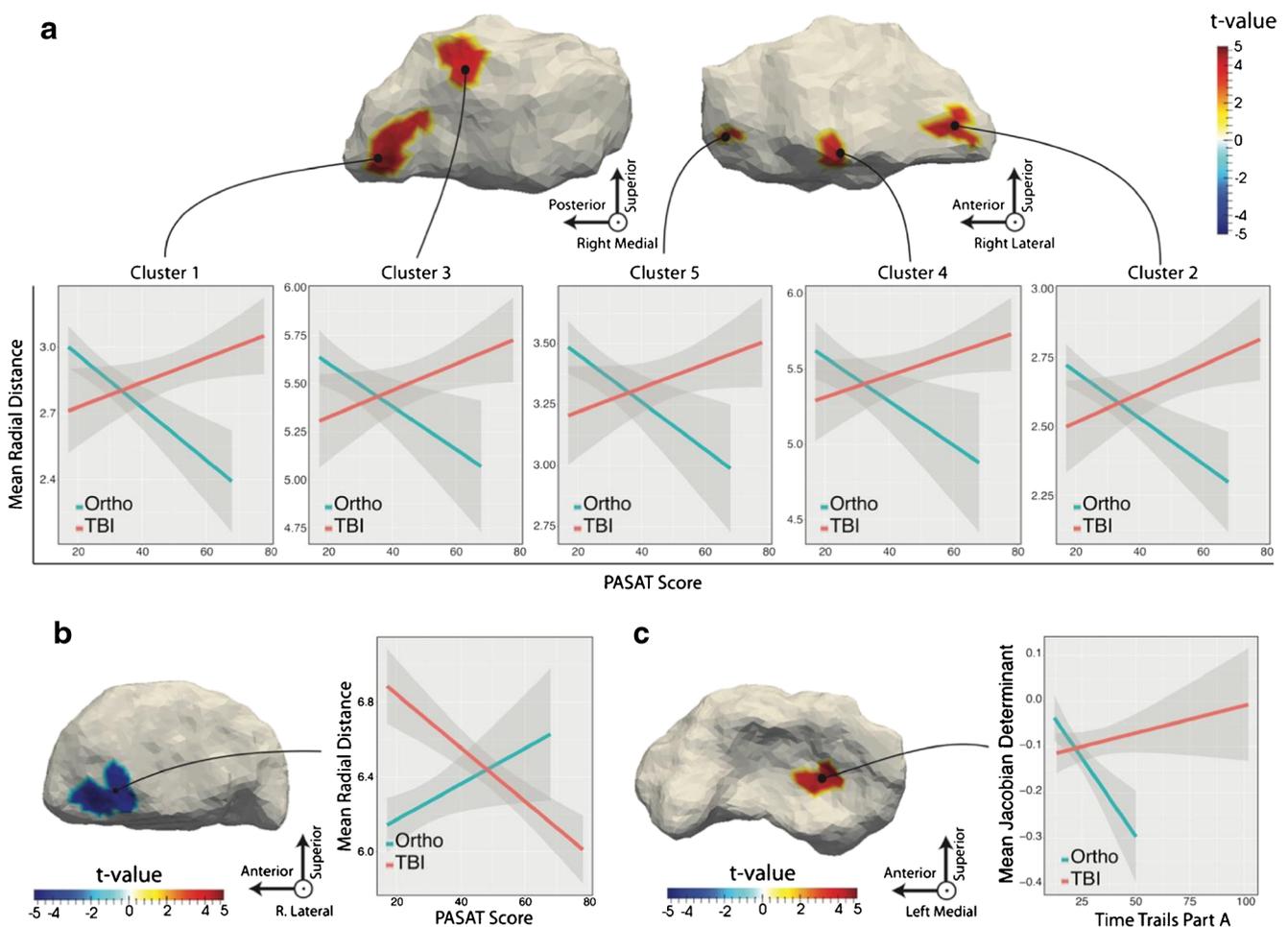


Fig. 1 Associations between subcortical shape and interactions between mTBI status and cognitive measures. **(a)** Illustrates regions exhibiting significant associations between the right pallidal thickness (radial distance) and the interaction of mTBI status and PASAT score in 5 clusters on the pallidal surface. In each cluster, the orthopedic-injured (OI) patients showed an inverse association between local thickness and PASAT score while mTBI patients exhibited positive associations between these measures. In **(b)** we show the same interaction in the right thalamus. Here the direction of this interaction is reversed with mTBI patients showing an inverse association between

the local thickness and PASAT score while OI patients have a positive association between these factors. **(c)** Highlights a region in the left putamen where there was a significant interaction between Time Trails A and mTBI status in predicting the local surface area (Jacobian determinant). There, OI patients had a strong inverse association between these measures while mTBI patients showed a moderately positive association. Statistics including the relative sizes of each cluster and their constituent statistical effect sizes are given in Table S1

the OI-only controls and the results are provided while controlling for *time since injury* (*TSI*), age, education, gender, and total intracranial volume. CS interacted significantly with the Wechsler Adult Intelligence Scale-IV (WAIS-IV) processing speed index score in determining the JD of the bilateral caudate. Among low-CS patients there were widespread inverse associations between processing speed and JD while associations were strongly positive among high-CS patients. Two separate, though neighboring, clusters were observed expressing this association in the right caudate where the extent of the first cluster, located in the caudate tail, included 4% of the

surface area (mean [SD] $T = 2.74$ [0.25]). The second cluster was located more anteriorly and covered 39% of the caudate surface (mean [SD] $T = 2.98$ [0.45], Fig. 2a). In the left caudate the extent of this interaction covered 59% of the caudate surface (mean [SD] $T = 3.16$ [0.60], Fig. 2b).

Long-delayed free recall memory scores (California Verbal Learning Test-II (CVLT-II)) were also differentially associated with the JD of the right medial caudate. Among low-CS patients, scores were inversely associated with the JD but positively associated with the JD among high-CS patients. This significant interaction was observed in a

cluster comprising 2.9% of the caudate surface (mean [SD] $T = 3.74$ [0.29], see Figure S1a).

This same differential association was inverted in the right posterior thalamic region; low-CS patients exhibited positive associations between long (percent of surface = 0.5%, mean [SD] $T = -4.41$ [0.26]) and short (percent of surface = 0.7%, mean [SD] $T = -4.13$ [0.22]) delay CVLT-II scores and the local RD (Figures S1b and S1c, respectively). CVLT-II total scores (sum of trials 1–5 total) were also differentially associated with the JD of the right

caudate as a function of CS. Here high-CS patients exhibited significantly more positive associations between the local JD and CVLT-II total scores than low-CS patients who had strong inverse associations between these factors. This effect was observed in three separate clusters ranging in size from 0.7 to 20% of the caudate surface area (mean T range = 3.23 to 3.31, see Figure S1d).

Time to completion of Trails A (another proxy of processing speed) was differentially associated with the left posterolateral caudate JD. Here low-CS patients exhibited

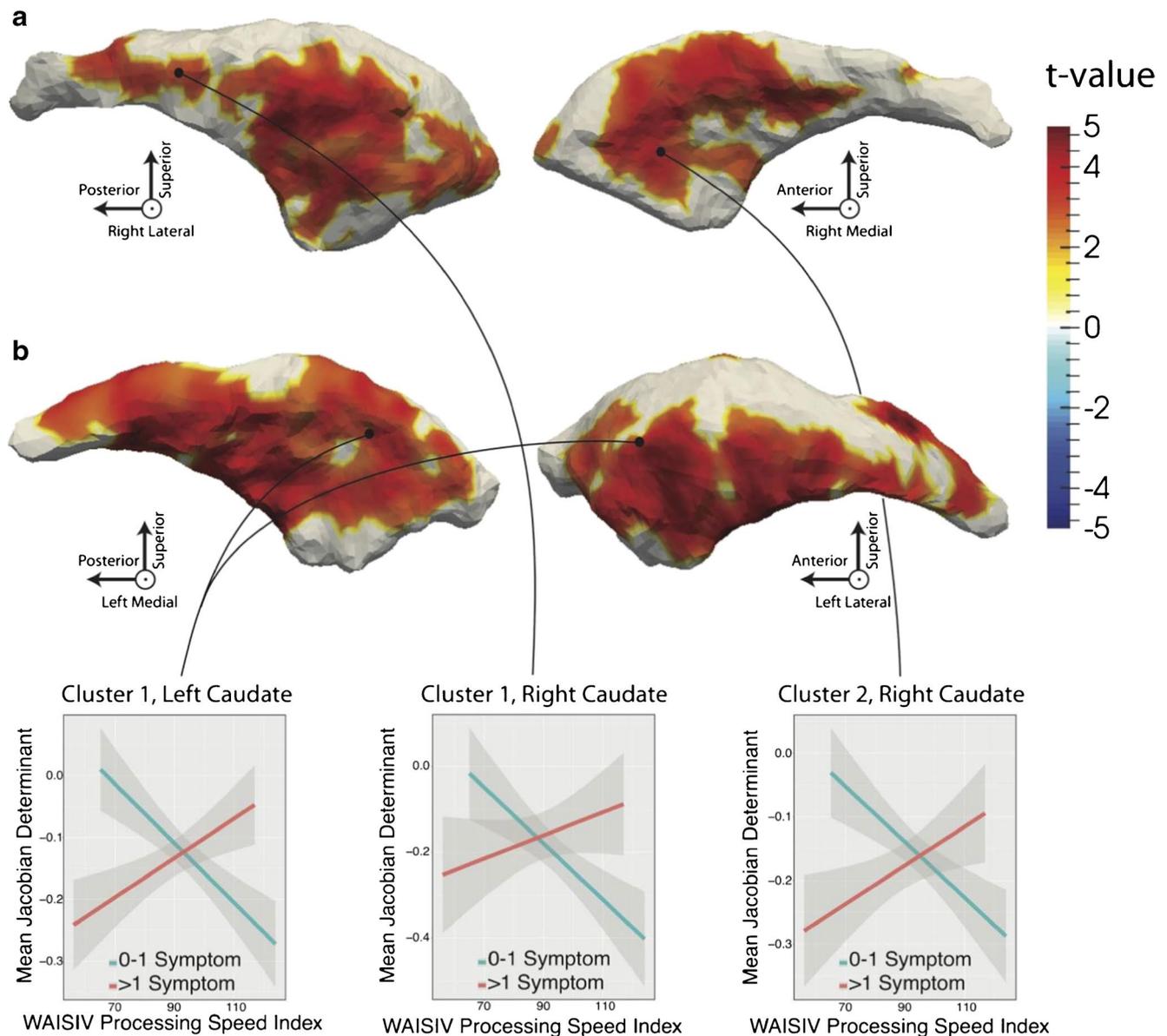


Fig. 2 Association between symptom severity index (SI) and WAIS-IV processing speed index in the prediction of (a) right and (b) left caudate local surface area dilation. In each case patients with lower SI exhibited sharp inverse associations between SI and processing speed

while high-SI patients had a significantly more positive association between these measures. These were widespread findings comprising 43% of the right and 59% of the left caudate surface areas. Descriptive statistics of these clusters are provided in Table S1

a positive association between Trails A and the local JD indicating that patients having less dilation in this region completed Trails A faster. The inverse was true for high-CS patients who showed a strong inverse association where patients with more dilation of this region completed Trails A faster. This association was observed within a cluster of the caudate tail comprising 0.3% of the total caudate surface area (mean [SD] $T = -4.39$ [0.26], see Figure S1e).

The WAIS-IV working memory score was positively associated with the JD of right medial amygdala among high-CS patients while showing little or no association among low-CS patients. This significant interaction was observed in a cluster covering only 0.6% of the amygdala surface (mean [SD] $T = 4.18$ [0.24], see Figure S1f).

Discussion

The results from this study support the general hypothesis that shape features are associated with performance on cognitive measures in patients with mTBI. Specifically, we observed the shape of several subcortical structures (i.e., caudate, putamen, thalamus) to be significantly associated with measures of attention, processing speed, and memory. This is one of the first mTBI studies to demonstrate significant functional associations using this advanced imaging processing method. Though our original findings did not implicate a group difference in the caudate (Tate et al. 2016), there was a very robust (~44% and ~60% of the total surface, right/left caudate respectively) relationship between processing speed performance and the shape of the caudate in mTBI patients that appeared to interact with the patient's subjective reports of injury severity. In addition, surface features from several subcortical structures (caudate, thalamus, amygdala) were associated with verbal memory performance.

The processing speed caudate finding requires additional comment as it was uniquely robust in this sample. This finding can be compared to studies where the caudate is associated with processing speed in other disorders (Almeida et al. 2012; Derauf et al. 2012; Harrington et al. 2014; Spies et al. 2016), though other studies do not necessarily find any association when considering TBI cohorts (Newsome et al. 2015). However, it is important to note that processing speed is often measured differently across studies and this may account for the equivocal results. In the current study, the score is a composite that incorporates performance across subtests that assess complex functional processes including visual perception, scanning speed, visual motor coordination, and motor and mental speed. Thus, the strong association noted here may be a reflection of the

complex nature of these cognitive tasks and the role the caudate plays in a broader range of networks (Grahn et al. 2008) including the thalamo-cortical network. It should be noted that caudate atrophy has been noted across several neurological conditions (i.e., Parkinson's disease, Obsessive Compulsive Disorder) and caudate dysfunction is associated with poorer performance on motor activities especially when the task has a spatial processing component (Postle and D'Esposito 1999, 2003). In addition, functional imaging studies demonstrate a clear link between the caudate and frontal areas of the brain known to be responsible for executive function (Grahn et al. 2008), especially those in which reaction time determine the outcome (Delgado et al. 2000, 2004; Elliott et al. 2000). So, this robust processing speed caudate finding may indeed reflect more complicated processes that cannot be directly assessed with this data and future studies will be needed to examine the complexity of these relationships more directly.

Clinically, the processing speed caudate finding also supports the idea that commonly assessed clinical variables (AOC, LOC, and PTA) can play an additional predictive role in the analyses when explored in conjunction with shape analyses. Though these variables have all been widely investigated separately (i.e., LOC (Barrett et al. 1994; Iverson et al. 2000; Martikainen et al. 2011; Norris et al. 2014; Reuber et al. 2016; Roitman et al. 2013)), there may be some rationale that reporting more than one of these measures may be an indication of a more significant injury. However, we must acknowledge that in this investigation our operational definition of CS is not common and cannot be independently verified. Nonetheless, the CS variable as defined in this study provided meaningful insights for data analysis and group comparisons. We also acknowledge that symptom over-reporting has been observed in service members and veterans, which may reflect a variety of non-neurological factors (Jurick, Twamley, et al. 2016). Importantly, on measures of symptom validity, this sample did not have any failures and this may mitigate concerns with regards for over-reporting. Regardless, these clinical variables continue to be routinely assessed and used in determining the initial severity of injury in patients with TBI. Also, there is often notable variability in how often patients report these measures in clinical and research settings (Clark et al. 2014) and examination of this variance may be important in developing new ways to conceptualize and examine common clinical measures of TBI severity. The results appear to validate this line of thinking as mTBI patients reporting more than one of these variables had more robust shape differences by cognitive function findings.

The distributed nature of the memory findings is of interest given the interconnected nature of subcortical nuclei and associated functional networks. Though it is reasonable to expect findings for a complex neuropsychological

test to be associated with a distributed network of structures these findings must be interpreted cautiously as they tend to only include small clusters relative to the overall size of the nuclei. Another important caveat or caution when interpreting these findings is that the direction of the results appears to be complicated as better cognitive function was observed to be associated with both increased and/or decreased shape values. For example, one cannot automatically assume that increases in RD or thickness would be associated with better cognitive outcomes (size matters argument (Bigler 2015)). Ultimately, it would be important to determine what might be considered a reparative and/or degenerative shape outcome so that accurate clinical judgments can be made regarding the direction of these findings. This not only includes clinical judgments about the direction of the shape changes, but ultimately the direction of relationship between shape and cognitive function. Imaging was only obtained at one time point, so any potential longitudinal shape change remains speculative at this point and these findings could be related to either adaptation or degenerative pathological changes. Furthermore, none of the Service Member participants had been previously scanned, so we do not know if the shape findings relate to pre-injury vulnerabilities or post-injury pathological changes. So, the findings leave many unanswered questions that will need to be addressed in future studies.

There are a number of limitations that should be considered when interpreting these findings. First, as already mentioned above, the direction of findings is difficult to interpret in this type of cross-sectional analyses. In order to be able to use these data to make clinical decisions, ultimately the direction of findings will require further elucidation. Second, with the exception of the processing speed/caudate finding, the other associated findings were often small (number of significant vertices) and distributed (multiple subcortical structures) in nature. This could be due to the fact that many of the cognitive tests require distributed networks but the size of these findings requires cautious interpretation and/or validation in additional datasets. Third, as with many data sets, additional demographic and clinical variables will need to be considered in future studies with increased sample sizes (i.e., race, alcohol/drug use, premorbid psychiatric, PTSD, etc.) as these may have moderating/mediating effects on these types of imaging findings. In the post-hoc data presented as [supplemental findings](#), we were able to examine the effects of PTSD symptom reporting on these imaging findings. Interestingly, including the score from the PCL-M did not significantly affect the magnitude or the direction of the findings. Thus, it appears that in this sample, the severity of PTSD symptom reporting was not a significant factor. Regardless, these results not only represent important initial clinical findings, but they also represent

initial hypothesis generating findings that can inform future studies.

Identifying objective biomarkers and predicting functional outcomes (i.e., symptom severity, cognitive performance, clinical symptoms) in the context of mTBI has proven difficult. Structural MRI has been at the forefront of efforts to improve diagnosis and prognostic accuracy. Discovery of brain behavior relationships, such as the ones identified in these data, significantly improve our understanding of the biological underpinnings of cognitive changes noted in patients who experience mTBI. Furthermore, these types of findings may also improve prognostic accuracy in an otherwise heterogeneous group, and lead to improved patient-centered treatment approaches.

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Compliance with ethical standards.

All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors have no conflicts of interest to disclose.

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