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Altered Brain Activation in Military Personnel with One or More Traumatic Brain Injuries Following Blast

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Abstract

Explosive blast is a frequent cause of traumatic brain injury (TBI) among personnel deployed to Afghanistan and Iraq. Functional magnetic resonance imaging (fMRI) with an event-related stimulus-response compatibility task was used to compare 15 subjects with mild, chronic blast-related TBI with 15 subjects who had not experienced a TBI or blast exposure during deployment. Six TBI subjects reported multiple injuries. Relative to the control group, TBI subjects had slightly slower responses during fMRI and increased somatic complaints and symptoms of post-traumatic stress disorder (PTSD) and depression. A between-group analysis indicated greater activation during stimulus-response incompatibility in TBI subjects within the anterior cingulate gyrus, medial frontal cortex, and posterior cerebral areas involved in visual and visual-spatial functions. This activation pattern was more extensive after statistically controlling for reaction time and symptoms of PTSD and depression. There was also a negative relationship between symptoms of PTSD and activation within posterior brain regions. These results provide evidence for increased task-related activation following mild, blast-related TBI and additional changes associated with emotional symptoms. Limitations of this study include no matching for combat exposure and different recruitment strategies so that the control group was largely a community-based sample, while many TBI subjects were seeking services. (*JINS*, 2012, *18*, 89–100)

Keywords: Brain concussion, Brain mapping, Executive function, fMRI, Post-concussion syndrome, PTSD

INTRODUCTION

Explosives are a frequent cause of injury among personnel wounded in Iraq and Afghanistan and blast exposure often results in traumatic brain injury (TBI) (Owens et al., 2008). Although the majority of blast-related TBIs are mild, many injured individuals remain in theatre and experience multiple blasts (Hoge et al., 2008). Civilians who sustain a single, mild TBI unrelated to blast generally show resolution of post-concussive symptoms during the initial weeks following injury and most perform well on standard neuropsychological tests (Binder, Rohling, & Larrabee, 1997). However, multiple mild injuries may be cumulative (Rabadi & Jordan, 2001) and it is not clear whether the neuropathology and symptoms associated with military, blast-related TBI are the same as those produced by acceleration/deceleration injury in civilians (Courtney & Courtney, 2009).

Primary blast injury results from changes in atmospheric pressure experienced as a wave of increased pressure (i.e., blast overpressure) followed by a relative vacuum and high velocity wind (Cernak & Noble-Haeusslein, 2010). Tissues that are exposed to the blast wave and have different densities may accelerate and be displaced to different degrees, resulting in stretching and shear strain (Taber, Warden, & Hurley, 2006). Secondary blast injury may occur when the individual is impacted by objects and, in some cases, tertiary injury results when the body is thrown (Warden, 2006). Tissue damage may result from other causes, as well, such as burns, substance inhalation, and collapsing objects (i.e., quaternary blast injury) (Finkel, 2006).

Most research on primary blast has been conducted with animals and little is known about the mechanisms that cause injury to the brain, but these have been postulated to include whiplash or head rotation (Bhattacharjee, 2008; Cernak &

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Noble-Haeusslein, 2010), direct passage of the blast wave through the skull or skull deformation (Cernak & Noble-Haeusslein, 2010; Ling, Bandak, Armonda, Grant, & Ecklund, 2009), and the transfer of pressure wave energy to the brain through the thorax and large blood vessels (Cernak, 2005). These mechanisms are not mutually exclusive and some, such as head rotation, may cause diffuse axonal injury in a manner similar to blunt head trauma (Cernak & Noble-Haeusslein, 2010). Other possible causes of neural injury, such as energy transfer through the vasculature, may differ from those presumed to underlie acceleration/deceleration injury (Cernak, 2005). Although there is some experimental evidence for a systemic mechanism involving blast-induced vascular changes (e.g., Long et al., 2009), this evidence is limited and the theory is controversial (Bhattacharjee, 2008). In addition, one study which compared neuropsychological findings in patients with TBI due to blast or blunt force found no differences in cognitive function, but there was a marginally higher incidence of posttraumatic stress disorder (PTSD) following blast-related TBI (Belanger, Kretzmer, Yoash-Gantz, Pickett, & Tupler, 2009).

Several somatic and cognitive postconcussive symptoms overlap with those of PTSD and depression and, in addition to blast exposure, such conditions may be related to other battlefield risk factors that reflect combat intensity and psychological trauma (Fear et al., 2009). Hoge et al. (2008) found that soldiers with mild TBI were more likely to report increased postconcussive symptoms, missed workdays, and poorer health than those with other injuries. However, with the exception of headache, mild TBI was no longer associated with these symptoms after the data were statistically adjusted for PTSD and depression. The overlap of postconcussive symptoms with depression and PTSD presents challenges for diagnosis and assessment (Brenner, Vanderploeg, & Terrio, 2009).

One method that has potential for identifying alterations in neural function following TBI is functional magnetic resonance imaging (fMRI). Civilians with moderate to severe TBI typically have greater and more distributed brain activation than uninjured subjects while engaging executive functions, such as working memory and inhibition (e.g., Christodoulou et al, 2001; Scheibel et al., 2007, 2009). These changes have included greater activation within the cingulate gyrus during an fMRI stimulus-response compatibility task, but the distribution of this over-activation within the cingulate gyrus and additional brain structures varied with injury severity (Scheibel et al., 2009). Investigations have also described changes in the modulation of activation in response to increased working memory load when a mild TBI was sustained within the past month (McAllister et al., 1999, 2001). Other studies have examined athletes with mild TBI and have revealed various patterns of increased or reduced activation (Chen, Johnson, Collie, McCrory, & Ptito, 2007; Chen, Johnson, Petrides, & Ptito, 2008a; Jantzen, Anderson, Steinberg, & Kelso, 2004). Chen et al. (2007) noted the variability in these findings, which they attributed to differences in the tasks and experimental design, and stated that the most striking result across fMRI studies is that individuals with mild TBI exhibit atypical brain activation. In addition, there is some evidence that depression can modify the activation pattern during working memory in athletes with mild TBI, including reduced activation within task-relevant brain areas (Chen, Johnson, Petrides, & Ptito, 2008b).

The current study examined individuals with mild, blast-related TBI using an fMRI stimulus-response compatibility task that has been reported to produce greater activation in civilians with moderate to severe TBI, relative to control subjects (Scheibel et al., 2007, 2009). The mild range of severity was selected for study because this is the injury that is most often reported for service personnel wounded in the current conflicts (e.g., Hoge et al., 2008) and because this allowed the composition of a more homogenous group. These subjects were compared to individuals who had also served in Afghanistan or Iraq, but had not sustained a TBI or been exposed to blast. Previous research with the block design version of the stimulus-response compatibility task did not reveal consistent activation in civilian orthopedic control subjects (Scheibel et al., 2007), but emotional factors were not considered within that statistical design. Studies with athletes have found that depression can modify the activation pattern during executive functions (Chen et al., 2008b) and, since Hoge et al. (2008) found that the relationship between mild TBI and postconcussive symptoms was eliminated after adjusting for PTSD and depression, the current study included measures of both depression and PTSD symptoms as covariates. We hypothesized that subjects with mild, blast-related TBI would have greater and more distributed brain activation relative to comparison subjects who had not sustained a TBI, including increased activation within the cingulate gyrus, but we also anticipated that the activation pattern may be modified by emotional factors.

METHODS

Participants

The study was approved by the Institutional Review Board and all subjects provided written informed consent. The participants consisted of 30 right-handed service personnel and veterans who had served in Afghanistan or Iraq. The U.S. Veterans Health Administration (VHA) has instituted a thorough screening and evaluation system to identify post-deployment veterans with possible TBI (Armistead-Jehle, 2010) and this is how many veterans get referred for TBI evaluation. Of the 15 subjects in the TBI group, 12 veterans and 1 active duty reservist were enrolled through the TBI clinic at the Michael E. DeBakey Veterans Affairs Medical Center, one veteran was referred by the center's psychiatrist, and another was initially contacted through a database of consented research subjects. The control group consisted of three active duty personnel recruited through advertisements at an army post, one veteran who was examined by the TBI clinic and found not to have experienced head trauma or blast, and 11 veterans who were identified through the

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research database. Blast exposure was initially assessed using a self-report questionnaire and all TBI subjects reported at least one post-blast period that included loss of consciousness (LOC), confusion, or retrograde amnesia consistent with Department of Defense criteria for TBI (French & Parkinson, 2008). This diagnosis was confirmed in an interview with a clinician who was experienced in the evaluation of individuals with combat injury. Mild TBI was defined as an injury with LOC less than 30 min, post-traumatic amnesia (PTA) duration of less than 24 hr, and no focal lesions on structural imaging. All provided estimates of LOC and PTA duration that met the eligibility criteria. Ten TBI subjects were able to provide quantitative estimates of post-blast PTA duration associated with their most severe injury ($M = 14.7$ min; $SD = 10.6$; range = 3 to 31 min). Three claimed to have had no LOC and, of the 12 who did, 7 were able to provide a quantitative estimate of LOC duration ($M = 4.7$ min; $SD = 5.3$; range = 1 to 15 min).

Eleven TBI subjects reported exposure to multiple blasts and, of these, six reported two or more separate events where they had experienced post-blast symptoms consistent with TBI (French & Parkinson, 2008). Ten indicated that they had probably experienced at least one secondary blast injury and seven reported tertiary injury. Cause of the blasts included improvised explosive devices ($n = 13$), mortars ($n = 6$), rocket propelled grenades ($n = 5$), and other types of explosives ($n = 6$). This was a chronic injury sample as reflected by the interval between the most recent blast-related TBI and the fMRI assessment ($M = 963.9$ days; $SD = 333.2$; range = 402 to 1511 days).

The comparison group consisted of subjects who had been deployed to Afghanistan or Iraq, but who had not been exposed to blast and reported no TBI. Five of these control subjects had experienced an orthopedic injury during deployment. None of the control or TBI subjects reported current drug or alcohol abuse, and none had a history of previous psychiatric disorder, learning disability, or pre- or post-deployment head injury. There were no significant between-group differences in self-reported medication use at the time of assessment (see Table 1). Also, whenever possible, the medications were withheld on the day of the behavioral and fMRI assessments.

Behavioral Measures and Demographic Information

All subjects completed the Brief Symptom Inventory (BSI) (Derogatis, 1975), the Neurobehavioral Symptom Inventory (NSI) (Cicerone & Kalmar, 1995), the Short Form (SF-12) Health Survey (Ware, Kosinski, Turner-Bowker, & Gandek, 2004), and the PTSD Checklist – Civilian (PCL-C) (Dobie et al., 2002). The PCL-C is a brief, self-report instrument that does not require specification of a particular event and does not assume that all traumatic experiences are related to combat. In addition, the subjects provided information to support a rating on the Glasgow Outcome Scale – Extended (GOS-E) (Teasdale, Pettigrew, Wilson, Murray, & Jennett, 1998) and calculation of the Barona IQ (Barona, Reynolds, & Chastain, 1984).

Arrows Stimulus-Response Compatibility Task

The stimulus-response compatibility task (Scheibel et al., 2007) was administered in the scanner as a rapid-presentation, stochastic event-related fMRI paradigm. Participants viewed arrows presented one at a time for 265 milliseconds (ms), with each followed by a blank screen for 200 ms and then a crosshair fixation point for a mean of 2235 ms, randomly jittered plus or minus 200 ms. Seventy-five percent of the arrows were blue, and 25% were red. For each color, 50% of the arrows pointed left and 50% pointed right. These different stimuli were randomly intermixed throughout each run of 80 arrows. When the arrows were blue the subjects were required to use their right or left index finger to press the response key that was on the same side that the arrow was pointing toward (i.e., stimulus-response compatible). When the arrows were red the subject pressed the response key

Table 1. Self-reported medication use by group

	Controls ($n = 15$)	TBI ($n = 15$)	Two-sided probability[a]
Antibiotic	1	0	1.00
Antidepressant	7	11	.14[b]
Antihistamine	4	1	.33
Antihypertensive	3	1	.60
Anticholesteremic	1	1	1.00
Gastrointestinal	2	1	1.00
Hypoglycemic	1	0	1.00
Mood stabilizer	1	2	1.00
Muscle relaxant	0	4	.10
No medication	3	3	1.00
Other medication	4	2	.65
Pain medication	7	8	.72[b]
Sleep aid	3	7	.12[b]

[a]Most comparisons were performed using Fisher's exact test because the χ^2 test was not valid due to inadequate cell frequencies.
[b]Comparisons where the χ^2 was used because it was valid.

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opposite to the direction of the arrow (i.e., stimulus-response incompatible). Responses were collected between 200 and 1200 ms after stimulus onset and the first two trials in the run were always from the compatible condition. There was a 20 second (s) fixation crosshair before the first trial to allow for magnetization equilibrium to occur and additional fixation rest periods of 2000 ms occurred after 16, 32, 48, and 64 trials. Each of the three runs lasted 244 s, with a 1-min rest period between runs, and the order of the runs was counterbalanced across subjects. Instructions and practice were provided within 2 hr before scanning until the subject performed with 65% accuracy or better in both conditions. During fMRI data acquisition the response accuracy, onset time, and reaction time (RT) were recorded for each stimulus and only correct responses were included in analyses for RT.

Image Data Acquisition

Whole brain imaging was performed using a multi-channel sensitivity encoding (SENSE) head coil on a Philips Achieva 3 Tesla system (Philips Healthcare, Best, The Netherlands). Blood oxygen level dependent (BOLD) T2* weighted single-shot gradient-echo echoplanar images (EPI) were acquired as 160 volumes with 32 axial slices of 3.75 millimeter (mm) thickness with a .5 mm gap, using a 240 mm field of view (FOV), 64 × 64 matrix, repetition time (TR) of 1700 ms, echo time (TE) of 30 ms, a 73 degree flip angle, and a SENSE factor of 2.0. The first 20 s of each run were discarded to allow for signal magnetization equilibrium to be achieved. A set of high-resolution T1-weighted 3D-turbo field echo anatomical images were also acquired in 132 axial slices of 1.0 mm thickness (no gap) with 240 mm FOV, 256 × 256 matrix, TR of 9.9 ms, TE of 4.6 ms, a 8.0 degree flip angle, and a SENSE factor of 1.2. Additional anatomical series were performed to assess neuropathology and these included T2-weighted gradient echo (25 axial slices, slice thickness = 5.0 mm, TR = 2500, TE = 32, FOV = 224 mm, flip angle = 30 to 40 degrees), T2-weighted fluid attenuated inversion recovery (25 axial slices; slice thickness = 5.0 mm with 1.0-mm gap; TR = 11,000; TE = 105; FOV = 240 mm; flip angle = 90 degrees), and T2-weighted spin echo imaging (25 axial slices, slice thickness = 5.0 mm; TR = 2141; TE = 80; FOV = 230 mm; flip angle = 90). A board certified neuroradiologist examined the anatomical imaging.

Image Post-Processing and Analysis

The fMRI data were subjected to voxel by voxel analyses using statistical parametric mapping (SPM) 2 software (Wellcome Department of Cognitive Neurology, University College, London, UK) implemented in Matlab (Mathworks Inc., Sherborn, MA). After slice-timing correction, the fMRI time series were realigned and unwarped to correct for head motion and susceptibility-by-movement interactions. Series with motion greater than 2.0 mm translational or 3.0 degrees rotational were eliminated from analysis. The fMRI time series were coregistered to the high-resolution anatomical scan, normalized to the Montreal Neurological Institute (MNI) template using the normalization parameters from the anatomical scan, resliced to 2 × 2 × 2 mm, and spatially smoothed using a 6 mm isotropic full width at half maximum (FWHM) Gaussian filter. A high-pass temporal filter with a cutoff period of 128 s was used to reduce low-frequency noise. First-level analyses were then conducted using the general linear model at each voxel for each subject, using only correct response trial events and with incorrect trials modeled as a nuisance regressor, to contrast the amplitude of the hemodynamic response (HRF) associated with the onset of red arrows (i.e., incompatible condition) with the HRF associated with the onset of blue arrows (i.e., compatible condition).

The incompatible minus compatible contrast image for each subject was carried forward into second-level SPM2 random effects analyses. These included *t* tests to examine the incompatible minus compatible contrast within each group, a *t* test to perform between-group comparisons (control *vs.* TBI), and an analysis of covariance (ANCOVA) model to examine between-group contrasts while controlling for several covariates (i.e., BSI Depression Scale, PCL-C Total Score, blue arrows RT, and red arrows RT). To confirm that the assumptions of ANCOVA were met, a set of preliminary slopes interaction analyses (Kleinbaum, Kupper, Muller, & Nizam, 1998) were completed with results indicating parallel slopes within both groups for each covariate. Follow-up analyses using separate SPM2 simple regressions were also performed with those covariates that were significant in the full ANCOVA model.

An additional ANCOVA was performed using scores from the BSI Somatization Scale as the only covariate to address the possibility that the subjects' somatic concerns may contribute to the between-group differences. The slopes interaction analysis for the BSI Somatization Scale indicated a single posterior cluster of 802 voxels where the assumptions of ANCOVA were not met. However, the results of this additional ANCOVA were considered to be valid for those voxels that did not overlap with that posterior cluster.

The cluster-defining (height) threshold for all second-level analyses was set at voxel-level t = 2.50. Reported clusters were statistically significant (corrected $p < .05$) at the cluster level of inference using the SPM Random Field Theory family-wise error correction for multiple comparisons over the whole brain volume. The location of statistically significant clusters was visually inspected and their coordinates were then assigned anatomical labels using the SPM anatomy toolbox (http://www.fz-juelich.de/inm/inm-1/spm_anatomy_toolbox).

RESULTS

Demographics and Outcome Measures

There were no significant between-group differences for age, education level, estimated IQ, or the Mental Component

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Table 2. Demographic characteristics, outcome measures, and cognitive task performance by group

	Controls[a] ($n = 15$)		TBI[b] ($n = 15$)		Wilcoxon or t Statistic[c]	Two-sided probability	Cohen's d
	Mean (*SD*)	Median	Mean (*SD*)	Median			
A. Demographic Variables and Outcome Measures							
Age (years)	30.93 (5.56)	33.00	28.73 (5.97)	26.00	1.04	.30	.38
Education (years)	13.60 (1.40)	13.00	13.80 (1.52)	14.00	−.37	.71	.14
Barona IQ	101.60 (7.13)	101.00	103.27 (5.75)	103.00	−.70	.49	.26
PCL-C Total Score[d]	38.87 (19.45)	31.00	55.13 (14.32)	56.00	−2.61	.01	.95
BSI Depression Scale	60.40 (12.89)	61.00	69.53 (9.80)	73.00	−2.18	.04	.80
BSI Somatization Scale	59.87 (11.62)	59.00	68.73 (9.56)	68.00	−2.28	.03	.83
NSI Cognitive Cluster Scale[e]	1.43 (1.21)	1.20	2.13 (0.64)	2.20	−2.00	.06	.73
NSI Total Score	24.47 (19.77)	17.00	39.80 (11.46)	42.00	−2.60	.02	.95
SF-12 Mental Component Score	42.98 (12.72)	43.78	41.40 (10.30)	45.08	.38	.71	.14
SF-12 Physical Component Score	46.80 (10.22)	51.04	38.33 (10.36)	36.82	2.25	.03	.82
GOS-E[f]	7.20 (1.01)	8.00	6.53 (0.52)	7.00	283.50[g]	.03	.83
B. Cognitive Task Performance Measures							
Training Red Accuracy[h,i]	80.00 (28.66)	87.50	80.59 (16.20)	75.00	133.50[g]	.43	.02
fMRI Red Accuracy[h]	81.44 (7.59)	83.33	82.89 (7.52)	80.00	−.52	.60	.19
fMRI Red Reaction Time (ms)	701.42 (103.47)	716.13	761.92 (76.62)	787.56	−1.82	.08	.66
fMRI Blue Accuracy[h]	86.21 (3.02)	86.67	85.89 (5.10)	87.86	.21	.84	.08
fMRI Blue Reaction Time (ms)	556.50 (82.95)	560.05	618.81 (91.24)	633.11	−1.96	.06	.71

Note. TBI = traumatic brain injury; PCL-C = PTSD Checklist – Civilian; BSI = Brief Symptom Inventory; NSI = Neurobehavioral Symptom Inventory; SF-12 = Short Form Health Survey; GOS-E = Glasgow Outcome Scale – Extended; fMRI = functional magnetic resonance imaging.
[a]One subject in the control group was female.
[b]All subjects in the TBI group were male.
[c]Two sample t-test.
[d]The PTSD Checklist is a 17-item self-report measure of Diagnostic and Statistical Manual IV (DSM-IV) PTSD symptoms. The military version (i.e., PCL-M) asks about reactions to military experiences, while the civilian version (PCL-C) has slightly different wording so that it is more general and can be used with any population. Each item is rated by the subject on a scale ranging from 1 ("Not at all") to 5 ("Extremely") for a maximum possible score of 85. A cutoff value of 50 is often used with the total score to indicate elevated symptoms of PTSD (e.g., Hoge et al., 2008).
[e]The Cognitive Cluster Scale was originally identified in a cluster analysis performed by Cicerone and Kalmar (1995). That analysis also identified affective, somatic, and sensory clusters.
[f]The Extended Glasgow Outcome Scale (GOS-E) uses a structured interview and examiner ratings to assign subjects to one of eight categories: Dead (1), Vegetative State (2), Lower Severe Disability (3), Upper Severe Disability (4), Lower Moderate Disability (5), Upper Moderate Disability (6), Lower Good Recovery (7), and Upper Good Recovery (8).
[g]The Wilcoxon two sample test (normal approximation) was used because the data distribution did not meet the assumptions for parametric statistical analysis.
[h]Percentage of correct responses.
[i]Accuracy during the first trial of the pre-scan training.

Score from the SF-12 (see Table 2). There was a trend favoring higher NSI Cognitive Cluster Scores within the TBI group ($p = .06$) and there were significant between-group differences indicating greater symptom severity among TBI subjects on the NSI Total Score, the BSI Depression and Somatization Scales, and the Physical Component Score from the SF-12. Scores on the PCL-C were higher within the TBI group and 11 of these subjects exceeded a cutoff score of 50, while four of the control subjects exceeded this cutoff. The TBI subjects also had worse outcomes as reflected by lower ratings on the GOS-E.

Anatomical MR Imaging

The 15 comparison subjects and the 15 TBI subjects had normal anatomical imaging. Two additional TBI subjects were also screened, but these had evidence of shear injury or gliotic lesions and were excluded from this study.

Behavioral Results

Initial red arrows accuracy during the pre-scan training did not differ between the groups (see Table 2). There were also no significant between-group differences for blue or red arrows accuracy during fMRI image acquisition, but there were nonsignificant trends favoring slightly slower responding among the TBI subjects for both the blue ($p = .06$) and red ($p = .08$) arrows. Analysis of variance (ANOVA) indicated slower responding among TBI subjects when both arrows conditions were combined [$F(1,28) = 4.35$; $p = .05$], slower responding for the red than for the blue arrows condition when subjects from both groups were pooled [$F(1,28) = 108.12$; $p = .001$], and no significant interaction [$F(1,28) = 0.00$; $p = .95$].

Separate analyzes were also performed to examine whether there were any between-group differences in red arrows RT after statistically controlling for the symptoms of PTSD and

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depression. For both models, the preliminary slope interaction analyses indicated that the assumptions of ANCOVA were met. The analysis using PCL-C scores as a covariate indicated increased RT for the TBI subjects relative to the control subjects [$F(1,27) = 4.29$; $p = .05$] and, within this model, the PCL-C covariate was not statistically significant [$F(1,27) = 0.99$; $p = .33$]. Similarly, an ANCOVA controlling for scores on the BSI Depression Scale also revealed slower responding for the TBI group [$F(1,27) = 4.62$; $p = .04$] and the covariate was not statistically significant [$F(1,27) = 1.42$; $p = .24$].

fMRI Results

Within-group activation

A within-group analysis indicated no significant activation for the control subjects. However, TBI subjects had significant task-related activation within the temporal and parietal lobes, the posterior cingulate gyrus, cerebellum, and other areas within the posterior cerebrum (see Table 3, part A, Figure 1).

Between-group comparisons

A between-group *t* test indicated there were no areas where control subjects had greater activation than the TBI group, but TBI subjects had significantly greater activation within the anterior and posterior cingulate cortex, medial frontal areas, the parietal lobes, and other regions as summarized in Table 3, part B, and Figure 1.

An ANCOVA using the BSI Depression Scale, the PCL-C Total Score, blue arrows RT, and red arrows RT as covariates revealed significantly higher activation for the TBI subjects, relative to the control group, within areas that had also exhibited differences with the between-group *t* test. These regions included the anterior and posterior cingulate, medial frontal, and parietal cortex (e.g., inferior parietal lobule). There were other areas, as well, where this ANCOVA revealed higher activation for the TBI group, including additional temporal and parietal structures (see Table 3, part C, and Figures 1 and 2).

A separate ANCOVA using scores from the BSI Somatization Scale as the only covariate revealed between-group differences that were similar to the model that had controlled for depression, PTSD, and RT. In a preliminary analysis using the BSI Somatization Scale, there was a posterior cluster of 802 voxels where this covariate failed to meet the assumptions of ANCOVA, but only 225 of these overlapped with the 9690 voxels that exhibited significant between-group differences. Thus, this ANCOVA provided valid results that generally replicated the findings of the primary image analysis (see Table 3, part D).

Simple regression analyses for the BSI Depression Scale and PCL-C

The blue and red arrows RT covariates were not significant when examined as part of the full ANCOVA model, but the BSI Depression Scale and the PCL-C covariates were significantly related to brain activation and follow-up analyses were performed for these. Preliminary analyses indicated no significant covariate × group interactions and, consequently, data from both groups were pooled for the separate simple regressions. There was no significant correlation between brain activation and scores on the BSI Depression Scale. However, there was a significant negative relation between activation and the PCL-C within posterior regions that included the cerebellum, right medial parietal cortex, and structures within both occipital lobes (see Table 3, part E, and Figure 2).

DISCUSSION

Impairments in executive functions, including cognitive control, are common following TBI (e.g., Cicerone, Levin, Malec, Stuss, & Whyte, 2006) and the present investigation used a stimulus-response compatibility task to examine military personnel who had sustained one or more blast-related injuries during deployment. This simple cognitive control paradigm has several characteristics that make it desirable for fMRI studies of TBI, including the ability to train neurologically impaired patients to perform at levels equivalent to healthy subjects (Price & Friston, 2002), relatively short scan duration, and previous reports of increased activation in civilians with moderate to severe TBI (Scheibel et al., 2007, 2009).

Relative to a post-deployment control group, the current study found increased brain activation during stimulus-response incompatibility in subjects with mild, chronic blast-related TBI after statistically controlling for differences in RT and symptoms of PTSD and depression. Using this ANCOVA model, the TBI subjects had greater activation within the anterior cingulate gyrus and medial frontal cortex. Increases were also found within posterior cerebral areas, including some (e.g., inferior parietal lobule, posterior cingulate gyrus) that are thought to be involved in visual perception, visual attention, and visual-spatial functions (e.g., Galati, Pelle, Berthoz, & Committeri, 2010; Orban, Van Essen, & Vanduffel, 2004). Areas of increased activation within the cingulate gyrus and medial prefrontal cortex are generally consistent with those previously reported by Scheibel el al. (2007) for a group of civilians with moderate to severe TBI, but the lateral posterior activation is more similar to that reported by Scheibel et al. (2009) for civilians with only severe TBI (i.e., GCS $\leq$ 8). These finding may reflect increased usage of neural substrates for visual processing and attention following mild, blast-related TBI in military personnel and in civilians with severe acceleration-deceleration injuries. Caution should be exercised while making these between-studies comparisons due to differences in the study design, the use of different statistical thresholds, and because the types of stressors and associated emotional factors are likely to differ for these populations. The results of these studies are clearly consistent, however, in that they reveal greater and more diffuse task-related activation following TBI.

Activation increases during cognitive fMRI paradigms are frequently observed in association with neuropathology and proposed interpretations for this finding have included the

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Table 3. Coordinates and anatomical region definitions for the results of the image analyses.

Cluster-level *p* value (corrected)	Cluster size (k)[a]	Most Significant Maximum MNI Coordinates (x, y, z; mm)	Anatomical Labels for Cluster Maxima[b]
A. T-Test TBI Within-Group Activation			
.001	2,977	−6, −68, 32	Calcarine gyrus (R), cuneus (B), fusiform gyrus (L), posterior cingulate cortex (L), precuneus (L)
.001	1,353	28, −38, −14	Fusiform gyrus (R), Heschl's gyrus (R), insula (R), medial temporal pole (R), Rolandic operculum (R), superior temporal gyrus (R)
.001	617	−58, −42, 12	Insula (L), medial temporal gyrus (L), superior temporal gyrus (L)
B. T-Test TBI > Controls			
.001	2,469	8, −80, 22	Cuneus (B), postcentral gyrus (L), precuneus (L), superior occipital gyrus (B), superior parietal lobule (L)
.001	802	−26, −52, −26	Cerebellum (L), fusiform gyrus (L), inferior temporal gyrus (L)
.001	783	18, 20, 46	Anterior cingulate cortex (B), medial frontal gyrus (R), middle cingulate cortex (B), superior frontal gyrus (R), supplementary motor area (L)
.034	414	−38, −26, 40	Postcentral gyrus (L), precentral gyrus (L)
C. ANCOVA TBI > Controls (covariates: BSI Depression Scale, PCL-C, Red Arrows RT, Blue Arrows RT)			
.001	3,211	−28, −58, 56	Calcarine gyrus (L), cuneus (L), paracentral lobule (B), precuneus (B), superior occipital gyrus (L), superior parietal lobule (L)
.001	2,566	24, −78, −24	Cerebellum (B)
.001	1,168	56, −28, 6	Insula (R), postcentral gyrus (R), Rolandic operculum (R), superior temporal gyrus (R)
.001	1,031	0, 38, 20	Anterior cingulate cortex (B), middle cingulate cortex (R), superior frontal gyrus (R), supplementary motor area (R)
.001	977	−50, −26, 4	Insula (L), superior temporal gyrus (L)
.001	798	24, −30, 66	Postcentral gyrus (R), precentral gyrus (R), superior frontal gyrus (R), superior parietal lobule (R)
.005	549	20, −66, 46	Angular gyrus (R), cuneus (R), middle occipital gyrus (R), precuneus (R), superior occipital gyrus (R)
D. ANCOVA TBI > Controls (covariate: BSI Somatization Scale)[c]			
.001	7,592	−26, −52, −26	Cerebellum (B), postcentral gyrus (R), superior parietal lobule (L), precuneus (L), cuneus (L), superior occipital gyrus (L)
.001	838	38, −32, 4	Superior temporal gyrus (R), fusiform gyrus (R), Rolandic operculum (R)
.001	765	18, 20, 46	Anterior cingulate cortex (B), middle cingulate cortex (R), superior frontal gyrus (R)
.013	495	−50, −28, 4	Superior temporal gyrus (L), middle temporal gyrus (L)
E. Negative Regression: PCL-C (all subjects)[d]			
.002	661	−4, −86, −8	Calcarine gyrus (B), cerebellum (L), lingual gyrus (B)
.026	441	6, −66, 36	Cuneus (R), posterior cingulate cortex (R), precuneus (R)
.043	400	−14, −34, −4	Cerebellar vermis (R), cerebellum (L), lingual gyrus (L), parahippocampal gyrus (L)

Note. MNI = Montreal Neurological Institute; TBI = traumatic brain injury; R = right side; L = left side; B = both sides or bilateral; BSI = Brief Symptom Inventory; PCL-C = PTSD Checklist – Civilian; RT = reaction time.
[a]Number of contiguous 2 × 2 × 2 mm voxels that exceed threshold.
[b]Labels obtained through the SPM Anatomy Toolbox.
[c]A preliminary analysis found a posterior cluster (i.e., bilateral precuneus, right superior parietal lobule) of 802 voxels where the assumptions of ANCOVA were not met, but these overlapped with only 225 (2.31%) of the 9,960 voxels reported here.
[d]Results of the simple regression of brain activation with the PCL-C Total Score. Data from both groups were pooled for this analysis.

disinhibition of duplicate neural systems, learning-related neuroplasticity, and cognitive reorganization (Price & Friston, 2002). When task performance is equated in comparisons with a control group the over-activation may reflect a higher level of effort, perhaps as a consequence of inefficient processing or as a form of compensation involving the allocation of additional cognitive and neural resources (Price & Friston, 2002; Ricker, Hillary, & DeLuca, 2001). In the present investigation, the task accuracy did not differ between the TBI and control groups, but there were significant differences for RT when PTSD or depressive symptoms were statistically controlled or when data from both arrows conditions were combined. There is the possibility that RT may have been slower in the TBI subjects before injury and this may reflect greater vulnerability to the effects of mild TBI, but preinjury data were not available for our analysis. Cognitive slowing associated with the TBI

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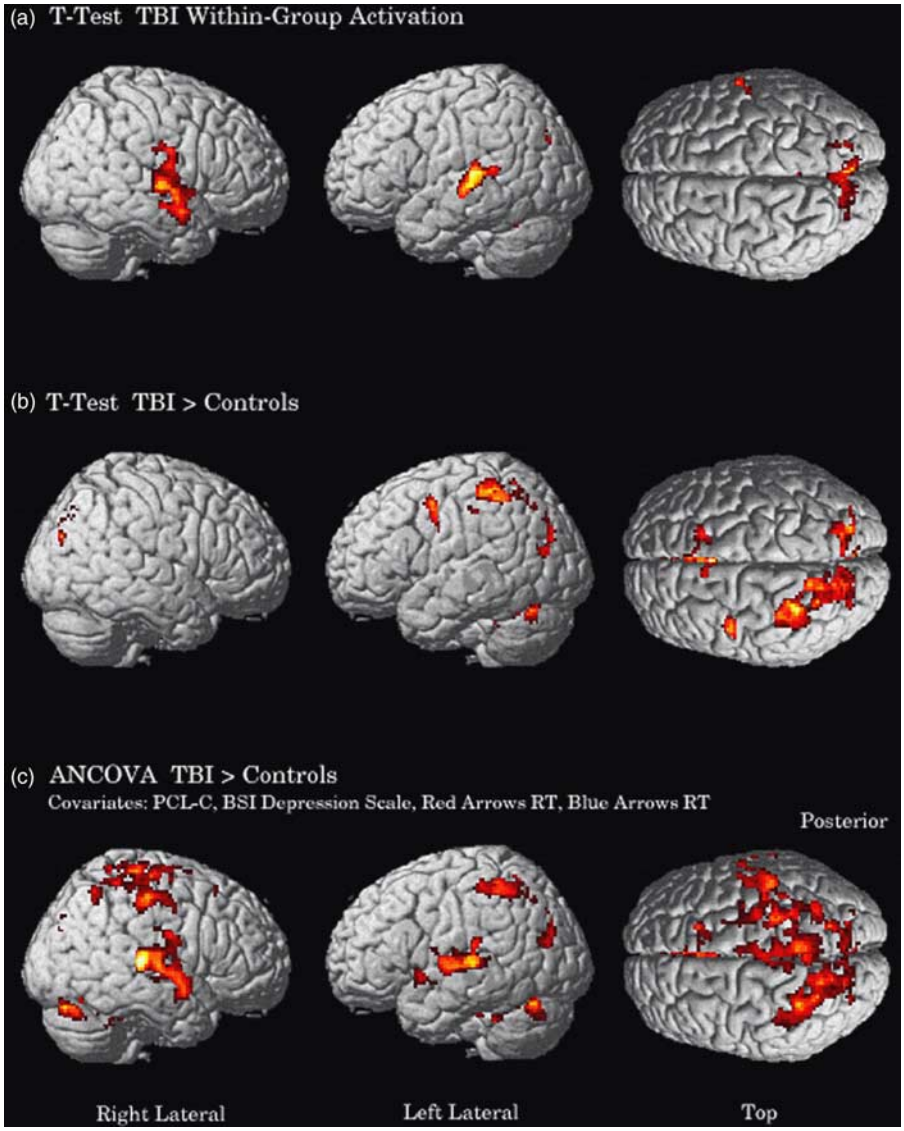

Fig. 1. Brain surface images displaying cortical areas with significant *t* test and analysis of covariance (ANCOVA) results: (A) significant activation in subjects with traumatic brain injury (TBI), (B) areas where the TBI group had greater activation than the control group, and C) areas where the TBI group had greater activation than the control group after controlling for blue arrows reaction time (RT), red arrows RT, and scores on the BSI Depression Scale and PCL-C.

is another possible explanation for the RT differences and this may have contributed to increased activation within the TBI group. However, these between-group RT differences were relatively small, both blue and red arrows RT were included in the primary image analysis as covariates, and the RT covariates were not significantly related to activation within that ANCOVA model. Thus, it is likely that neural injury made some contribution to increased activation that was not mediated by changes in response speed.

Relative to the control group, ratings on the GOS-E were consistent with decreased functioning within the TBI group and depressive, PTSD, and somatic symptoms were elevated. Statistically controlling for scores on the BSI Somatization Scale did not alter the results of the primary between-group comparison and it is unlikely that somatic symptoms or the subjects' concern about their injury is responsible for the major fMRI findings. Likewise, scores from the PCL-C and BSI Depression Scale were used as covariates in the primary image analysis that revealed greater activation in the TBI subjects. The BSI Depression Scale was a significant covariate within the ANCOVA model, but it did not exhibit a significant relation with brain activation when examined alone in a simple regression analysis. This failure to confirm a strong significant relation is surprising in light of the attenuated prefrontal activation reported by Chen et al. (2008b) for concussed athletes with depression. However, Chen et al. (2008b) had used a different cognitive task with civilians whereas the current study examined a vastly different population that included individuals with elevated PTSD symptoms, some of which may overlap with the emotional and somatic symptoms of depression. There is the possibility that the effects of depression on brain activation were masked or altered by the presence of these other conditions.

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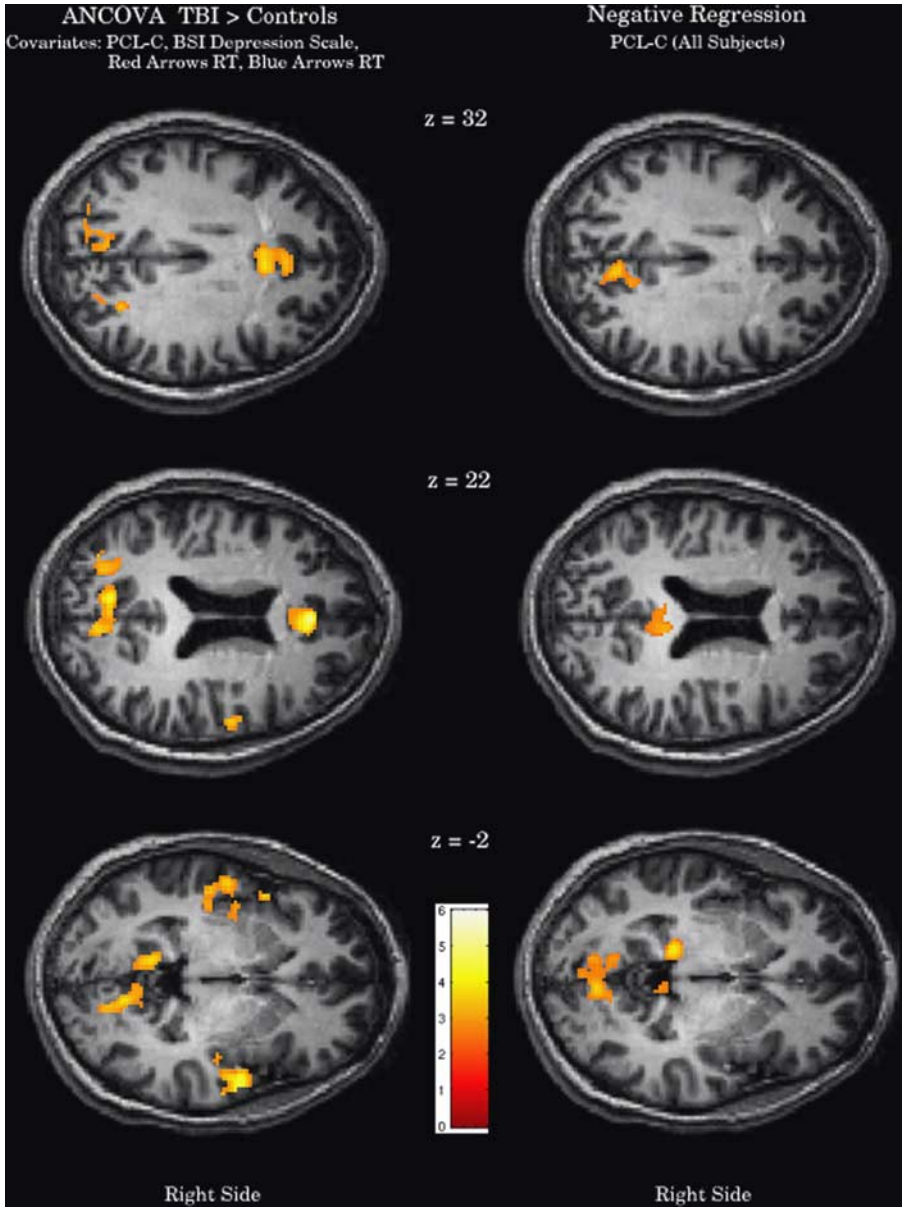

Fig. 2. Brain structures where the traumatic brain injury (TBI) group had greater activation than the control group when the analysis of covariance (ANCOVA) model included the BSI Depression Scale, PCL-C total score, blue arrows reaction time (RT), and red arrows RT as covariates, as well as areas where there was a significant negative relation between brain activation and scores on the PCL-C (all subjects). The statistical parametric maps are overlaid onto high resolution T1-weighted images from a typical control subject.

Morey, Petty, Cooper, LaBar, and McCarthy (2008) examined Iraq war veterans and found that ventral frontal and limbic activation was positively correlated with PTSD symptoms during the presentation of combat-related images, while such symptoms were negatively correlated with dorsal frontal and parietal activation during a simple executive function task. Their findings were interpreted as providing support for interrelated dorsal executive and ventral emotional processing networks that are differentially affected by PTSD (Morey et al., 2008). In addition, they proposed that individuals with PTSD may have a hyper-responsive limbic system that interferes with processing in other brain areas so that activation during executive functions is reduced. The current study also used a simple executive function task and found decreased activation in association with higher scores on the PCL-C, but the brain areas exhibiting these reductions differed some from those reported by Morey et al. (2008). This discrepancy may reflect differences in the cognitive task and analysis procedures, but another possibility is that other pathology present in our sample contributed to the activation pattern.

In the present investigation, the symptoms of PTSD were associated with reduced brain activation in both the ANCOVA and a simple regression analysis, but the results of the TBI within-group analysis indicated significant activation within

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several brain areas. Control subjects, in contrast, had elevated PTSD symptoms and did not exhibit a significant level of activation in their within-group analysis. Therefore, it appears that TBI increases brain activation during stimulus-response incompatibility to the point where task-related activation is observable, despite the presence of PTSD symptoms and any suppressive effects they might have. When considered in combination, the overall level and pattern of activation observed during this task seems to reflect the influence of both neural injury and emotional distress upon brain function. Relationships among these various conditions may be further complicated by the possibility that brain injury, in itself, may be a risk factor for the development of PTSD (Bryant, 2008) and depression (Jorge et al., 2004). However, the finding that PTSD symptoms are associated with reduced activation, while TBI has the opposite effect, suggests that the influences of PTSD and neural injury on brain function may be partially dissociable with functional neuroimaging.

The methodology used in the present investigation, fMRI, reveals changes at the network level of analysis and it is difficult to speculate upon underlying mechanisms of neural injury using these findings, alone. The results of the current study do have some parallels with those of Scheibel et al. (2007, 2009), including over-activation following TBI. Those previous findings were said to suggest deafferentiation due to diffuse axonal injury (Scheibel et al., 2009), and this is similar to the interpretation presented by Huang et al. (2009), who found abnormalities on magnetoencephalography and diffusion tensor imaging (DTI) in subjects with mild TBI. There is currently inconsistent evidence for white matter injury in combatants who have sustained a blast-related TBI of mild to moderate severity. Levin et al. (2010) reported that DTI findings in personnel imaged after an average interval exceeding 2 years after blast-related mild to moderate TBI did not differ from data obtained in a control group. In contrast, MacDonald et al. (2011) recently found DTI evidence of microstructural white matter injury in 29% of service members who had been medically evacuated from theater and initially imaged within 90 days following exposure to blast and other mechanisms of TBI. Evidence of white matter injury persisted in a subgroup with repeat DTI six to 12 months later. The role of white matter injury and other possible mechanisms of blast-related TBI is clearly an area that requires additional research.

The present study used a modified version of an fMRI paradigm that is sensitive to TBI severity in civilians (Scheibel et al., 2009), but the research design has several limitations. The identification of subjects with TBI and estimates of injury severity were based entirely on self-report, often involving recollection of events that occurred in the combat theatre many months earlier, and such information may be subject to recall biases and reliability problems (Fear et al., 2009). However, the design for this project included the screening of a much larger number of subjects with possible injury, an experienced clinician performed an interview to confirm the diagnosis, and subjects were not enrolled in the TBI group unless they clearly recalled events that met Department of Defense criteria (French & Parkinson, 2008). The Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995) is a superior instrument for measuring PTSD symptoms and for supporting a diagnosis of that disorder, but the CAPS often requires over 45 min to complete and use of the PCL-C allowed the acquisition of PTSD covariate data and completion of other study procedures during a single session. Other limitations of the current study include the use of only mild TBI subjects who had been injured many months before study (i.e., chronic injury), the presence of multiple injuries in some TBI subjects, the presence of orthopedic injury in only 5 of the 15 control subjects, no matching for combat exposure, and differences in recruitment strategy so that the control group was largely a community-based sample, while many TBI subjects were probably seeking services. Due to limited access to records there was no way to confirm how many subjects in each group had accessed services for mental health or physical complaints. Findings from this sample should not be generalized to more severe or more acute blast-related TBI and relevance for civilian, non-blast TBI populations is likely to be limited due to possible differences in the mechanism of injury, multiple injuries, and emotional factors such as PTSD. Future research on blast TBI may benefit from the use of an additional fMRI paradigm that relates more directly to emotional symptoms and the inclusion of a non-blast TBI group.

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