NeuroImage: Clinical 8 (2015) 543–553

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Disruption of caudate working memory activation in chronic blast-related traumatic brain injury

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ARTICLE INFO

Article history:
Received 29 March 2015
Received in revised form 29 April 2015
Accepted 30 April 2015
Available online 8 May 2015

Keywords:
Traumatic brain injury
fMRI
Cortical plasticity
Working memory
Concussion
Veteran

ABSTRACT

Mild to moderate traumatic brain injury (TBI) due to blast exposure is frequently diagnosed in veterans returning from the wars in Iraq and Afghanistan. However, it is unclear whether neural damage resulting from blast TBI differs from that found in TBI due to blunt-force trauma (e.g., falls and motor vehicle crashes). Little is also known about the effects of blast TBI on neural networks, particularly over the long term. Because impairment in working memory has been linked to blunt-force TBI, the present functional magnetic resonance imaging (fMRI) study sought to investigate whether brain activation in response to a working memory task would discriminate blunt-force from blast TBI. Twenty-five veterans (mean age = 29.8 years, standard deviation = 6.01 years, 1 female) who incurred TBI due to blast an average of 4.2 years prior to enrollment and 25 civilians (mean age = 27.4 years, standard deviation = 6.68 years, 4 females) with TBI due to blunt-force trauma performed the Sternberg Item Recognition Task while undergoing fMRI. The task involved encoding 1, 3, or 5 items in working memory. A group of 25 veterans (mean age = 29.9 years, standard deviation = 5.53 years, 0 females) and a group of 25 civilians (mean age = 27.3 years, standard deviation = 5.81 years, 0 females) without history of TBI underwent identical imaging procedures and served as controls. Results indicated that the civilian TBI group and both control groups demonstrated a monotonic relationship between working memory set size and activation in the right caudate during encoding, whereas the blast TBI group did not ($p < 0.05$, corrected for multiple comparisons using False Discovery Rate). Blast TBI was also associated with worse performance on the Sternberg Item Recognition Task relative to the other groups, although no other group differences were found on neuropsychological measures of episodic memory, inhibition, and general processing speed. These results could not be attributed to caudate atrophy or the presence of PTSD symptoms. Our results point to a specific vulnerability of the caudate to blast injury. Changes in activation during the Sternberg Item Recognition Task, and potentially other tasks that recruit the caudate, may serve as biomarkers for blast TBI.

1. Introduction

Mild traumatic brain injury (TBI) is typically defined as a loss of consciousness (LOC) up to 30 min, posttraumatic amnesia (PTA) not exceeding 24 h, or any period of confusion or disorientation associated with a non-penetrating head injury (Kristman et al., 2014) in which a patient presents for health care with a Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) score of 13–15. A moderate TBI is defined by PTA up to 7 days and loss of consciousness up to 24 h. Both mild and moderate TBI (TBI) can have long term consequences on cognition (Vanderploeg et al., 2005; Salmond et al., 2006; Ruttan et al., 2008; Silver et al., 2009). The most commonly studied type of TBI results from blunt-force trauma encountered in falls, vehicle accidents, contact sports, and assaults (Andriessen et al., 2011). Diffuse axonal injury, which occurs when the brain accelerates and decelerates within the

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http://dx.doi.org/10.1016/j.nicl.2015.04.024

skull (Adams et al., 1989), is considered to be the primary mechanism of blunt-force TBI.

In contrast, the most common type of TBI in military personnel is the result of exposure to improvised explosive devices and grenades. TBI, largely due to blast exposure, has been estimated to occur in 15–30% of service personnel (Hoge et al., 2008; Tanelian and Jaycox, 2008). Blast explosions can result in several types of injury: primary blast resulting from changes in pressure within the brain that lead to injury; secondary blast caused by contact with external objects that are animated by the blast; and tertiary blast occurring when the õindividual is thrown against an external surface, such as the ground or a wall. Any other injury resulting from the explosion, e.g., burns, is referred to as a quaternary blast. While the mechanisms behind secondary and tertiary blast TBI are similar to those found in non-blast settings, less is known about the effects of primary blast on the brain.

Blast explosions are associated with transient increases in air pressure (overpressure) that produce a dose dependent increase in intracranial pressure (Saljo et al., 2009), and have been linked to neuronal injury, hemorrhage, and edema (Cernak et al., 2001; Saljo et al., 2011). Blast has also been associated with acceleration of the brain (Courtney and Courtney, 2011; Goldstein et al., 2012; Sosa et al., 2013). Animal studies of primary blast TBI have revealed a variety of types of damage to structures. Molecular changes have been reported in the thalamus, hypothalamus, and hippocampus in mice (Woods et al., 2013), as well as cell death in the nucleus accumbens in rats (Sajja et al., 2013). In the brainstem, activated microglia, indicators of neuroinflammation, have been found in the substantia nigra of rats exposed to blast (Readnower et al., 2010), consistent with loss of dopaminergic neurons in the substantia nigra of rats with non-blast TBI (Hutson et al., 2011). However, less is known about pathological changes subsequent to blast-related TBI in humans. For example, the brainstem may be equally or even more vulnerable to the effects of blast (Taylor and Ford, 2009; Yeh et al., 2014) than the frontal and temporal regions associated with blunt-force TBI. These regional differences between blast and blunt-force injuries may influence the pattern of neural and cognitive sequelae of TBI.

Studies that have directly compared blast and blunt-force TBI on symptom, neurocognitive, and psychiatric measures have typically reported no differences between the groups (Kennedy et al., 2010; Belanger et al., 2011; Luethcke et al., 2011; Cooper et al., 2012; Mendez et al., 2013; Dretsch et al., 2014; Mac Donald et al., 2014). In one study (Lippa et al., 2010), veterans with blast TBI endorsed elevated cognitive symptoms on the Neurobehavioral Symptom Inventory (NSI) (Cicerone and Kalmar, 1995), a measure of postconcussion symptoms, approximately 3 years after injury, and the severity of symptoms was similar to those reported by veterans with non-blast TBI; however, the NSI queries general cognitive functioning and may not identify subtle differences. Belanger et al. (2009) administered four standardized tests measuring visual and verbal memories, interference resolution, and IQ to veterans and reported no differences in performance between the two types of TBI.

Another approach to identifying potential differences between blast and blunt-force injuries involves structural brain imaging. Our group found no differences when directly comparing blast and blunt-force TBI groups on the presence of brain lesions and brain region volumes (Fischer et al., 2014). Another study (Jorge et al., 2012) used diffusion tensor imaging (DTI) to investigate changes in white matter in veterans with blast TBI and civilians with blunt-force TBI by measuring fractional anisotropy (FA) of whole white matter tracts and examining heterogeneity in FA, or "potholes". The authors reported no significant group differences when measurements were taken for an entire tract, but civilians with acute blunt-force TBI had more potholes than veterans with blast TBI. In a recent DTI study (Yeh et al., 2014), no white matter differences were found between blast and blunt-force TBI groups in a whole brain diffusion measure; however, when hemispheric asymmetries of FA were examined using tract-based spatial statistics (Smith et al., 2006), the blast TBI group demonstrated more asymmetries than a blunt-force TBI group in tracts extending inferiorly to superiorly. In an autopsy study, identical neuropathology was found in the brains of veterans and mice exposed to blast and athletes with blunt-force TBI (Goldstein et al., 2012).

The strongest evidence for identifying differences between blast and blunt-force TBI comes from functional imaging studies. Patients with blast TBI showed greater hypometabolism on positron emission tomography (PET) than patients with blunt-force TBI in the right superior parietal lobe (Mendez et al., 2013). Within the blast group, higher postconcussive symptom severity scores were related to decreased metabolism in the posterior cingulate cortex, while poorer performance on the Paced Auditory Serial Addition Test (Gronwall, 1977), a task involving sustained attention, cognitive processing speed, and working memory, was associated with hypometabolism in the medial frontal gyrus. In a functional magnetic resonance imaging (fMRI) study using the stop signal activation task, a measure of response inhibition, our group differentiated blast from blunt-force TBI by identifying alterations in an orbitofrontal–striatal inhibitory control circuit more than 4 years after blast exposure (Fischer et al., 2014). When correctly performing the inhibition task, veterans with blast TBI had alterations in activation similar to those in a civilian control group with TBI. However, when failing to inhibit, the blast TBI group demonstrated increased activation in the caudate nucleus, consistent with other studies that link the striatum, particularly the caudate, to successful response inhibition (Li et al., 2008; Ghahremani et al., 2012; Ness and Beste, 2013). Moreover, increased activation was also found in cortical regions that enervate the striatum, the lateral orbitofrontal, anterior cingulate, and inferior temporal gyri (Alexander et al., 1986), suggesting that striatal pathways may be particularly vulnerable to blast injury.

An additional frontostriatal circuit involving the dorsolateral prefrontal cortex (DLPFC) has been closely linked to working memory (Levy et al., 1997), an executive function involved in maintaining and manipulating information in short term memory (Baddeley, 1986). The DLPFC–striatal working memory circuit extends from the DLPFC to the caudate, which in turn projects to other subcortical structures (globus pallidus, brainstem, and thalamus) and then back to the DLPFC. Given the vulnerability of the orbitofrontal–striatal inhibitory control circuit to blast as evidenced by the stop signal task in our previous study (Fischer et al., 2014), we hypothesized that blast injury may also have a selective effect on the DLPFC–striatal working memory circuit. To address this hypothesis, we compared veterans with blast TBI (military TBI; milTBI) and civilians with blunt-force (acceleration–deceleration) TBI (civTBI) performing a working memory task, the Sternberg Item Recognition Task (SIRT) (Sternberg, 1966), during fMRI. Veterans and non-veteran civilians without histories of blast exposure or TBI served as control groups. We also studied the presence of long term neuropsychological sequelae in the TBI groups (Vanderploeg et al., 2005; Lippa et al., 2010). We predicted that the two TBI groups would demonstrate differing activation patterns in working memory circuits.

2. Methods

2.1. Participants

All procedures and recruitment strategies were reviewed and approved by the institutional review boards of the Cleveland Clinic, Baylor College of Medicine (BCM), Louis Stokes Veterans Affairs Medical Center (VAMC) (Cleveland), Michael E. DeBakey VAMC (Houston), and the U.S Department of Defense. Four groups of participants were enrolled: (1) veterans who had been deployed in the Afghanistan and Iraq wars (Operation Enduring Freedom and Operation Iraqi Freedom, OEF–OIF) who had experienced blast-related TBI (milTBI), (2) OEF–OIF veterans who had never experienced blast and/or head injury and who served as controls to the milTBI group (milCON), (3) civilians with TBI (civTBI)

due to sports or motor vehicle accidents, and (4) civilians with orthopedic injuries who served as controls for the civTBI group (civCON). Data were collected at the Cleveland Clinic and BCM. Seventy subjects were studied at the Cleveland Clinic (16 milTBI, 21 milCON, 16 civTBI, and 17 civCON), and 30 subjects were seen at BCM (9 milTBI, 4 milCON, 9 civTBI, and 8 civCON).

The military recruitment pool consisted of all OEF–OIF veterans who had registered for VAMC-related services (not restricted to head injury). Letters were sent to those individuals describing the study and inviting them to participate if they suffered a head injury (milTBI) or served but did not suffer a head injury (milCON). Veterans were also recruited via referral to the study from Michael E. DeBakey VA physicians, ongoing projects, a registry of veterans interested in participating in research, and through advertisements posted at local colleges and in newspapers. In Cleveland, civilian participants were recruited primarily through informational mailings sent from their treating physician at the Cleveland Clinic, and in Houston, civilian participants were recruited from ongoing projects, advertisements, and referrals from friends.

Potential participants initially underwent telephone screening to determine eligibility. Those participants meeting inclusion/exclusion criteria (see below) were invited to undergo neuroimaging. Attempts were made to match the groups on age, gender, education, and, for the TBI participants, time since injury. Please see Table 1. Specific details of the inclusion/exclusion criteria for each group are as follows.

milTBI participants sustained a blast-related TBI during deployment between 1 and 6 years prior to participation in this study. Eligibility for the milTBI group included report of a blast-induced injury that resulted in LOC, a period of PTA, or alteration of consciousness (AOC) following the event. This was assessed via self-report, but with trained interviewers who probed and clarified responses in an attempt to obtain the most accurate information possible. If there was a LOC, it did not exceed 24 h in duration and, if PTA occurred, it did not exceed 7 days. GCS scores were not available. Two milTBI subjects (8%) were characterized as having an injury of moderate severity due, in one case, to a self report of LOC of 150 min after the injury and, in the other case to a report of PTA of approximately 5 days. Moderate classification in both TBI groups was based solely on self-report of LOC/PTA, which is inherently subjective, especially when queried years after injury.

For those participants with repetitive head injuries, the most severe served as the "index injury" for purposes of estimating time since injury. Any subject who reported a TBI during the post-deployment period was excluded.

milCON participants served in active duty within the prior 6 years but had no history of brain injury, blast exposure, or LOC during or prior to their deployment. This group controlled for the nonspecific emotional distress associated with combat. The number of deployments was comparable for the milTBI and milCON groups.

civTBI participants sustained a mild to moderate TBI through common non-blast mechanisms, such as motor vehicle accident or sports-related injuries. Head injury occurred 1–6 years prior to enrollment. Participants were excluded if intracranial injury was seen on prior brain imaging (if available). A GCS score (Teasdale and Jennett, 1974) between 9 and 15 was also an eligibility criterion if available. As with milTBI participants with multiple head injuries, the most severe civTBI served as the "index injury" for estimating time since injury. Duration of LOC and PTA, derived from medical records and self-report, did not exceed 24 h and 7 days, respectively, in 23 subjects (92%). Two civTBI subjects (8%) were characterized as having an injury of moderate severity due, in one case, to a reported PTA of "about one year" and, in the other case, "a couple of weeks after the accident".

civCON participants were chosen to control for nonspecific effects of injury on cognitive and brain imaging data. These participants had no history of brain injury or LOC, and no primary blast exposure. Extracranial injuries were experienced during the previous 6 years and included ligament damage and fractures of the arms and legs due to sports or motor vehicle accidents.

All prospective participants were excluded if any of the following were present: not fluent in English, history of neurologic disorders associated with cerebral dysfunction and/or cognitive deficit (e.g., cerebral palsy, mental retardation, epilepsy), history of severe psychiatric disorder (e.g., bipolar disorder, schizophrenia) with the exception of PTSD, penetrating gunshot wound to the brain or contraindications to undergoing MRI (e.g., pregnancy, metal implants, claustrophobia). Potential participants were also excluded based on significant alcohol and/or drug abuse by administration of the Alcohol Use Disorders Identification Test (AUDIT) (Babor, 2001) (cutoff score < 20) and the Drug Abuse Screening Test-10 (DAST-10) (Skinner, 1982) (cutoff score < 7).

2.2. Self-report measures

The Neurobehavioral Symptom Inventory (NSI) (Cicerone and Kalmar, 1995), determined to be valid and reliable in veterans with blast TBI (King et al., 2012), was administered to characterize commonly self-reported symptoms following concussion. Severity of PTSD symptoms over the past month was measured with the PTSD Checklist — Civilian (PCL-C) version (Weathers et al., 1993). Self-reported depression symptoms were assessed with the Center for Epidemiological Study of Depression Scale (CES-D) (Radloff, 1977). Self-report of pain and fatigue was measured using visual analog scales ranging from 0 to 10.

2.3. Neuropsychological measures

Participants completed a standard battery of neuropsychological tests designed to measure cognitive deficits most commonly associated

Table 1
Demographic, injury, and self-report scales.

	milTBI	milCON	civTBI	civCON	2 × 2 ANOVA		
Variable	(n = 25)	(n = 25)	(n = 25)	(n = 25)	TBI vs CON[a]	mil vs civ[a]	Interaction[a]
Age — yrs	29.8 (6.01)	29.9 (5.53)	27.4 (6.68)	27.3 (5.81)	—	0.039 (mil > civ)	—
Education — yrs	13.1 (1.62)	13.6 (1.75)	14.3 (1.38)	14.2 (2.41)	—	0.021 (civ > mil)	—
Sex — number (%) female	4 (16%)	0	1 (4%)	0	—	—	—
Months since last TBI	50.1 (17.98)	NA	27.1 (15.03)	NA	—	—	—
Number (%) with >1 blast	14 (56%)	NA	NA	NA	—	—	—
Number of deployments	1.82 (0.7)	2.04 (1.6)	NA	NA	—	—	—
PCLC — total	50.9 (17.46)	27.4 (16.70)	25.9 (7.95)	26.6 (10.23)	< 0.001 (TBI > CON)	< 0.001 (mil > civ)	< 0.001 (milTBI > civCON, civTBI, milCON)
CESD — total	19.5 (12.16)	7.9 (9.75)	8.4 (7.60)	9.0 (7.84)	0.004 (TBI > CON)	0.010 (mil > civ)	0.002 (milTBI > civCON, civTBI, milCON)
Pain — total	3.1 (2.63)	0.8 (1.59)	0.8 (1.84)	1.0 (1.87)	0.009 (TBI > CON)	0.015 (mil > civ)	0.003 (milTBI > civCON, civTBI, milCON)
Fatigue — total	4.2 (2.94)	2.4 (2.38)	1.9 (2.33)	2.8 (2.60)	—	—	0.011 (milTBI > civTBI)
NSI — total	32.5 (14.82)	10.0 (13.63)	11.9 (10.31)	10.2 (10.83)	< 0.001 (TBI > CON)	< 0.001 (mil > civ)	< 0.001 (milTBI > civCON, civTBI, milCON)

TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, PCLC = PTSD Checklist - Civilian Version, CESD = Center for the Epidemiological Study of Depression Scale, NSI = Neurobehavioral Symptom Inventory. – = not significant. Mean (SD).
[a]p-Value (pairwise post hoc analysis).

with TBI. The battery included measures of processing speed, executive function, and memory: written and oral forms of the Symbol Digit Modalities Test (SDMT) (Smith, 1982), parts A and B of the Trail Making Test (TMT) (Reitan, 1958), Controlled Oral Word Association Test (COWAT) (Benton et al., 1983), and the California Verbal Learning Test-II (CVLT-II) (Delis et al., 2000).

2.4. Sternberg Item Recognition Task

The Sternberg working memory task (Sternberg, 1966) consisted of a total of 72 trials distributed over three imaging runs. A schematic of the task is presented in Fig. 1. During the Encode phase, participants were asked to commit to memory 1, 3, or 5 consonants (set size, SS) over a 1800 ms interval. The number of encoded items constituted the working memory load, or set size, with 24 trials for each set size; trials were pseudo-randomized across set size. To maintain the same amount of visual information across the set sizes, asterisks were used to replace letters for set sizes 1 and 3 (see Fig. 1). Immediately following the Encode phase, participants viewed a centrally fixated "+" for 4300 ms (Maintenance phase). This was followed by the Response phase, in which a single probe letter appeared on the screen for 2800 ms. On 50% of trials, the probe letter matched one of the items presented during the Encode phase. Participants were instructed to respond with one of two fingers if the probe letter matched a letter in the Encode stimulus and with the other finger if the target did not match. The inter-trial interval consisted of a centrally fixated "+" that varied in duration from 3830 to 14,330 ms to introduce jitter into the time series for the analysis of this event-related fMRI task. The task was programmed using E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA) and displayed in the scanner using a back-projection video system (Cleveland: Avotec Inc., Stuart, FL; BCM: Sharp USA, Mahwah, NJ). To ensure that participants understood how to perform the task, individual training sessions were provided prior to the scan, and all subjects reached a criterion of 80% accuracy on SS1 during all runs.

2.5. MR image acquisition

Scanning was conducted at the Cleveland Clinic and Houston sites using a Siemens TIM Trio 3 T MRI scanner (Erlangen, Germany) equipped with a 12-channel receive-only head coil. Whole-brain fMRI scans were acquired with a gradient-echo, echoplanar (EPI) pulse sequence [31 4-mm thick contiguous axial slices, TE = 29 ms; TR = 2800 ms, flip angle (FA) = 80°; FOV = 256 × 256 mm; matrix = 128 × 128; in-plane resolution = 2 × 2 mm]. The EPI sequence at the Cleveland Clinic was modified to store the full 24-bit acquisition, but otherwise scanning at the Houston sites and the Cleveland Clinic were identical. The SIRT was performed over three imaging runs, each lasting a total of 585 s (209 volumes per imaging run). High resolution structural MRI scans [T1 with T1-weighted inversion recovery turboflash (MPRAGE), 120 axial slices, thickness 1–1.2 mm, FOV = 256 × 256, TI/TE/TR/FA 900 ms/1.71 ms/1900 ms/80, matrix 256 × 128, receiver band width (BW) 62 kHz] were acquired for registration with lower resolution EPI images. To facilitate combining data across sites, experienced MR physicists (MJL and EB) set up and tested identical MRI protocols at both sites. Comparison of acquired phantom data indicated similar image quality and signal-to-noise ratio. Frequent quality assurance scans were performed at each institution to ensure that imaging data were free of scanner artifacts and comparable across sites.

2.6. Image analysis (structural MRI)

All structural MRI scans were reviewed for TBI-related and incidental pathology by board-certified neuroradiologists (RA and SEJ). Quantitative regional brain volumes were obtained using the parcellation method incorporated in Freesurfer 5.1 software (http://freesurfer.net/fswiki) using the Desikan atlas (Desikan et al., 2006). Results for each participant were visually inspected by a single rater to ensure accuracy of the cortical surface reconstruction. Manual editing, where necessary, was performed to optimize accuracy. The surface inaccuracies involving skull stripping or frank exclusion of brain parenchyma were edited either by (1) adding control points to aid FreeSurfer in the identification of white matter (since it uses the WM/GM boundary as a starting place for reconstructing the pial surface), (2) by fixing the skull strip by removing remaining dura, or (3) by adding back in the sections of brain that were inadvertently automatically removed. Correction for intracranial volume (ICV) was achieved by dividing the volume of interest by ICV and multiplying by 100.

2.7. Image analysis (fMRI)

The first 4 pre-steady-state volumes of the EPI time series were removed. The remaining images were time-shifted, motion corrected, and spatially filtered using a 2D 4 mm full width at half maximum (FWHM) Gaussian filter in the Fourier domain. A deconvolution analysis was used to extract the hemodynamic response function (HRF) to the task for each of the set sizes (SS1, SS3, and SS5). For data reduction purposes, the analysis for this study focused on the Encode phase, which was characterized by the sum of the HRF points 2.8 and 5.6 s post stimulus onset. Individual subject Encode t-maps for SS1, SS3, and SS5 trial types were converted to z-maps and transformed to Talairach stereotaxic space (Talairach and Tournoux, 1988). Because brain activity during errors can be different than that during correct responses, to report brain activation that corresponds with working memory processing, events for which responses were errors were omitted from analysis.

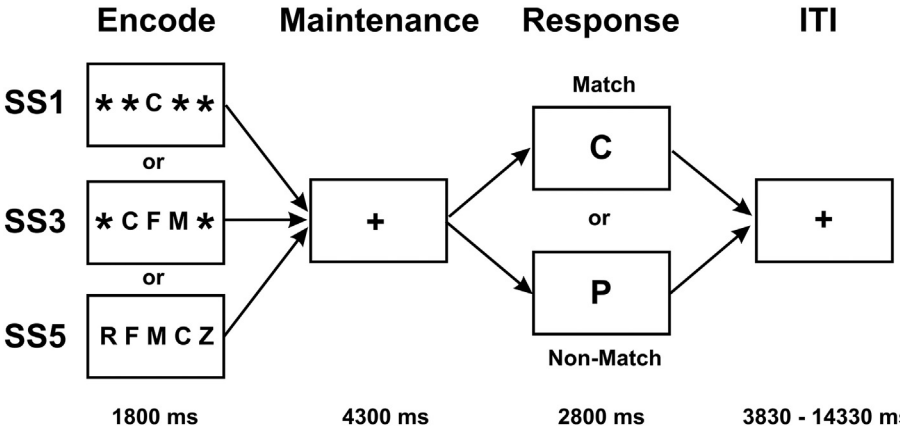

Fig. 1. Schematic of the encoding, maintenance, and response events in the Sternberg Item Recognition Task. ITI = inter-trial interval; SS = set size.

Results in the functional regions of interest (fROI) were defined by brain regions that demonstrated working memory load effects during the Encode phase. T-maps of load effect were generated for each of the four groups (milTBI, milCON, civTBI, and civCON). A significant cluster was defined by an individual voxel probability ($p < 0.005$) and a minimum cluster size (0.684 ml), for an overall family-wise error of $p < 0.05$. A disjunction mask was created by combining the suprathreshold voxels from the group t-maps. Large fROIs were divided along local minima in the averaged t-maps. Within each fROI and set size, z-statistics were averaged for each subject.

For each fROI, a 3 (SS1, SS3, and SS5) × 2 (TBI/CON) × 2 (mil/civ) ANOVA was conducted. The within-subject factor was set size and between subject factors were TBI/CON and mil/civ. False discovery rate (FDR) was used to correct for multiple comparisons. For those two-way (TBI/CON × Load; mil/civ × Load) and three-way (TBI/CON × mil/civ × Load) interactions surviving the FDR correction, Tukey B post hoc analyses were used to identify which groups contributed to the significant interaction. Finally, to examine the specificity of the role of any regions distinguishing military from civilian TBI groups, exploratory analyses were conducted that related regions that were significant in the three-way ANOVA to SIRT performance and neuropsychological variables. To understand the role of potential neurodegeneration, significant regions were also related to time since injury.

3. Results

The final sample consisted of 100 participants, with 25 in each group (see Table 1). No significant group differences in gender were observed, with the majority of the participants being male. The military groups were older by 2 years ($p = 0.039$) and reported a year less education ($p = 0.021$) than the civilian groups. Time since the most severe injury was significantly longer for milTBI than civTBI participants ($p = 0.001$). For the milTBI group, 11 participants (44% of the sample) had been exposed to a single blast event, 5 (20%) reported 2 blast exposures, and the remaining 9 (36%) reported multiple blast exposures (range 3–20).

3.1. Self-report measures

Participants in the milTBI group endorsed significantly more concussion-related symptoms (NSI), posttraumatic stress disorder (PTSD) (PCL-C), depression (CES-D), and pain compared to the participants in the three other groups (Table 1). The milTBI group also reported significantly more fatigue relative to the civTBI group.

3.2. Neuropsychological and Sternberg performance

Two-way (TBI/CON vs. mil/civ) ANOVAs were conducted on each neuropsychological test (Table 2). No differences in performance were identified between the groups for the neuropsychological measures.

Behavioral performance on the SIRT was measured in terms of accuracy and reaction time. Responses that were errors were excluded from analyses. Overall accuracy, collapsed across set sizes, had a significant group effect, with the milTBI group showing the lowest accuracy rates. At the most difficult working memory condition (SS5), the milTBI group was less accurate than the other three groups (milCON, civTBI, civCON) (see Fig. 2). Despite these group differences, all four groups performed well above chance (50%).

Analysis of reaction time was conducted in three different ways. First, the average reaction time was calculated across all set sizes. There were no significant differences between the means of overall reaction time between the groups. Second, the reaction times were analyzed for each individual set size (see Table 2 and right panel of Fig. 2). At SS1, the TBI groups (civTBI and milTBI) were significantly slower than the control groups (civCON and milCON). Finally, a linear regression was fit for each subject, with reaction time as the dependent variable and set size as the independent variable. From this regression, the slope and intercept were extracted and compared using a 2 × 2 ANOVA. The average intercept of the TBI groups was significantly greater than the average intercept of the control groups (Table 2). No significant group differences were observed for slope.

3.3. Structural MRI

None of the participants had lesions consistent with TBI on conventional MRI. Groups did not differ on gray matter, white matter, or cerebrospinal fluid whole brain volumes (Table 2). No significant group differences were observed following False Discovery Rate correction for individual cortical and subcortical volumes and cortical thickness measures (Supplementary Tables 2–4).

3.4. fMRI

The disjunction analysis identified 25 Encode fROIs that demonstrated differential activation based on set size (Fig. 3 and Supplementary Table 1). As noted above, all fROIs were analyzed for set size by group effects using a 3 × 2 × 2 ANOVA. False discovery rate was used to control for multiple comparisons. None of the regions had a significant interaction

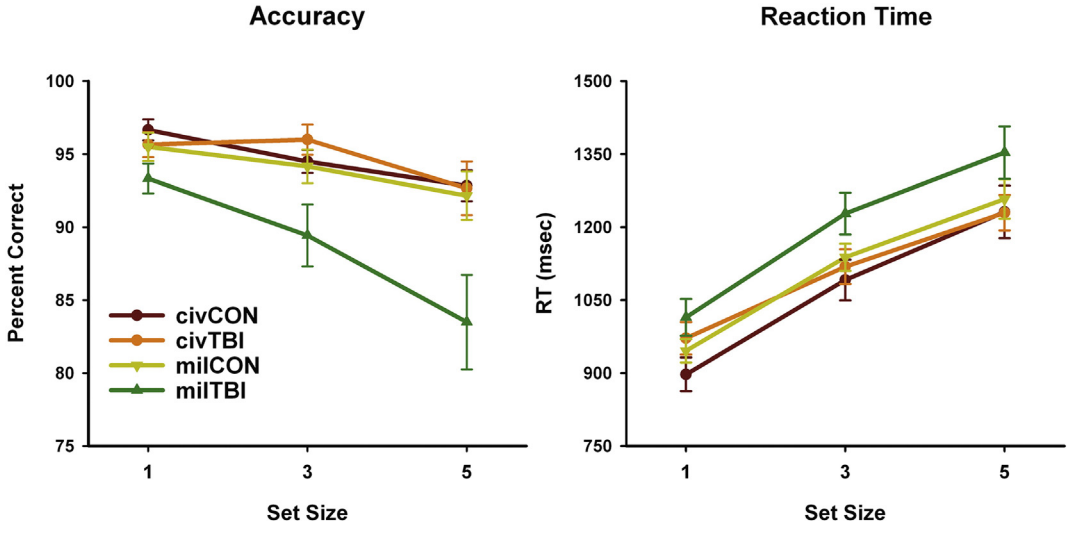

Fig. 2. Accuracy and reaction time as a function of memory set size, or load, for each group. For load 3, the military TBI subjects were significantly less accurate than the civilian TBI subjects and civilian control subjects. For load 5, the military TBI subjects were significantly less accurate than all other three groups, which did not differ from each other.

Table 2
Neuropsychological testing, Sternberg task performance, and whole brain volumes.

Variable	milTBI	milCON	civTBI	civCON	2 × 2 ANOVA		
					TBI vs CON[b]	mil vs civ[b]	Interaction[b]
Neuropsychological testing							
Trails A — sec	25.6 (9.6)[a]	23.5 (4.6)	23.6 (5.7)	25.8 (11.0)	—	—	—
Trails B — sec	71.0 (40.7)	60.2 (24.9)	57.8 (19.1)	76.2 (44.0)	—	—	—
Trails B—A — sec	45.3 (35.8)	36.6 (22.7)	34.2 (18.5)	50.4 (41.1)	—	—	—
CVLT short delay — total	10.8 (3.2)	10.1 (3.1)	11.5 (2.0)	10.7 (2.9)	—	—	—
CVLT long delay — total	10.5 (3.6)	10.5 (2.8)	11.9 (2.0)	10.8 (2.9)	—	—	—
SDMT — written correct	51.5 (10.9)	57.0 (8.1)	58.9 (13.8)	57.0 (10.6)	—	—	—
SDMT — oral correct	58.8 (11.3)	64.2 (11.9)	64.0 (12.7)	65.7 (14.2)	—	—	—
Sternberg task							
Accuracy — % (SD)							
Set size 1	93.3 (5.1)	95.5 (4.8)	95.7 (4.2)	96.7 (3.6)	—	—	—
Set size 3	89.4 (10.6)	94.2 (5.8)	96.0 (5.2)	94.5 (3.9)	—	0.014 (mil < civ)	0.025 (milTBI < civCON, civTBI)
Set size 5	83.5 (16.2)	92.2 (8.3)	92.7 (9.2)	92.8 (5.3)	0.038 (TBI < CON)	0.021 (mil < civ)	0.047 (milTBI < civCON, civTBI, milCON)
Overall	88.8 (8.4)	93.9 (4.6)	94.8 (4.5)	94.7 (3.0)	0.023 (TBI < CON)	0.003 (mil < civ)	0.018 (milTBI < civCON, civTBI, milCON)
Reaction time — ms (SD)							
Set size 1	1014.4 (189.0)	945.7 (119.6)	971.5 (167.0)	897.3 (174.3)	0.032 (TBI > CON)	—	—
Set size 3	1227.9 (214.8)	1137.9 (139.2)	1118.7 (179.1)	1091.4 (209.0)	—	0.041 (mil > civ)	—
Set size 5	1353.2 (270.1)	1257.7 (202.6)	1229.7 (182.7)	1231.3 (270.3)	—	—	—
Average	1198.5 (209.9)	1113.8 (133.6)	1106.6 (159.1)	1073.3 (207.3)	—	—	—
Reaction time — intercept	944.4 (193.4)	879.8 (134.3)	913.0 (180.7)	822.9 (164.4)	0.025 (TBI > CON)	—	—
Reaction time — slope	84.7 (46.5)	78.0 (45.7)	64.5 (35.9)	83.5 (41.0)	—	—	—
Whole brain volumes[c]							
Gray matter	35.37 (2.30)	35.74 (2.71)	36.83 (3.46)	36.83 (2.57)	—	—	—
White matter	45.75 (2.49)	46.89 (4.05)	48.82 (4.65)	48.3 (2.99)	—	—	—
Cerebrospinal fluid	0.08 (0.02)	0.08 (0.01)	0.09 (0.02)	0.08 (0.01)	—	—	—

TBI = traumatic brain injury, CON = controls, mil = military, civ = civilian, COWAT = Controlled Oral Word Association Test, CVLT = California Verbal Learning Test, SDMT = Symbol Digit Modalities Test, — = not significant.
[a]Mean (SD).
[b]*p*-Value (pairwise post hoc analysis).
[c]mm^3, corrected for intracranial volume.

effect between military service (mil vs. civ) and working memory load (Table 3).

Seven regions demonstrated significant interaction effects of working memory load and the presence/absence of a TBI (Table 3 and Fig. 4). These included 3 cortical regions (left insula/inferior frontal gyrus, bilateral middle orbital frontal gyrus, and right middle occipital gyrus), 3 subcortical regions (right head/body of the caudate, right tail of the caudate, and left caudate/putamen/pallidum), and the cerebellar vermis. In 5 regions (left insula/inferior frontal gyrus, right head/body of the caudate, right tail of the caudate, left caudate/putamen/pallidum, and cerebellar vermis), the two non-injured control groups demonstrated a monotonic increase in fMRI signal intensity with increasing load; the two TBI groups failed to demonstrate this monotonic increase (Fig. 4). In 2 regions (bilateral middle orbital frontal gyrus, and right middle occipital gyrus), the two control groups demonstrated a decrease in activation ("deactivation")

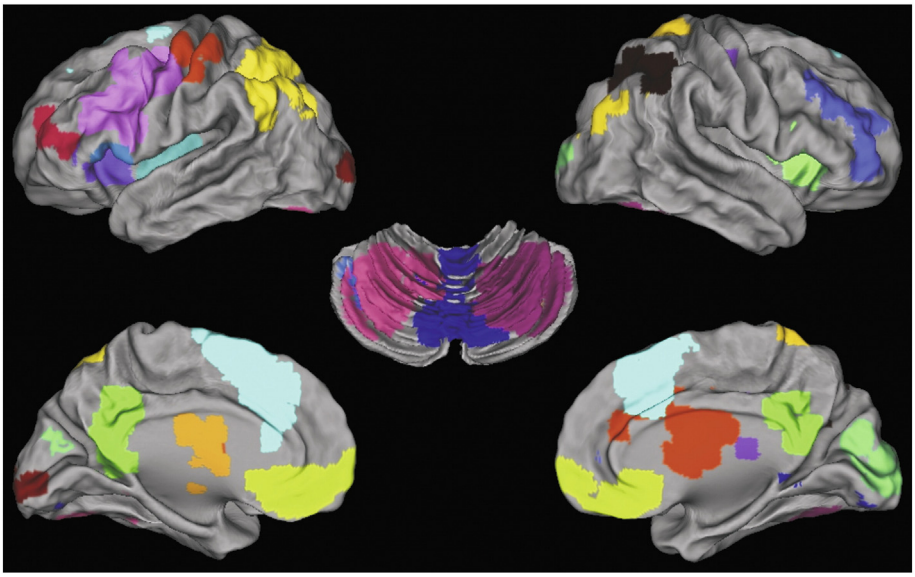

Fig. 3. Regions that showed a load effect (i.e., greater activation in load 5 than load 3, and greater activation in load 3 than load 1) in all four groups during Encode events.

Table 3
Regions demonstrating significant two- and three-way interactions with WM load.

#	Side	Region	BA	Tailarach coordinates			Vol (ml).	TBI/CON * Load	mil/civ * Load	TBI/CON * mil/civ * Load
				x	y	z				
1	L	Insula, inf. frontal gyrus	45	−32	22	4	4.0	*	—	—
2	B	Mid. orbital gyrus	12	0	42	−10	4.9	*	—	—
3	R	Angular gyrus	39	50	−74	29	1.7	*	—	—
4	R	Caudate (head, body)	—	16	9	18	12.3	*	—	*
5	R	Caudate (tail)	—	23	−22	28	2.9	*	—	*
6	L	Caudate (head), putamen, pallidum	—	−18	−2	14	9.0	*	—	—
7	B	Cerebellar vermis	—	2	−63	−24	7.2	*	—	—

*$p < 0.05$.

at SS3; in contrast, the TBI groups did not demonstrate deactivation at SS3 (Fig. 4).

Two regions demonstrated 3-way interactions: right tail of the caudate and right head/body of the caudate (see row 3, middle and rightmost graphs in Fig. 4). In both of these ROIs, activation in the milTBI group did not change with working memory load, whereas the three other groups demonstrated a monotonic increase associated with working memory load. Effects were still significant after covarying for age, education, PTSD, depression, pain, and fatigue (Supplementary Table 5) and after removing subjects with moderate TBI.

3.5. Relation of SIRT performance, neuropsychological, and post-injury interval to caudate activation

Exploratory analyses revealed that activation of the right caudate head/body was significantly related to reaction time slope in the civilian

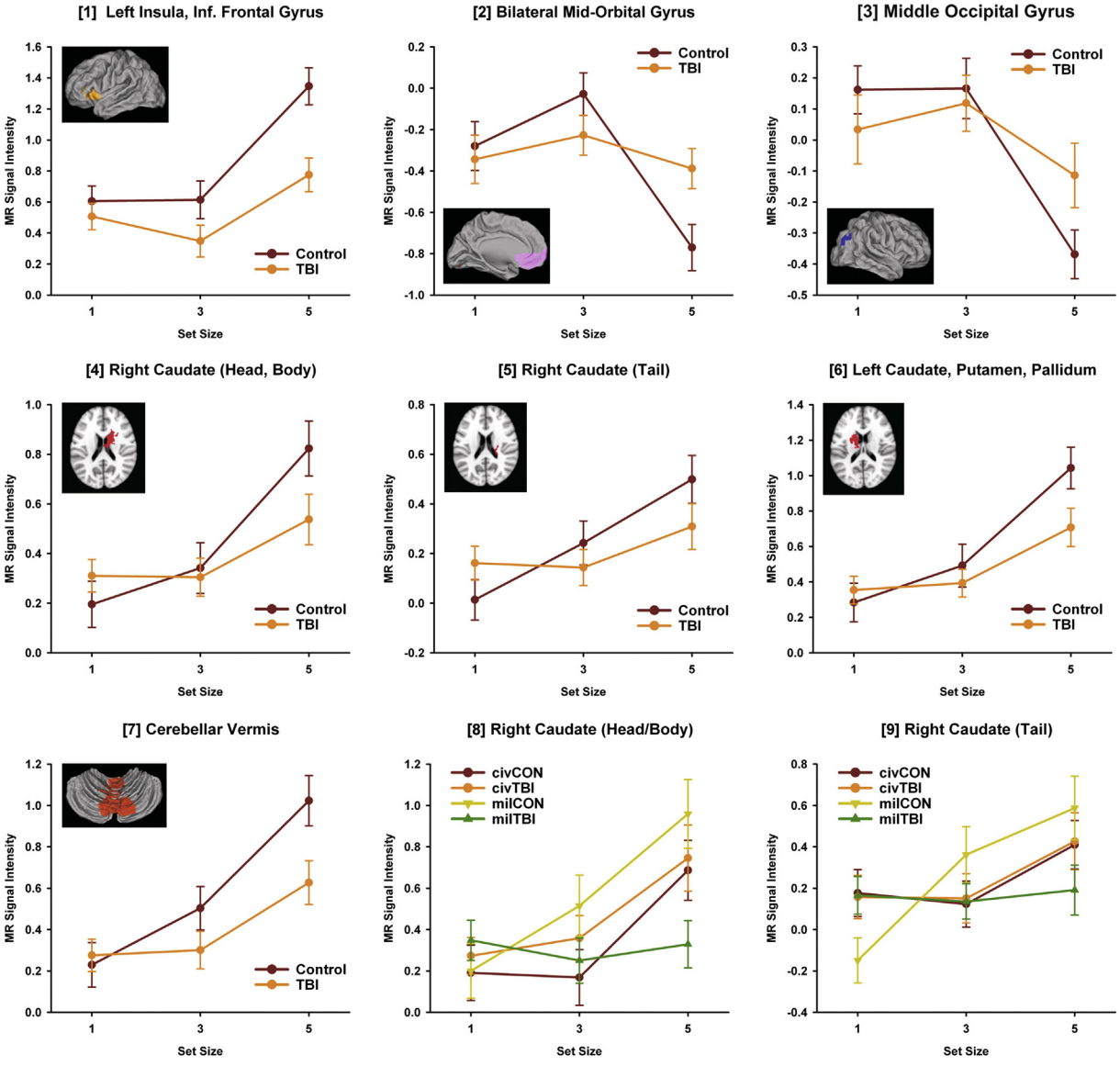

Fig. 4. Significant two-way interactions (1–7) between group (control vs. TBI) and set size (1, 3, 5) and significant three-way interactions (8–9) between group (control vs. TBI), set size (1, 3, 5) and military status (military vs. control).

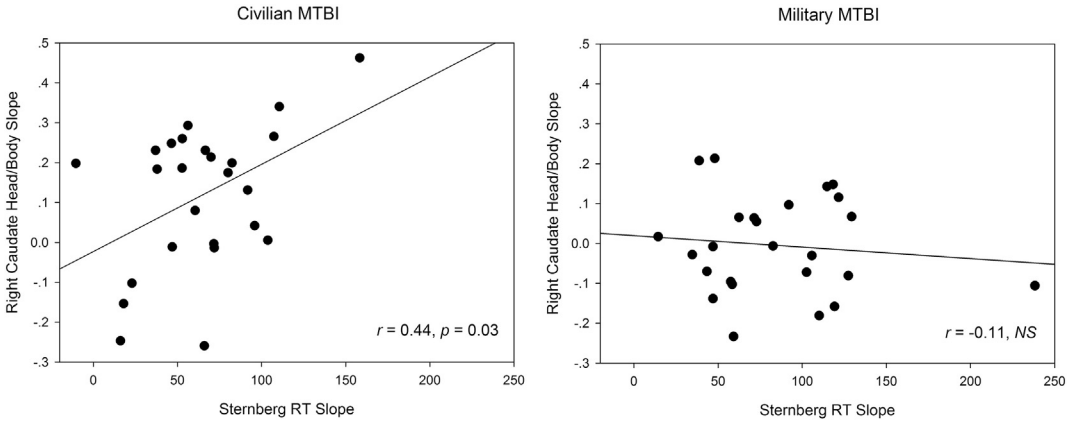

Fig. 5. Slopes for activation in the right caudate head/body and reaction time were positively correlated in the civilian TBI group, but not in the military TBI group, suggesting a dissociation between the two groups.

TBI group ($p < 0.029$), while no region was related to reaction time slope or any other task performance measure in the military TBI group (Fig. 5). Conversely, the military TBI group showed significant or marginally significant negative relations between caudate activation and two DSM-IV clusters of PTSD, re-experiencing ($p = 0.047$) and avoidance ($p = 0.054$), in addition to a pain measure ($p = 0.068$), that were not observed in the civilian TBI group. Regarding post-injury interval, there were no significant relations with caudate in either TBI group; however, the military TBI group showed a negative relation between post-injury interval and slope of activation in bilateral middle orbital gyri, a region that was significant in the two-way (Group × Set Size) interaction.

3.6. Number of blasts

Fourteen of 25 military TBI subjects (56%) were exposed to two or more blasts. Subjects with one blast were compared to those who had experienced two or more blasts on all outcome measures and encoding activation. Except for pain, which was significantly greater in subjects with two or more blasts, all results were NS (Supplementary Tables 6 and 7).

4. Discussion

Our fMRI study provides support for the hypothesis that the basal ganglia, in particular the caudate nucleus, may be specifically vulnerable to the effects of blast injury. The blast TBI group (milTBI), in contrast to the blunt-force TBI group (civTBI) and both control groups, failed to demonstrate a monotonic relation between set size and activation in the caudate nucleus (head, body, tail). The lack of a monotonic effect in the blast TBI group could not be attributed to working memory errors, since these trials were removed from the image analyses. Notably, reduced activation in the caudate in the blast TBI group was significant even when age, education, PTSD, depression, fatigue, and pain symptoms were taken into account.

The caudate has long been implicated in verbal working memory. Set size effects have previously been found in the caudate of healthy subjects (Braver et al., 1997; Cairo et al., 2004; Chang et al., 2007). The caudate is active during working memory encoding (Chein and Fiez, 2001; Chang et al., 2007), maintenance (Chein and Fiez, 2001; Chang et al., 2007), manipulation (Lewis et al., 2004), retrieval (Chang et al., 2007), and in preparation of a motor response to a working memory stimulus (Postle and D'Esposito, 1999). In addition, functional connectivity of the caudate has been reported to have a positive relation with performance in an n-back working memory task (Gordon et al., 2015).

The caudate has been suggested to facilitate updating contents in working memory by receiving dopamine from the brainstem for transmission to the dorsolateral prefrontal cortex (Murty et al., 2011) and by disinhibiting the mediodorsal nucleus of the thalamus (Ashby et al., 2005). It has also been shown to be functionally and structurally connected to both prefrontal cortex and thalamus (Robinson et al., 2012). Further, altered activation during working memory tasks in patients with civilian TBI has been suggested to be related to a disrupted dopamine system (McAllister et al., 2004; Wishart et al., 2011) and modulated by dopaminergic genes (McAllister, 2009). Recently, Yeh et al. (2014) identified white matter disruptions in the fronto-striatal circuit and brainstem in active duty military personnel with blast TBI, suggesting that connections from brainstem to prefrontal cortex via the thalamus and caudate may be particularly vulnerable to blast injury.

What characteristics of the caudate may have contributed to deficits in working memory activation after blast exposure? The lack of significant differences in brain volume or cortical thickness suggests that altered activation was not driven by atrophy of the caudate. However, a report of blast-related white matter hemispheric asymmetries in the internal capsule (Yeh et al., 2014), adjacent to the caudate, could have implications for impaired neural transmission. Moreover, the striatum (caudate and putamen) is a highly plastic area linked to changes in both learning and disease (Kreitzer and Malenka, 2008), thereby affecting the caudate's role in working memory. As well, neuroplasticity of the caudate has been found after intensive training on a task involving attention and working memory (Nikolaidis et al., 2014), and changes in caudate activation during that task further predicted individual differences during performance of a second, unpracticed, task — the SIRT (Nikolaidis et al., 2014).

In a post-mortem study of brains of athletes and veterans who had a history of repetitive TBI, chronic traumatic encephalopathy (CTE), a type of progressive neurodegeneration linked to increased tau pathology, was found in 80% of the brains (McKee et al., 2013), suggesting that veterans from the Iraq and Afghanistan wars may be at risk for CTE. Macroscopic changes in CTE are preceded by subtle changes in memory and attention (McKee et al., 2009; McKee et al., 2013), and it is plausible that the performance deficits observed during the SIRT could be related to early CTE symptoms. Veterans from older wars who experienced TBI were found to be more likely to develop dementia than veterans who did not experience TBI (Barnes et al., 2014). However, the majority of the veterans in the Barnes et al. (2014) report had more severe TBI than the veterans in this paper, and a recent meta-analysis of civilian mild TBI suggests there is insufficient evidence for an association of single or repetitive mild TBI with dementia (Godbolt et al., 2014). Additionally, increased endorsement of PTSD symptoms in the military TBI group may suggest alterations in cognition and pathology as a result of PTSD (Tian et al., 2014). TBI and PTSD may share neurocircuitry susceptible to neurodegeneration, possibly similar to how CTE has been linked to Parkinson's disease, Alzheimer's disease, motor neuron disease, and frontotemporal dementia (McKee et al., 2013), and by

impacting the caudate, blast TBI may join other diseases that are involved with striatal degeneration (Kreitzer and Malenka, 2008). However, because of the cross-sectional nature of the present study, it is unclear whether changes in the caudate are related to chronic neurodegeneration or to static effects of injury that occurred approximately 4 years earlier.

While there is currently little support for a relationship between isolated mild TBI and Parkinson's disease (Marras et al., 2014), repetitive mild and more severe TBI have been linked to Parkinson's disease (Bower et al., 2003; Shahaduzzaman et al., 2013). The caudate is implicated in Parkinson's disease, where it is among the first structures to receive and transmit depleted amounts of dopamine (Cools, 2006), which could be related to the working memory processes measured here. Subjects newly diagnosed with Parkinson's disease showed reduced activation in the caudate while performing the 2-back working memory task compared to healthy controls, with no group differences in prefrontal cortex, consistent with the gradual depletion in dopamine from striatum to frontal structures (Cools, 2006; Marklund et al., 2009). Future studies may test the presence of additional similarities between patients with PD and blast TBI along different time points in the progression of the disorders to understand the extent to which PD may be a model for advanced blast TBI.

Our group (Scheibel et al., 2012; Fischer et al., 2014) has previously documented alterations in activation during conflict monitoring and response inhibition in veterans approximately two to four years after blast exposure, suggesting that effects of blast TBI on brain activation are long-lasting. The present study provides additional evidence for a long term blast-related TBI effect on brain activation in another executive function, working memory.

In our previous fMRI study (Fischer et al., 2014) we detected no performance differences between blast and blunt-force TBI despite differences in brain activation. In the present investigation, we identified decrements in accuracy for working memory loads 3 and 5 in the blast TBI group. The SIRT, therefore, may serve as a sensitive cognitive test for distinguishing TBI due to blast from blunt-force. Alteration in activation patterns unaccompanied by changes in performance suggests an ability of the brain to adapt to disruption that may not have a direct effect in everyday performance. However, the altered activation and performance decrements found in the present study suggest that veterans may experience problems in everyday life situations which impose working memory demands, e.g., multitasking, conversing, and reasoning (Just and Carpenter, 1992; Johnson-Laird, 1994; Acheson and MacDonald, 2009).

Exploratory analyses revealed an association between activation in the caudate and reaction time in the civilian TBI group that was not observed in the military TBI group (Fig. 5), further suggesting how blast TBI may differ from civilian TBI. Lack of a positive relation with reaction time is consistent with the lack of a set size effect in the military TBI group, since larger set sizes would take longer to process. However, the military TBI group did show significant or marginally significant negative relations between caudate activation and measures of PTSD and pain that were not observed in the civilian TBI group, suggesting that these symptoms may be related to the disrupted caudate activation. The caudate has been associated with physical pain (Erpelding and Davis, 2013). Future studies may explore how re-experiencing and avoiding memories of physical and emotional pain are associated with working memory processing in the caudate. Future studies may also investigate the effect of blast on orbitofrontal gyri in light of our exploratory analyses demonstrating that the blast TBI group demonstrated a negative relation between post-injury interval and bilateral orbitofrontal activation. Bony protuberances near orbitofrontal cortex that are responsible for axonal tearing in blunt-force trauma may also play a role in brain tissue impacted by blast movement.

We would like to highlight some limitations of our study. We investigated effects of blast on verbal working memory; it would be desirable to determine if our findings would be replicated using non-verbal working memory tasks. While all military subjects had TBI as a result of blast exposure, some may have had additional pathology due to acceleration–deceleration or blunt-force trauma due to secondary blast; however, no civilian TBI patients had injuries related to blast. Thus, our group comparison likely represented a blast + blunt-force TBI versus blunt-force TBI. Approximately half of the blast TBI subjects had experienced more than one blast injury, and it is possible that even though criteria for severe TBI were not met in any subject, multiple blasts could augment some symptoms to be similar to those observed in severe TBI patients; significantly greater Neurobehavioral Symptom Inventory (NSI) (Cicerone and Kalmar, 1995) scores in the blast TBI group than in the other three groups is consistent with this possibility. However, number of blasts did not appear to impact age, education, or scores on the PCL-C, CESD, NSI and fatigue scales, although pain was significantly greater in subjects with two or more blasts. Number of blasts also did not impact the significance of activation in any of the seven fROIs. The TBI sample included two moderate TBI subjects, raising the possibility that the results could have been skewed by their greater severity. However, removing the moderate subjects did not alter the result of the right caudate being significant. It is notable that symptoms were greater in the blast TBI group than in the civilian TBI group, even though the blast group had a significantly longer post-injury interval than the civilian group; in this study, post-concussion effects of blast TBI appear to be more long-lasting than effects of blunt-force TBI.

The military groups were not matched on combat exposure. TBI and high levels of combat intensity during deployment have been shown to increase the risk of post-deployment psychological distress, including PTSD (Yurgil et al., 2014). Not surprisingly, in our study, military personnel who had been exposed to blast reported greater levels of psychological distress compared to military personnel not exposed to blast on self-report measures of PTSD symptoms, depression, fatigue, and pain. Given the higher levels of psychological distress reported by soldiers exposed to blast, we may assume that blast exposure is associated with higher levels of self-reported combat stress, although this variable was not measured. For purposes of this study, however, the key question is whether the amount of psychological distress reported by veterans nearly 4 years post-deployment can explain our brain imaging findings involving a working memory task. Importantly, when we entered self-report psychological distress variables as covariates in the group analyses, the overall fMRI results were unchanged, indicating that chronic psychological distress is not influencing our brain imaging findings.

Could combat exposure influence brain imaging results independent of psychological distress? A prospective, longitudinal brain imaging study by van Wingen et al. (2012) conducted pre- and postdeployment demonstrated that higher intensities of combat exposure are associated with alterations in brain attentional networks even in soldiers who do not report psychological distress or psychiatric complaints. Importantly for the current study, these brain alterations normalized within 1.5 years postdeployment. Our military TBI personnel were evaluated on average 4 years postdeployment.

5. Conclusions

In both blunt-force and blast TBI groups, activation was altered throughout the brain in frontal (orbitofrontal, inferior frontal gyri/insula), posterior (angular gyrus, cerebellum), and subcortical (caudate, putamen, pallidum) regions. However, only blast TBI disrupted a monotonic relation between the number of items to be remembered in the Sternberg Item Recognition Task and activation in the caudate during encoding. Blast TBI was also associated with worse performance on the SIRT, although no group differences were found on neuropsychological measures of memory, inhibition, and general processing speed. With this and our previous study (Fischer et al., 2014), we have identified chronic blast-specific changes in brain activation within the dorsolateral and orbitofrontal striatal circuits which engage the caudate nucleus. fMRI patterns in response to the SIRT and Stop Signal tasks,

and potentially other tasks that recruit the caudate, may serve as biomarkers for blast TBI.

Acknowledgements

This study was supported by grants from the U.S Department of Defense (W81XWH-08-2-0124, W81XWH-10-1-0609) and was supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Rehabilitation Research and Development, Project #B6812C Traumatic Brain Injury Center of Excellence. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs. There are no potential conflicts of interest, including financial, between any of the authors and the work presented in this manuscript. We are grateful to the veterans taking part in the research. Thanks to laboratory members who provided helpful contributions: Gregory Vogt, Xiaodi Lin, Tricia Merkley, Rebecca Marsh, Brian Taylor, and Mark Walker.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2015.04.024.

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