Functional Neuroimaging Distinguishes Posttraumatic Stress Disorder from Traumatic Brain Injury in Focused and Large Community Datasets

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Running Title: Functional Neuroimaging Distinguishes PTSD from TBI

Abstract

Background:

Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are highly heterogeneous and often present with overlapping symptomology providing challenges in reliable classification and treatment. Functional neuroimaging modalities including single photon emission computed tomography (SPECT) may be advantageous in the early diagnosis and assessment of these comorbid disorders.

Methods:

Subjects were selected from a multisite database, where rest and on-task SPECT scans were obtained on a large group of neuropsychiatric patients. Two groups were analyzed: Group 1 with TBI (n=104), PTSD (n=104) or both (n=73) closely matched for demographics and comorbidity, compared to each other and healthy controls; Group 2 contained all patients with TBI (n=7,505), PTSD (n=1,077) or both (n=1,017) compared to n=11,147 without either. TBI was diagnosed by clinical evaluation and classified based on the Department of Defense Clinical Practice Guidelines. ROIs and visual readings (VRs) were analyzed using a binary logistic regression model with predicted probabilities inputted into a Receiver Operating Characteristic analysis to identify sensitivity, specificity, and accuracy. Forward stepwise logistic regression identified the most diagnostically significant regions.

Results:

For Group 1, baseline and on-task ROIs and VRs showed significant separations from PTSD, TBI and combined conditions. This comorbid matched group separated 100% sensitivity,

specificity and accuracy for the ROI analysis and at 89% or above for VRs. Group 2 had lower sensitivity, specificity and accuracy, but still in the clinically relevant range. Compared to subjects with TBI of varying severity levels resulting from blunt force trauma, PTSD showed increases in the limbic regions, cingulate, basal ganglia, insula, thalamus, prefrontal cortex and temporal lobes.

Conclusions:

This study demonstrates the ability to separate PTSD and TBI from a healthy group and from each other using SPECT. This modality may offer a viable clinical option for aiding in the diagnosis and treatment of these conditions.

Introduction:

Traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) are complex, comorbid disorders in which clinical symptoms often overlap, creating challenges in diagnosis and treatment. Advanced neuroimaging techniques are providing insights into ways to detect the underlying pathological and physiological changes and biomarker studies offer the potential to differentiate these disorders at acute stages, when interventions have the greatest potential to yield effective outcomes. Imaging in TBI is indicated for the identification of skull fractures, contusions and bleeds, but newer technologies used in the research setting offer the ability to detect more subtle abnormalities not observed on computed tomography (CT) or magnetic resonance imaging (MRI) including perfusion deficits, diffuse axonal injury and alterations in anatomical connections [1]. While mild TBI is often undetected using conventional structural imaging techniques [2], perfusion deficits observed with functional imaging techniques like single photon emission computed tomography (SPECT) are often reported in the orbitofrontal cortex, temporal poles, and anterior cingulate [3], and correlate with cognitive and psychiatric symptomology. Imaging of PTSD has revealed the underlying neurocircuitry associated with the core symptoms that define the disorder which include volumetric and perfusion changes in the amygdala [4], corpus callosum [5], insula [6], anterior cingulate [7-9] and hippocampus [5,10,11]. Given the overlapping symptomology between TBI and PTSD and the high prevalence of these disorders within our active duty U.S. military personnel [12,13] and civilian population [14,15], there is a need to identify diagnostic tools that can clearly distinguish these disorders. Research into the use of neuroimaging modalities like SPECT have demonstrated its clinical utility for the improved detection of TBI [3,16-18] and delineation of the neural circuitry underlying PTSD [19-26], offering the potential of this modality to identify functional

115 biomarkers useful in differential diagnosis.

116 Traumatic brain injury (TBI), especially from blast and blunt force trauma, has been
117 designated as the "signature wound" of the Iraq and Afghanistan wars [27,28]. The prevalence of
118 these brain disorders in active duty U.S. military personnel is on the rise, with the Department of
119 Defense reporting 307,283 diagnosed cases of TBI from 2000-2014 [12] and the Congressional
120 Research Service reporting 103,792 diagnosed cases of PTSD from 2000-2012 [13]. The
121 economic costs to society for treatment of PTSD and TBI are significant, with the Rand
122 Corporation estimating an annual cost for TBI between $591 and $910 million. Within the first
123 two years after returning from deployment, they estimate that costs associated with PTSD and
124 major depression for 1.6 million service members range between $4.0 to $6.2 billion [29].

125 Service members exposed to TBI have been shown to have a higher incidence of PTSD
126 [30-32]. An observational study by Taylor et al. reported 73% of service members met the
127 criteria for PTSD [33]. The RAND survey of returning warfighters also reported that 50% had
128 witnessed the death or injury of a friend, 10% had been injured themselves, and over 19% had
129 symptoms consistent with PTSD [29]. Hoge et al. found that 90% of combatants had
130 experienced a traumatizing event [30]. Over 400,000 military personnel and veterans have been
131 diagnosed with PTSD or TBI since 2001 [12,13], and many have been diagnosed with both. Both
132 of these conditions are also common in the U.S. civilian population with 7.7 million suffering
133 from PTSD [14] and 2.5 million annual visits to emergency rooms for suspected TBI [15].
134 Research suggests that long-term consequences of seemingly innocuous head injuries may be
135 significant [34,35] and it is now understood that repetitive TBI can lead to long-term morbidity
136 [36-41].

137 TBI is diagnosed based on injury severity and may be classified based on three

mechanisms: injury severity scale, physical mechanism of injury or the anatomic features observed with imaging [42]. The U.S. Department of Defense differentiates the severity levels of TBI based on the following classification strata: Mild TBI is defined as head trauma associated with a loss of consciousness for 30 minutes or less, alteration of consciousness for 24 hours or less, posttraumatic amnesia for 24 hours or less and a Glasgow Coma Scale (GCS) score of 13-15. Moderate TBI involves loss of consciousness between 30 minutes and 24 hours, posttraumatic amnesia between 1 and 7 days and GCS score of 9 to 12. Severe TBI involves a more extended loss of consciousness and posttraumatic amnesia which typically results in more severe cognitive impairment and a GCS of 8 or less [43]. The majority of TBIs from combat and civilian injuries are categorized as mild [31,44] with the Department of Defense reporting the percentage of U.S. military service members diagnosed with a TBI as 82.4% mild (n=253,350), 8.3% moderate (n=25,370) and 1.0% severe (n=3,088) [12].

Due to the heterogeneous nature of TBI and the fact that mild TBI is less likely to yield chronic symptoms, the reliance of diagnosis on self-report and the overlap of physical and psychological symptoms between PTSD and TBI emphasize the need for biomarkers in order to accurately diagnose the disorder, provide the proper interventional therapies and improve long-term health outcomes. Studies among civilians with TBI indicate that 49% had evidence of psychiatric illness in the year subsequent to injury [45-47]. While TBI symptoms can resolve over time, a significant proportion of cases develop a persistent post-concussive syndrome (PCS) [48]. Some symptoms of PCS [49,50] overlap those of PTSD and can include: headache, dizziness, irritability, memory impairment, slowed reaction time, fatigue, sleep disturbances, sensitivity to light and noise, impulsivity, anxiety and depressive symptoms [39-41,48,51-58]. Soldiers who experience blast related TBI are at greater than double the risk for developing

PTSD [31]. It can be very challenging to tease apart the symptoms, historical details, and other factors to adequately distinguish TBI from PTSD. Indeed, the overlap of these two populations has been estimated at 33% [29,30] to 42% [56]. Recollection of traumatic events, particularly if assessment occurs after significant time has elapsed, can be inconsistent [59,60]. The treatments for PTSD and TBI/PCS are different, therefore, reliably separating them, as well as identifying cases in which both are present, emerges as a critical diagnostic need [53,57,61]. To our knowledge, no widely accepted biomarker to distinguish TBI from PTSD has been reported.

There are a variety of neuroimaging modalities available which provide significant clinical utility in the context of TBI and PTSD. CT and MRI are used to measure changes in anatomical or physiological parameters of TBI (hemorrhage, edema, vascular injury, intracranial pressure) but for most cases of mild TBI, CT and MRI often show no abnormalities [2]. Diffusion tensor imaging (DTI) has been used to detect axonal injury for mild to moderate TBI, but results are inconsistent and require further investigation [31]. Functional MRI (fMRI) is often used to differentiate TBI from control groups [62], and has been used to study activation patterns in patients with TBI [63]. Fluorodeoxyglucose positron emission tomography (FDG-PET) measures glucose uptake and metabolism and is used to detect subtle changes in brain function from TBI that are not observed with structural imaging modalities like CT or MRI [64]. SPECT is used to measure cerebral blood flow and activity patterns and is indicated for the evaluation of TBI in the absence of anatomical findings [65]. Brain activation studies have been performed to identify the underlying circuits in PTSD using PET, fMRI and SPECT [19-22,66-68]. Furthermore, the relationship between TBI and PTSD has been studied with functional imaging using FDG-PET in veterans with mild TBI and/or PTSD compared to community volunteers [69].

SPECT is a widely available imaging modality and has been studied in the research literature for over 30 years, yet is underutilized in clinical settings because of its perceived lower resolution to MRI and PET. Advances in this neuroimaging modality have provided higher resolution with multi-headed gamma cameras and sophisticated image rendering software, demonstrating that SPECT scans can provide clinically meaningful information [70]. A recent review of three decades of research by Raji and colleagues concluded that SPECT for TBI 1) has improved lesion detection compared to CT/MRI; 2) helps to predict clinical outcomes; and 3) can help direct treatment. Based on their review, the authors suggest that SPECT should be part of a clinical evaluation in the diagnosis and management of TBI [3]. This review cited 19 longitudinal studies that demonstrated Level II A evidence (i.e., evidence from at least one controlled trial without randomization) for SPECT in identifying lesions in the clinical setting of TBI [3,71-74]. SPECT has high sensitivity in TBI cases [16-18,71]. Jacobs et al. found a 91% sensitivity < 3 months after injury and 100% thereafter and strong (96% to 100%) negative predictive value, thus, indicating that a negative SPECT scan is a reliable indicator of a positive outcome for head injury [71]. SPECT also has shown potential in the evaluation of psychiatric conditions. For example, PTSD presents with particular findings that are distinct from those of TBI. Specifically, increased perfusion of the caudate has been associated with anxiety disorders and PTSD [23], and preliminary data investigating cerebral perfusion patterns in SPECT and PTSD [20-23] suggests it has a potential role in distinguishing PTSD from TBI.

Previous studies have explored the relationship between PTSD and TBI using neuroimaging [69,75-77], but to the best of our knowledge, no study has identified imaging biomarkers differentiating PTSD from TBI using brain SPECT imaging. In this retrospective study, two groups were analyzed; i) a small, well-defined group with the diagnosis of TBI and/or

PTSD at one clinical site closely matched for demographics and comorbidity compared to a healthy dataset, and ii) a large, generalized group of all TBI and/or PTSD patients regardless of comorbidity across multiple-sites which were also compared to healthy controls. Both region of interest (ROI) and visual readings (VRs) were analyzed to assess the diagnostic accuracy in using SPECT to better assess and diagnose these conditions.

Methods:

Study Subjects:

This study was conducted in accordance with the STARD guidelines (http://www.stard-statement.org/). All subjects were obtained for retrospective analysis from a large multisite psychiatric database, involving 20,746 patients who came for evaluation of complex, treatment resistant issues to one of nine outpatient clinics (Newport Beach, Costa Mesa, Fairfield, and Brisbane, CA, Tacoma and Bellevue, WA, Reston, VA, Atlanta, GA and New York, NY) from 1995-2014. Diagnoses were made by board certified or eligible psychiatrists, using all of the data available to them, including detailed clinical history, mental status examination and DSM-IV or V criteria, consistent with the current standard of care. Anonymized data was extracted from a research database using a data mining technique within a protocol deemed appropriate by an independent IRB IntegReview (http://www.integreview.com/) to be exempt from human subjects review in accordance with 45 CFR 46.101(b)(4) (IRB #004).

Included in the database are n=116 healthy adult volunteers who had rest and on-task SPECT studies. The exclusion criteria for the healthy subjects were: 1) current or past evidence of psychiatric illnesses as determined by clinical history, mental status examinations, and the

Structured Clinical Interview for Diagnosis for DSM-IV; 2) current reported medical illnesses or medication; 3) history of brain trauma; 4) current or past drug or alcohol abuse; 5) first degree relative with a psychiatric illness. Written informed consent was obtained from all healthy subjects under an approved IRB protocol (WIRB # 20021714).

Two groups were extracted from the larger database for analysis. Group 1 (n = 397) is described in Table 1 and Figure 1.

Insert Table 1 and Figure 1 Here

Group 1 represents a select cohort from the Newport Beach site matched closely by demographics and co-morbidities, including the healthy cohort. In this group, variance due to comorbid diagnoses was minimized and Ns were matched closely (n = 104 for TBI or PTSD, n = 73 for TBI + PTSD, n = 116 for controls) as the main inclusion criteria. The primary selection criterion for TBI in clinical trials is the GCS, which is used to assess the level of consciousness following a TBI [78]. It rates a patient's level of consciousness based on the ability to open his or her eyes, talk and move. As this was a retrospective chart review and subjects were not assessed for TBI at the time of injury, we were unable to use the GCS as an assessment of injury severity. Therefore, subjects were classified according to injury severity categories of mild, moderate or severe based on the Department of Defense Clinical Practice Guidelines [43]. Further classification included type of injury (blunt, penetrating, unknown) and mode of injury (accident, assault, fall, sport, accident, unknown) as shown in Table 2 and 3.

Of the 104 patients with TBI only, 65 were classified as mild, 11 moderate and 18 severe. Ten patients could not be categorized based on information provided in the chart. Of

these 10 patients, 8 showed abnormal brain SPECT scans: four subjects were diagnosed with temporal lobe dysfunction; one subject with prefrontal lobe dysfunction and temporal lobe dysfunction; one subject with cerebellar dysfunction, parietal lobe dysfunction and temporal dysfunction; one subject with frontal lobe syndrome and prefrontal lobe dysfunction; and one subject with post-concussion syndrome. Of the 73 patients with TBI+PTSD, 47 were classified as mild, 8 moderate and 8 severe. Ten patients could not be categorized based on information provided in the chart. Of these 10 subjects, 6 had abnormal findings on SPECT scans indicating trauma: one patient showed frontal lobe syndrome, limbic system dysfunction, parietal lobe dysfunction and temporal dysfunction; one subject was diagnosed with post-concussion syndrome; one subject showed occipital lobe hyperperfusion, parietal lobe dysfunction and temporal dysfunction; one subject showed prefrontal lobe and temporal dysfunction; and two subjects showed frontal lobe syndrome and temporal dysfunction.

Insert Tables 2 and 3 Here

The patients in the TBI group had a chart diagnosis of intracranial injury with a brief or extended loss of consciousness (n=62) or concussion (n=42). The patients with PTSD met the DSM-IV criteria. Patients in the subgroup with TBI were compared to those with PTSD, those with TBI+PTSD, and to healthy controls. Similarly, each of the other subgroups was compared to the remaining subgroups in the method described below.

Group 2 consists of a generalized group with much larger cohorts of patients in each diagnostic area, but unmatched for demographics or comorbidity across all sites. The patients in the TBI and PTSD groups both had a chart diagnosis for their specific disorders. Group 2 reflects the full range of psychiatric co-morbidities across the larger cohorts (n = 7,505 for TBI, n =

1,077 for PTSD, n = 1,017 for TBI+PTSD, n = 11,147 which do not include TBI or PTSD). Group 2 is described in Table 4 and Figure 2. Each subgroup was compared to the other subgroups as described below.

Insert Table 4 and Figure 2 Here

SPECT Imaging Acquisition:

All SPECT scans were performed using a high resolution Picker (Philips) Prism XP 3000 triple-headed gamma camera (Picker Int. Inc., Ohio Nuclear Medicine Division, Bedford Hills, OH, USA) with low energy high resolution fan beam collimators. SPECT was performed as previously described [79,80]. For each procedure, an age- and weight-appropriate dose of technetium Tc99m exametazime was administered intravenously at rest and while performing a concentration task. For the rest scans, patients were injected while they sat in a dimly lit room with eyes open. Patients were scanned approximately 30 minutes after injection. For the on-task scans, patients were injected three minutes after starting the Conners Continuous Performance Test (Conners Continuous Performance Test, CCPT-II, Multi-Health Systems, Toronto, Ontario). Approximately 30 minutes after the injection, subjects were scanned. Data was acquired in 128x128 matrices, yielding 120 images per scan with each image separated by three degrees spanning 360 degrees. The original image matrix obtained at 128x128x29 with voxel sizes of 2.16mm x 2.16mm x 6.48mm were transformed and resliced to a 79x95x68 matrix with voxel sizes of 2mm x 2mm x 2mm consistent with the MNI template. Images were smoothed using an 8mm FWHM isotropic Gaussian kernel. The slice thickness was 6mm. A low pass filter was applied with a high cutoff. Chang attenuation correction was performed [81].

Transaxial slices oriented horizontal to the AC-PC line were created along with coronal and sagittal images (6.6mm apart, unsmoothed).

SPECT Region of Interest Analysis

ROI counts were derived from the anatomical regions in the AAL atlas [82]. These quantitative ROI metrics were in no way used to aid in the clinical diagnosis of PTSD or TBI. To account for outliers, T-score derived ROI count measurements were derived using trimmed means [83] that are calculated using all scores within the 98% confidence interval ($-2.58 < Z < -2.58$). The ROI mean for each subject and the trimmed mean for the sample are used to calculate T with the following formula: T = 10*((subject ROI_mean – trimmed regional_avg)/trimmed regional_stdev)+50.

SPECT Visual Reading Analysis

All scans were read visually by experienced SPECT readers (6-23 years of experience). Methods for visual readings have been fully described in previously published work [79,80]. Briefly, 14 cortical regions of interest (ROIs) in orthogonal planes were visually inspected and rated using the Mai Atlas of the Human Brain [84]: left and right prefrontal poles; left and right inferior orbits; left and right anterior/lateral PFC; left and right midlateral PFC; left and right posterior frontal region; left and right parietal lobes; and left and right occipital lobes. In like manner, the left and right cerebellar hemispheres and vermis were rated. In addition, subcortical regions were rated, including the dorsal, genu and ventral aspect of the anterior cingulate gyrus; middle and posterior cingulate; left and right insula; left and right caudate nuclei; and left and right putamen. Raters did not have access to detailed clinical information, but did know age,

gender, medications, and primary presenting problem. The following nonlinear scheme was used to visually rate rCBF: activity rated above the top 95% was assigned a score of 4+; 91%-95% was scored 3+; 86%-90% was scored 2+; 81%-85% was scored 1+; 61%-80% was scored 0; 56%-60% was scored –1; 51%-55% was scored –2; 46%-50% was scored –3; and 41%-45% was scored –4, resulting in a rating scale ranging from +4 to -4 in a-point intervals.

Statistical Analyses:

All analyses were performed using Statistical Package for Social Science (SPSS, version 22, IBM, Armonk, NY). Data were analyzed first at UCLA (C.R.) with analyses repeated and results verified independently at the Amen Clinics (D.A.) and Thomas Jefferson University (A.N.). Multiple imputation analysis did not identify any significant missing data (<10%). In doing the analyses, the following steps were invoked: First, binary logistic regression models were built using either rest ROIs, rest VRs, on-task ROIs, or on-task VRs as predictor variables. Cerebellar and vermis regions were averaged to carefully optimize subject to variable ratios. Paired comparisons between the groups described in Tables 1 and 4 were performed. Covariates in the analysis were age, gender, race and psychiatric co-morbidities listed in Tables 1 and 4. For Group 2, an additional covariate of study site ID was included in the analysis. Predicted probabilities from binary logistic regression models were then inputted into a Receiver Operating Characteristic (ROC) analysis to identify sensitivity, specificity, and accuracy in delineating between the various clinical groups with 95% confidence intervals. Finally, forward stepwise logistic regression was invoked in SPSS to identify the most diagnostically significant regions in comparing PTSD to TBI and a One Way ANOVA with Least Square Differences (LSD) for correcting for multiple comparisons were done to confirm statistically significant difference (p<

.05) and to determine if increases or decreases in these diagnostically important regions were the main predictors of diagnostic utility of the SPECT regions tested.

Results:

For Group 1, rest and on-task ROIs and VRs show significant separations from PTSD, TBI and combined conditions. The non-comorbid group separates 100% with the method described for the ROI analysis and above 89% for accuracy for the VRs. The larger comorbid group has lower sensitivity, specificity and accuracy, but these remain in the clinically relevant range. See Tables 5 and 6.

The most significant regions separating PTSD from TBI for the Group 1 ROI analysis of rest and on-task scans are: limbic regions (amygdala, hippocampus, anterior, middle and posterior cingulate, and thalamus), anterior cerebellum, basal ganglia (caudate and putamen), insula, areas of the prefrontal cortex (inferior orbits, operculum), and temporal lobes (middle and superior temporal lobes and temporal poles). All PTSD regions were more active, reflecting increased perfusion on SPECT, than the TBI regions that were comparatively hypoperfused. See Table 7.

The most significant regions from Group 1 VRs of rest and on-task scans are: limbic regions (right amygdala, left hippocampus, anterior and middle cingulate, thalamus), cerebellum, basal ganglia (caudate during on-task), right insula at rest, multiple areas of the prefrontal cortex (inferior orbits and anterior lateral prefrontal cortex), and temporal lobes (temporal poles and anterior lateral temporal lobes). All PTSD regions were more active than the TBI regions. See Table 8.

The most significant regions from Group 2 ROI analysis of rest and on-task scans are:

limbic regions (amygdala, hippocampus, anterior, middle and posterior cingulate, thalamus), anterior cerebellum, basal ganglia (caudate and putamen), insula, areas of the prefrontal cortex (inferior orbits, operculum), and temporal lobes (middle and superior temporal lobes and temporal poles). All PTSD regions were more active than the TBI regions. See Table 7.

The most significant regions from Group 2 VRs of rest and on-task scans are: limbic regions (amygdala, hippocampus, and anterior and middle cingulate), cerebellum, basal ganglia (caudate), occipital and parietal lobes, multiple areas of the prefrontal cortex (inferior orbits, anterior lateral prefrontal cortex and prefrontal pole– only left side at baseline), and temporal lobes (temporal poles and anterior, mid and posterior lateral temporal lobes). All PTSD regions were more active than the TBI regions. See Table 8.

Figure 3 visually displays with 3-D rendered SPECT maps the different findings in TBI versus PTSD and in persons with both conditions.

Insert Tables 5-8 Here

Insert Figure 3 Here

Discussion:

The present study examines at rest and on-task rCBF differences which distinguish PTSD from TBI with varying degrees of severity primarily from blunt force injuries, either disorder from TBI+PTSD, and all three conditions from normal controls. When compared in a larger population with high psychiatric morbidity, TBI, PTSD and TBI+PTSD could be distinguished from non-TBI/non-PTSD with reasonable ROC characteristics which are similar across rest and task states, whether using quantitative or visual analysis. Since visual analysis of resting state

391 brain perfusion SPECT is a routinely performed and widely-available nuclear medicine
392 procedure, the potential exists for the use of this test in clinical settings.

393 Furthermore, the absence of any requirement for symptom-provocation, a commonly
394 employed technique in functional imaging studies of PTSD, may make this study more
395 acceptable to individuals with active symptoms and to referring physicians. This investigation
396 also uses the non-distressing Conners Continuous Performance Test for an activation task in all
397 cases. Thus, we expect and, indeed, find numerous differences.

398 Compared to multiple severity levels of TBI incurred primarily from blunt force, PTSD
399 showed increases in the limbic, cingulate, basal ganglia, insula, thalamus, prefrontal cortex and
400 temporal lobes, which makes intuitive sense, as TBI damages brain structures often resulting in
401 hypoperfusion, while PTSD has been demonstrated to activate the emotional neurocircuitry.

402 These findings are consistent with and replicate the functional neuroimaging literature.
403 At baseline, both military and civilian PTSD subjects show increased perfusion in the
404 caudate/putamen area, right temporal, orbitofrontal cortex, limbic regions, anterior cingulate
405 gyrus, cerebellum, and medial prefrontal cortex [19-26,85-87]. Peterson et al.'s recent survey
406 takes a network-based approach to findings in 11 fMRI studies which met her quality threshold
407 over the survey period, 2009 to mid-2013 [88]. They report a positive correlation between
408 default mode network (DMN) connectivity in PTSD severity in five studies, negative in two.

409 Similarly, the present data replicate SPECT findings in TBI. Specifically, hypoperfusion
410 in the orbitofrontal cortex, temporal poles, and anterior cingulate replicate the most frequent
411 findings in the TBI literature [3].

412 The symptoms of chronic TBI can often overlap with those of PTSD [27,41,48,52,55,56].
413 About 15-19% of returning service members have probable mild TBI [29,30], while an estimated

8-19% meet criteria for PTSD [52,57,89,90]. The overlap of these two populations has been estimated at approximately 40% [29,30,56]. These two overlapping populations have potentially different treatment requirements and different prognoses. Neuropsychological testing has been unsuccessful in clearly differentiating these two disorders [91,92]. Given this situation: 1) TBI is underappreciated as a contributing factor to the persistent symptoms experienced by service members, athletes [93,94], and others who experience mild TBI [95,96]; 2) differentiating TBI from PTSD is difficult based on symptoms alone or by neuropsychological testing; and 3) the treatment for TBI is considerably different from that for PTSD, a specific and sensitive biomarker is needed that can readily distinguish TBI from PTSD [53,57,61].

The present study demonstrates a novel application of brain SPECT imaging to differentiate TBI from PTSD with the sensitivity, specificity and accuracy required to inform clinical decision-making. The strengths of this work include the use of both rest and concentration task scans from an objectively validated functional imaging modality, detailed quantitative analysis, and an extensively chacterized psychiatric population obtained across multiple sites. The large sample size, while a critical attribute, is further enhanced by the separate analysis of a carefully matched smaller cohort that still has a relatively large sample size.

This study also includes several potential limitations. First, this was a retrospective analysis and we acknowledge that higher levels of evidence can be derived from either prospective studies or randomized clinical trials. Second, subjects in this study had varying degrees of injury severity. While this improves the overall generalizability of our results, future studies investigating a particular class of injury severity (mild, moderate, severe) within a specific cohort (veteran, civilian) with a specific type of injury (blast, penetrating) will be prudent in validating these findings. Third, this dataset did not have accompanied structural

imaging data, which would have provided useful information on atrophy associated hypoperfusion, particularly in TBI.

Conclusion:

In summary, this is the first SPECT imaging study performed at rest and on-task demonstrating the ability to differentiate PTSD from TBI of varying degrees of severity in large patient cohorts with multiple comorbidities using both ROI and visual analysis with a high level of sensitivity, specificity and accuracy. When compared to subjects with TBI, increases were observed in PTSD across areas mediating emotional arousal including the limbic regions, cingulate, basal ganglia, insula, thalamus, prefrontal cortex and temporal lobes. These results suggest that TBI is associated with hypoperfusion while PTSD is associated with regional hyperperfusion in areas associated with emotional regulation, providing important insights regarding pathophysiological differences between the disorders. Replication of this work provides the basis for identification of biomarkers distinguishing TBI from PTSD, and has the potential to yield significant prognostic value in treating veteran, active military and civilian populations.

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Figure Legends:

Figure 1. Proportional Demographics for Group 1. Demographics of Group 1 with number of patients, number of males, number of females and age expressed in absolute numbers, and all other values expressed as percentages.

Figure 2. Proportional Demographics for Group 2. Demographics of Group 2 with number of patients with age expressed in years and all other numbers expressed as percentages.

Figure 3. Brain SPECT Images of Healthy, PTSD, TBI and PTSD Co-morbid with TBI Perfusion Patterns. Top row, underneath surface scans, threshold set at 55%, looking at top 45% of brain perfusion. Bottom row, underneath active scans where blue = 55%, looking at top 45% of brain perfusion, red = 85% and white 93%. Healthy shows full even, symmetrical perfusion with most active area in cerebellum. Classic PTSD shows increased anterior cingulate, basal ganglia and thalamus perfusion. Classic TBI shows multiple areas of low perfusion seen on surface scans (top row). TBI and PTSD show both.

Tables

Table 1: Subject Demographics for Group 1

Variable	PTSD (n=104)	TBI (n=104)	Both PTSD and TBI (n=73)	Healthy (n=116)
Age	36.7 ± 12.9	37.2 ±12.9	40.7 ± 13.8	41.4 ± 17.9
Gender(M/F)	65/39	65/39	36/37	46/70
Race% Caucasian	57	67	66	64
Dementia%	4	5	4	0
Depression%	41	41	41	0
Bipolar%	6	6	6	0
Epilepsy%	5	4	6	0
Schizophrenia%	3	1	3	0
Substance Abuse%	16	16	16	0
ADHD%	58	58	58	0

884
885 **Table 2. TBI Classification for Group 1**
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Severity	Type of Injury	Mode of Injury	Number of Patients
Mild	blunt	accident	18
		assault	5
		fall	14
		sports	17
	penetrating	accident	2
	unknown	unknown	9
Moderate	blunt	accident	4
		assault	1
		fall	5
		sports	1
Severe	blunt	accident	13
		assault	1
		fall	2
		sports	2
Unknown Severity	blunt	accident	1
		assault	1
		fall	2
		sports	1
	unknown	unknown	5

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Table 3. TBI Classification with Comorbid PTSD for Group 1

Severity	Type of Injury	Mode of Injury	Number of Patients
Mild	blunt	accident	20
		assault	5
		fall	8
		sports	8
		unknown	1
	unknown	accident	1
		unknown	4
Moderate	blunt	accident	3
		assault	1
		fall	1
		sports	2
	penetrating	assault	1
Severe	blunt	accident	5
		assault	1
		fall	1
		sports	1
Unknown Severity	blunt	accident	3
		assault	2
		fall	1
		sports	2
	unknown	accident	1
		unknown	1

Table 4. Subject Demographics for Group 2

Variable	PTSD (n=1077)	TBI (n=7505)	Both PTSD and TBI (n=1017)	Neither PTSD or TBI (n=11147)
Age	40.7 ± 13.9	40.5 ± 15.6	41.9 ± 13.7	40.6 ± 16.5
Gender% Male	35	66	46	46
Race% Caucasian	69	68	73	65
Depression%	51	31	40	42
Bipolar%	12	7	13	8
Epilepsy%	1	1	2	1
Schizophrenia%	2	3	2	2
Drug abuse%	5	19	23	16
ADHD%	50	58	59	45

Table 5. Group 1 ROC Analysis of Task vs. Rest Scans
Comparison of Quantitative ROIs with Visual Readings (VR)

Group 1 ROC Analysis (ROI/VR) (%)		TBI from PTSD	PTSD From Co-Occurrence	TBI from Co-Occurrence	TBI from Control	PTSD from Control	Co-Occurrence from Control
Sensitivity on-Task		100/100	100/84	100/100	100/100	100/100	100/100
Sensitivity at Rest		100/86	100/82	100/84	100/100	100/100	100/100
Specificity on-Task		100/100	100/80	100/100	100/100	100/100	100/100
Specificity at Rest		100/81	100/80	100/76	100/100	100/100	100/100
Accuracy on-Task		100/100*	100/90	100/100*	100/100*	100/100*	100/100*
	(p-value, 95% C.I.)		.00, .85-.95				
Accuracy at Rest		100/94	100/92	100/89	100/100*	100/100*	100/100*
	(p-value, 95% C.I.)	.00, .89-.97	.00, .88-.96	.00, .83-.93			

* p = .000, 95% C.I. = [1-1]

Table 6. Group 2 ROC Analysis of Task vs. Rest Scans
Comparison Quantitative ROIs with Visual Readings (VR)

Group 2 ROC Analysis (ROI/VR) (%)		TBI from PTSD	PTSD from Co-Occurrence	TBI from Co-Occurrence	PTSD from Control	TBI from Control	Co-Occurrence from Control
Sensitivity on-Task		82/80	70/70	70/70	70/70	70/67	70/70
Sensitivity at Rest		80/80	70/70	70/70	70/70	70/70	70/70
Specificity on-Task		60/61	61/61	55/56	58/55	54/58	58/57
Specificity at Rest		62/60	60/62	55/56	54/54	54/54	60/59
Accuracy on-Task		78/78	73/71	68/69	68/67	66/66	70/69
	(p-value, 95% C.I.)	.00, .76-.80/.00, .77-.80	.00, .71-.75/.00, .69-.74	.00, .66-.70/.00, .67-.71	.00, .65-.69/.00, .66-.70	.00, .65-.67/.00, .65-.67	.00, .68-.72/.00,.67-.71
Accuracy at Rest		78/77	72/71	68/68	67/66	67/66	70/69
	(p-value, 95% C.I.)	.00, .77-.80/.00, .75-.79	.00, .69-.74/.00, .69-.74	.00, .66-.70/.00, .66-.70	.00, .65-.69/.00, .65-.68	.00, .66-.68/.00, .65-.67	.00 .69-.72/.00, .67-.71

Table 7. Regional Increases in rCBF that Differentiate PTSD from TBI using ROI Analysis

Table 7. Regional increases in rCBF that differentiate PTSD from TBI using ROI analysis				
Brain Region	**Group 1: TBI vs PTSD At Rest**	**Group 1: TBI vs PTSD On-Task**	**Group 2: TBI vs PTSD At Rest**	**Group 2: TBI vs PTSD On-Task**
Limbic	Amygdala	Amygdala	Amygdala	Amygdala
	Hippocampus	Hippocampus	Hippocampus	Hippocampus
	Ant Cingulate Cortex	Ant Cingulate Cortex	Ant Cingulate Cortex	Ant Cingulate Cortex
	Mid Cingulate Cortex	Mid Cingulate Cortex	Mid Cingulate Cortex	Mid Cingulate Cortex
	Post Cingulate Cortex	Post Cingulate Cortex	Post Cingulate Cortex	Post Cingulate Cortex
	Thalamus	Thalamus	Thalamus	Thalamus
Basal Ganglia	Caudate	Caudate	Caudate	Caudate
	Putamen	Putamen	Putamen	Putamen
Insula	Insula	Insula	Insula	Insula
Prefrontal Cortex	Inferior Orbits	Inferior Orbits	Inferior Orbits	Inferior Orbits
	Operculum	Operculum	Operculum	Operculum
Temporal Lobes	Middle Temporal Lobe	Middle Temporal Lobe	Middle Temporal Lobe	Middle Temporal Lobe
	Superior Temporal Lobe	Superior Temporal Lobe	Superior Temporal Lobe	Superior Temporal Lobe
	Temporal Poles	Temporal Poles	Temporal Poles	Temporal Poles
Cerebellum	Anterior Cerebellum	Anterior Cerebellum	Anterior Cerebellum	Anterior Cerebellum

Table 8. Regional Increases in rCBF that Differentiate PTSD from TBI using Visual Readings (VR)

Table 8. Regional increases in rCBF that differentiate PTSD from TBI using Visual Readings				
Brain Region	**Group 1: TBI vs PTSD At Rest**	**Group 1: TBI vs PTSD On-Task**	**Group 2: TBI vs PTSD At Rest**	**Group 2: TBI vs PTSD On-Task**
Limbic	Amygdala	Amygdala	Amygdala	Amygdala
	Hippocampus	Hippocampus	Hippocampus	Hippocampus
	Ant Cingulate Cortex	Ant Cingulate Cortex	Ant Cingulate Cortex	Ant Cingulate Cortex
	Mid Cingulate Cortex	Mid Cingulate Cortex	Mid Cingulate Cortex	Mid Cingulate Cortex
	Thalamus	Thalamus	Thalamus	Thalamus
Basal Ganglia		Caudate	Caudate	Caudate
Insula	Insula			
Prefrontal Cortex	Inferior Orbits	Inferior Orbits	Inferior Orbits	Inferior Orbits
	Ant Lateral Prefrontal Cortex	Ant Lateral Prefrontal Cortex	Ant Lateral Prefrontal Cortex	Ant Lateral Prefrontal Cortex
			Pole prefrontal cortex	Pole prefrontal cortex
Temporal Lobes	Temporal Poles	Temporal Poles	Temporal Poles	Temporal Poles
	Ant Lateral Temporal Lobe	Ant Lateral Temporal Lobe	Ant Lateral Temporal Lobe	Ant Lateral Temporal Lobe
			Mid Lateral Temporal Lobe	Mid Lateral Temporal Lobe
			Post Lateral Temporal Lobe	Post Lateral Temporal Lobe
Cerebellum	Cerebellum	Cerebellum	Cerebellum	Cerebellum
Occipital Lobe			Occipital Lobe	Occipital Lobe
Parietal Lobe			Parietal Lobe	Parietal Lobe

Tables 7-8 legend**:** PTSD shows increased rCBF in the limbic centers, basal ganglia, insula, prefrontal cortex, temporal lobes, cerebellum, occipital lobe and parietal lobe as compared to TBI both at rest and during a concentration task in Groups 1 and 2 using (7) ROI analysis and (8) visual readings. Legend for Abbreviations: Ant = Anterior; Lat = Lateral; Mid = Middle; Post = Posterior.