Effects of Severity of Traumatic Brain Injury and Brain Reserve on Cognitive-Control Related Brain Activation

Randall S. Scheibel,¹ Mary R. Newsome,¹ Maya Troyanskaya,¹ Joel L. Steinberg,²
Felicia C. Goldstein,³ Hui Mao,⁴ and Harvey S. Levin¹

Abstract

Functional magnetic resonance imaging (fMRI) has revealed more extensive cognitive-control related brain activation following traumatic brain injury (TBI), but little is known about how activation varies with TBI severity. Thirty patients with moderate to severe TBI and 10 with orthopedic injury (OI) underwent fMRI at 3 months post-injury using a stimulus response compatibility task. Regression analyses indicated that lower total Glasgow Coma Scale (GCS) and GCS verbal component scores were associated with higher levels of brain activation. Brain-injured patients were also divided into three groups based upon their total GCS score (3–4, 5–8, or 9–15), and patients with a total GCS score of 8 or less produced increased, diffuse activation that included structures thought to mediate visual attention and cognitive control. The cingulate gyrus and thalamus were among the areas showing greatest increases, and this is consistent with vulnerability of these midline structures in severe, diffuse TBI. Better task performance was associated with higher activation, and there were differences in the over-activation pattern that varied with TBI severity, including greater reliance upon left-lateralized brain structures in patients with the most severe injuries. These findings suggest that over-activation is at least partially effective for improving performance and may be compensatory.

Key words: brain reserve; cognitive control; functional MRI; Glasgow Coma Scale; traumatic brain injury

Introduction

IMPAIRMENTS IN COGNITIVE CONTROL (Miller and Cohen, 2001) and other executive functions are common following traumatic brain injury (TBI) associated with closed head trauma and are often a focus of rehabilitation (Cicerone et al., 2006; Levine et al., 2000). Studies using functional neuroimaging have found that patients with moderate to severe TBI typically have more distributed brain activation than uninjured subjects while performing executive function tasks such as working memory and inhibition (Christodoulou et al., 2001; Scheibel et al., 2003). Scheibel et al. (2007) found that activation specific to a condition of stimulus-response incompatibility was elevated in TBI patients within multiple areas, including the left precentral gyrus and bilateral cingulate, medial frontal, middle frontal, and superior frontal gyri. In addition, these TBI patients did not exhibit a relation between performance accuracy and activation that was observed within the anterior cingulate gyrus and medial prefrontal regions of uninjured subjects. Because activation was

increased but unrelated to task performance in the TBI group, this increased neural activity may reflect the inefficient utilization of neural resources.

Functional neuroimaging of mild TBI, as defined by Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) scores of 13–15, has disclosed alterations in the modulation of activation level by cognitive load (McAllister et al., 2001). In contrast, more severe injuries tend to increase the overall level of brain activity and produce more distributed activation patterns (Levin and Scheibel, 2005). Most functional magnetic resonance imaging (fMRI) studies of TBI have used small samples which have limited investigation of the relation between brain activation and TBI severity. Newsome et al. (2007) examined activation during a working memory task in relation to TBI severity in 10 patients, but the range of GCS scores was limited (i.e., 3–5). Their results indicated a significant negative correlation between activation and GCS score for a low working memory load condition and a positive correlation for a higher load condition. Scheibel et al. (2007) reported that the GCS score was negatively related to

¹Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, Texas.

²Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, Houston, Texas.

Departments of ³Neurology and ⁴Radiology, Emory University School of Medicine, Atlanta, Georgia.

activation during stimulus-response incompatibility within the anterior cingulate gyrus, basal ganglia, and insula of patients with moderate to severe TBI. However, this relation was relatively weak, the sample size was limited, and other potential mediators (e.g., age, education) were not explored.

The GCS is widely used to grade the overall severity of acute TBI and numerous studies have documented a relation between GCS scores and survival (Moore et al., 2006), quality of global recovery (Rovlias and Kotsou, 2004), and cognitive performance (Temkin, 1995). Individual GCS component scores have also been related to outcome measures with some evidence that the motor score may have the highest predictive validity (Al-Salamah et al., 2004; McNett, 2007). At the same time, classifying the severity of TBI according to GCS is often complicated by pharmacologic paralysis and sedation of critically injured patients and this approach does not consider other findings such as brain imaging (Saatman et al., 2008).

Age is also related to outcome following TBI, with older patients having poorer outcomes, and predictive models of TBI outcome often include age, health variables, injury characteristics, and GCS (Cremer et al., 2006; Rovlias and Kotsou, 2004; Temkin, 1995). Age-related activation increases and reduced functional asymmetry during fMRI with cognitive tasks have been reported in prefrontal areas (Cabeza, 2002) and in other brain regions, such as the parietal lobes (Nielson et al., 2002). Similar to age (Satz, 1993), education and intellectual function may also be important variables to control because these are thought to relate to brain reserve capacity and vulnerability to cognitive impairment following injury (Solé-Padullés et al., 2009). Brain reserve capacity, as indexed by age, education level, and general intelligence, is a construct which was proposed to explain threshold differences in the onset of clinical symptoms in individuals with neurological disorders (Satz, 1993).

In the current study, we examined the relation between acute severity of TBI, as measured by the GCS total and component scores, and brain activation during the performance of a stimulus-response compatibility task by patients who had sustained moderate to severe TBI. Regression analyses were used to examine the relation between brain activation and GCS scores and to evaluate the contribution of age, education, and estimated preinjury IQ (Barona et al., 1984) which we used as proxy measures of brain reserve. An additional analysis compared brain activation among different GCS severity levels and a comparison group with orthopedic injury (OI). Subjects with OI were used to control for host factors (e.g., risk-taking behavior) that predispose to injury and nonspecific effects of injury such as posttraumatic stress that could affect brain activation (Bryant et al., 2005). Our primary hypothesis was that TBI severity would be associated with greater and more distributed brain activation. We also hypothesized that older age, lower education level, and lower estimated pre-injury IQ would be related to increased activation during the task.

Methods

Participants

The study was approved by the Interinstitutional Review Board at all participating institutions, and all subjects provided written informed consent in accordance with the Declaration of Helsinki. Twenty-one patients who had sustained moderate to severe TBI and 10 patients with OI, but no evi-

dence of TBI, were prospectively recruited from two major trauma centers and a rehabilitation hospital in Houston, Texas. Nine additional TBI patients were recruited through a Level 1 trauma center at the Emory University School of Medicine in Atlanta, Georgia. Five TBI patients and three OI patients were women, and two of the TBI patients were left-handed. None of the patients had a history of severe neurological or psychiatric disorders or alcohol or drug dependency. The TBI subjects were grouped by the first available post-resuscitation GCS score: moderate (GCS = 9–12, or 13–15 with brain lesion on computed tomography performed within 24 h after injury), severe (GCS = 5–8), and very severe (GCS = 3 or 4; Table 1). Medical records indicated that none of the GCS scores were modified due to intubation or the use of sedation or paralytic agents. Functional imaging for this study was deferred until post-traumatic amnesia (PTA) had resolved (Levin et al., 1979), and there were no physical injuries or pain that could interfere with completion of the scanning procedures. The nominal injury-study interval was 3 months, but there was variation in scheduling due to individual differences in resolution of PTA.

Functional outcome measure and depression rating scale

The Center for Epidemiologic Studies–Depression (CES-D) rating scale (Radloff, 1977) and the Extended Glasgow Outcome Scale (GOS-E) (Wilson et al., 1998) were completed on the same occasion as fMRI. The GOS-E is a rating scale that classifies functional outcome into eight categories based on information obtained during a structured interview.

Stimulus response compatibility task

The Integrated Functional Imaging System (MRI Devices Corporation, Orlando, FL) was used to present task stimuli and record responses during fMRI scanning for subjects studied in Houston. An equivalent system utilizing a button box response recording device (Current Designs, Philadelphia, PA), a video projector and rear projection screen, and E-prime software (Psychology Software Tools, Pittsburgh, PA) running on a notebook PC was used for subjects examined in Atlanta. Ten alternating blocks of arrows stimuli were presented to the subjects; five blocks had stimuli that were spatially compatible with the required response, and five had spatially incompatible stimuli. There were 20 arrows within each block, half of which pointed left and half of which pointed right, and there were no intervening stimuli or delays between the blocks. Each arrow was presented for 265 msec, with an inter-stimulus interval of 935 msec and total run duration of 4 min. During compatible blocks, the subject saw blue arrows that pointed either left or right and pressed the spatially compatible response key with the ipsilateral index finger. During incompatible blocks, the arrows were red and the subject pressed the response key with the index finger that was contralateral to the direction the arrow was pointing.

Centrally active medications were withheld on the day of the fMRI assessment, and all subjects completed a visual screening. Vision correction was used, if necessary. Training was provided within several hours prior to scanning to ensure that all of the subjects understood the instructions and were able to perform the task with equivalent accuracy (Price et al., 2006). Following presentation of the task instructions,

TABLE 1. SUMMARY OF INJURY CHARACTERISTICS, DEMOGRAPHIC VARIABLES, AND OUTCOME MEASURES FOR THE PATIENT GROUPS

	OI (n = 10)			Moderate TBI (n = 9)			Severe TBI (n = 8)			Very severe TBI (n = 13)		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
First available GCS score	NA	NA	NA	12.67	1.22	12.00	6.62	1.30	6.50	3.15	0.38	3.00
Motor component	NA	NA	NA	5.00	1.19	5.00	3.38	1.30	4.00	1.00	0.00	1.00
Verbal component	NA	NA	NA	3.78	0.83	4.00	1.75	0.46	2.00	1.00	0.00	1.00
Eye opening component	NA	NA	NA	3.89	0.33	4.00	1.50	0.76	1.00	1.15	0.38	1.00
Demographics, depression, lesions, and outcome												
Age at injury (years)	30.79	10.46	33.25	46.32	7.29	45.90	22.46	3.99	21.95	24.12	7.04	21.80
Education (years)	12.50	3.24	11.00	14.56	2.74	14.00	13.50	2.51	13.50	12.54	1.94	12.00
Estimated preinjury IQ	93.40	10.90	92.00	101.89	10.89	106.00	93.50	9.01	91.50	99.08	9.45	101.00
Depression (CES-D)	13.20	9.75	12.50	12.56	11.91	6.00	13.62	8.55	16.00	14.54	7.07	12.00
Time since injury (years)	0.38	0.24	0.32	0.31	0.06	0.30	0.30	0.04	0.30	0.34	0.10	0.30
Lesion count ^a	NA	NA	NA	9.44	17.02	4.00	34.75	61.83	3.50	47.23	50.23	40.00
GOS-E score	7.20	1.40	8.00	6.89	0.93	7.00	5.25	1.16	5.00	5.92	1.50	6.00

GCS, Glasgow Coma Scale; CES-D, Center for Epidemiologic Studies–Depression; GOS-E, Extended Glasgow Outcome Scale; NA, not applicable; OI, orthopedic injury; TBI, traumatic brain injury.

^aThere was high variability within the severe TBI group: One patient had 97 focal lesions (shearing, contusions), and another had 161 (hemosiderin deposits, contusions). All other severe TBI patients had nine lesions or less.

structured pre-scan practice was provided until the subject performed with 65% accuracy or better during both the compatible and incompatible task conditions. Behavioral data recorded during scanning included the total number of correct responses and reaction time (RT) to correct responses for the compatible and incompatible conditions. Although the block design methodology includes fMRI data for incorrect responses in addition to correct responses, we selected this design because the scanning time was shorter than event-related paradigms (Price and Friston, 2002).

Magnetic resonance imaging scan acquisition

In Houston, a GE Signa CV/i 1.5-Tesla (T) scanner (General Electric Medical Systems, Milwaukee, WI) with standard quadrature headcoil was used to obtain whole-brain images. A Philips Intera 1.5-T scanner (Philips Medical Systems, Best, The Netherlands) was used in Atlanta. Blood oxygen level dependent (BOLD) T2*-weighted gradient-echo echoplanar images (EPI) were acquired in 21 axial slices of 6-mm thickness with a 1-mm gap, using a 240-mm field of view (FOV), 64×64 matrix, and a TR of 3000 msec, TE 50 msec, and 90-degree flip angle. A total of 86 volumes were acquired, and the first six were discarded to allow for signal equilibrium. A set of high-resolution T1-weighted 3D-SPGR images was also acquired in 124 sagittal slices of 1.5 mm thickness with no gap and 240 mm FOV, 256×256 matrix, TR of 4.6 msec, TE of 26 msec, and 30-degree flip angle, and was used to co-register with the functional images. Additional structural imaging was performed to assist with the identification of lesions, including an axial FLAIR, an axial T2-weighted GRE, and an axial T1-weighted series. A board certified neuroradiologist completed a coding form indicating the location and pathology type (e.g., contusion, gliosis) for each lesion.

Image analysis

The EPI volumes were realigned to each other using Statistical Parametric Mapping (SPM) software (Friston et al.,

1995) and aligned with the high-resolution 3D-SPGR anatomical scan using the SPM99 mutual information coregistration procedure. None of the series had greater than 2 mm or 2 degrees of motion. Functional and anatomical data were then transformed to Talairach stereotactic coordinates using AFNI proportional transformation. The Talairach-transformed images were resliced to 2×2×2 mm resolution and convolved with a 6-mm full-width at half-maximum (FWHM) isotropic Gaussian filter. A high-pass temporal filter cutoff of 96 sec was used to reduce low-frequency noise. SPM99 analyses using the general linear model were then conducted at each voxel for block design boxcar basis functions convolved with the SPM canonical hemodynamic response function, in which activation was defined as the parameter estimate during the incompatible blocks minus the parameter estimate during the compatible blocks (incompatible minus compatible [IMC]).

The IMC contrast data were collapsed to a single activation contrast image for each patient. Controlling the smoothness of echo-planar images is an important factor when data from multiple scanners are combined (Friedman et al., 2006), and because data were acquired using two different systems, AFNI was used to smooth the contrast images to a common level.

Statistical analysis

These data were then entered into the second level of an SPM2 random effects analysis, where statistical significance was defined as a one-tailed probability level less than 0.05 after random field theory correction for multiple comparisons over the whole brain volume at the cluster level of inference. The initial cluster-defining (i.e., height) threshold for these analyses was $p = 0.05$ (uncorrected), but a more conservative threshold was systematically used if there was a significant cluster at the $p = 0.05$ cluster level, corrected, that exceeded 2,000 voxels. In such situations, a more conservative threshold was chosen until the analysis produced one or more significant clusters that all had a size equal to or less than 2,000

voxels, or until the cluster had been reduced in size as much as possible while remaining significant.

Three separate SPM analyses were performed, including a random effects multiple regression analysis to examine the relation of IMC activation with total GCS score, age, education, and estimated IQ for all of the subjects who had sustained a TBI. Although the subjects had been trained to have similar levels of task performance during fMRI scanning, accuracy during the incompatible blocks was included as an additional control for this factor. All of the regressors were group-mean corrected and all were included within the model simultaneously. An equivalent multiple regression model used the same accuracy and demographic variables, but examined the relation between activation and each of the GCS component scores (i.e., eye opening, motor response, verbal response) within the TBI sample. Finally, the SPM multiple regression procedure was used to perform an analysis of covariance analysis (ANCOVA) comparing the four groups (moderate TBI, severe TBI, very severe TBI, OI controls) and with group-mean corrected values for age, education, estimated IQ, and accuracy included as covariates. A matlab (Mathworks, Natick, MA) script was then used to extract all coordinates within the significant clusters and anatomical labels associated with these coordinates were identified using the Talairach Daemon (Lancaster et al., 2000).

Results

Demographics and injury severity

The nonparametric Kruskal-Wallis test was used to compare all four groups on age ($p = 0.001$), education ($p = 0.194$), estimated IQ ($p = 0.198$), and time since injury ($p = 0.803$). Lesion count was compared among the three TBI groups ($p = 0.074$; Table 1). Age was the only variable with a statistically significant difference and pairwise Wilcoxon tests showed that patients with moderate TBI were older than the subjects within the OI ($p = 0.010$), severe TBI ($p = 0.004$), and very severe TBI groups ($p = 0.002$). Fisher's Exact test indicated no significant differences among the four groups for handedness ($p = 0.332$) and gender ($p = 0.378$).

Outcome and depression measures

A nonparametric Kruskal-Wallis test revealed a significant difference among the four groups on the three month GOS-E ($p = 0.008$; Table 1). Pairwise comparisons using the Wilcoxon test indicated better outcome in OI patients relative to patients with either severe ($p = 0.017$) or very severe TBI ($p = 0.045$), while patients with moderate TBI had better outcome than

patients in the severe TBI group ($p = 0.019$). However, there was no significant difference between patients with moderate TBI and patients with either very severe TBI ($p = 0.11$) or OI ($p = 0.254$) and the groups with severe and very severe TBI did not differ on the GOS-E ($p = 0.217$). The Kruskal-Wallis test also indicated no significant differences among the four groups for depressive symptoms, as assessed by the CES-D ($p = 0.865$; Table 1).

Task performance during scanning

Procedures that were implemented to equalize group performance on the stimulus-response compatibility task during fMRI data acquisition were successful. During compatible trials the groups did not differ in accuracy, $F(3,36) = 1.93$, $p = 0.143$, or RT, $F(3,36) = 0.74$, $p = 0.537$ (Table 2). Similarly, during the incompatible trials accuracy, $F(3,36) = 1.97$, $p = 0.136$, and RT, $F(3,36) = 0.76$, $p = 0.525$, did not differ among the groups.

Relation of Glasgow Coma Scale total score to brain activation

Coordinates for voxels greater than 16 mm apart are summarized in the tables, and selected Brodmann areas (BAs), as given in the Talairach atlas, are identified in parentheses. More detailed information is presented in the text. Because of anatomical differences between individuals, the BAs and the anatomical labels are approximate.

There were no areas with a significant positive regression coefficient between the GCS total score and IMC brain activation, but lower GCS scores were associated with greater activation (i.e., significant negative regression coefficient) within a primarily midline cluster that included parts of the left anterior cingulate gyrus (BA24, BA32), both thalami, the basal ganglia (left globus pallidus, right putamen), and the right precentral (BA6), inferior frontal, and middle frontal gyri (BA6; Fig. 1 and Table 3a).

Relation of Glasgow Coma Scale component scores to brain activation

Brain activation was not related to scores on either the motor or eye opening components of the GCS. However, there were two clusters representing a significant negative association between activation and the GCS verbal score (Fig. 1 and Table 4a). The most anterior of these clusters included parts of bilateral medial (bilateral BA9, left BA10) and the left middle and superior frontal gyri (BA9), as well as both anterior cingulate gyri (bilateral BA24, BA32, BA33) and the right

TABLE 2. SUMMARY OF COGNITIVE PERFORMANCE MEASURES FROM THE STIMULUS-RESPONSE COMPATIBILITY TEST FOR THE PATIENT GROUPS

	OI (n = 10)			Moderate TBI (n = 9)			Severe TBI (n = 8)			Very severe TBI (n = 13)		
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median
Compatible accuracy (%)	92.90	3.25	93.50	89.11	9.21	92.00	92.63	4.66	93.00	86.69	8.53	89.00
Compatible RT (msec)	380.10	61.31	368.00	397.89	44.26	396.00	406.50	75.79	390.50	364.69	84.59	340.00
Incompatible accuracy (%)	92.70	4.64	93.00	83.89	11.25	85.00	86.12	10.03	88.00	84.46	9.69	84.00
Incompatible RT (msec)	417.00	82.15	392.50	479.78	97.34	465.00	462.63	119.70	427.00	424.62	122.76	399.00

RT, reaction time; TBI, traumatic brain injury.

FIG. 1. Areas with a significant negative regression coefficient between brain activation and the GCS total score (left column, height threshold $T = 2.89$, $p = 0.004$) or verbal component score (right column, height threshold $T = 2.74$, $p = 0.006$) of TBI patients overlaid on axial anatomical images from a typical orthopedic injury patient. Procedures for determining the height threshold are specified within the text.

caudate nucleus (body, head). The more posterior cluster encompassed bilateral areas of the basal ganglia (bilateral putamen, left globus pallidus), thalami, and cingulate gyri (bilateral BA23). This cluster also extended into the right parahippocampal gyrus (BA27, BA30).

Comparisons among the TBI and OI Groups

An ANCOVA was performed to further examine the relation between brain activation and TBI severity, with assignment to the different TBI groups based upon the total GCS

TABLE 3. STATISTICAL PARAMETRIC MAPPING SUMMARY TABLES FOR MULTIPLE REGRESSION ANALYSIS OF ARROWS ACTIVATION (INCOMPATIBLE MINUS COMPATIBLE CONDITIONS) WITH TOTAL GCS SCORE, DEMOGRAPHIC VARIABLES, AND ACCURACY^a

Corrected ^b cluster $p \leq$	k^c	x^d	y	z (mm)	Location
3a. Negative regression of total GCS with arrows activation					
0.002	1949	6	-3	15	Near right thalamus
		-8	7	14	Left caudate nucleus (body)
		-16	9	31	Left cingulate gyrus
		32	-4	30	Right frontal lobe (white matter)
		16	7	27	Right cingulate gyrus
Height threshold ^e : $p = 0.004$ ($T = 2.89$, degrees of freedom = 24). Smoothness FWHM = 9.1 9.6 9.1 {voxels}. Search volume = 93545 voxels = 104.8 resolution elements (resels).					
3b. Positive regression of age with arrows activation					
0.015	1972	6	1	17	Near right caudate nucleus (body)
		-16	9	31	Left cingulate gyrus
		-12	-3	13	Left thalamus (ventral anterior nucleus)
		22	24	15	Right frontal lobe (white matter)
		24	7	16	Right frontal lobe (white matter)
		34	-4	30	Right frontal lobe (white matter)
		18	-13	41	Right cingulate gyrus
0.014	2000	-30	-38	20	Near left insula
		-32	-53	19	Left temporal lobe (white matter)
		-26	-69	15	Left cuneus
		-22	-85	4	Left lingual gyrus
Height threshold ^e : $p = 0.008$ ($T = 2.59$, degrees of freedom = 24). Smoothness FWHM = 9.1 9.6 9.1 {voxels}. Search volume = 93545 voxels = 104.8 resolution elements (resels).					
3c. Negative regression of BEPIQ with arrows activation					
0.004	3259	-12	-26	22	Left corpus callosum
		28	-8	30	Right frontal lobe (white matter)
		8	-22	25	Right corpus callosum
		53	5	16	Right inferior frontal gyrus (BA44)
		20	-38	50	Right parietal lobe (white matter)
		6	-5	13	Right thalamus (anterior nucleus)
		22	-32	15	Right caudate nucleus (tail)
		18	-19	47	Right frontal lobe (white matter)
Height threshold ^e : $p = 0.011$ ($T = 2.45$, degrees of freedom = 24). Smoothness FWHM = 9.1 9.6 9.1 {voxels}. Search volume = 93545 voxels = 104.8 resolution elements (resels).					
3d. Positive regression of red accuracy with arrows activation					
0.010	5405	-51	-39	26	Left inferior parietal lobule
		-34	-55	21	Left temporal lobe (white matter)
		-14	-34	26	Left cingulate gyrus
		14	-41	30	Right cingulate gyrus (BA31)
		42	-33	0	Right temporal lobe (white matter)
		26	-55	30	Right parietal lobe (white matter)
		-26	-76	24	Left temporal lobe (white matter)
		8	-48	58	Right precuneus (BA7)
		-40	-70	-3	Left inferior occipital gyrus
		-38	-77	9	Left middle occipital gyrus
		32	-63	16	Right middle temporal gyrus
		16	-68	42	Right precuneus
		36	-37	28	Right inferior parietal lobule

Height threshold^e: $p = 0.026$ ($T = 2.04$, degrees of freedom = 24).

Smoothness FWHM = 9.1 9.6 9.1 {voxels}.

Search volume = 93545 voxels = 104.8 resolution elements (resels).

Brodmann areas are reported within parentheses. BA, Brodmann area; BEPIQ, Barona estimated preinjury IQ; FWHM, full width at half maximum; GCS, Glasgow Coma Scale; OL, orthopedic injury; TBI, traumatic brain injury.

^aRelative maxima shown are greater than 16 mm apart.

^bProbability at the cluster level of significance after random field theory correction over the whole brain search volume.

^cNumber of voxels within a cluster.

^dNegative values along the x -axis are defined to be in the patient's left hemisphere.

^eCluster defining threshold (see text for cluster defining procedures).

TABLE 4. STATISTICAL PARAMETRIC MAPPING SUMMARY TABLES FOR MULTIPLE REGRESSION ANALYSIS OF ARROWS ACTIVATION (INCOMPATIBLE MINUS COMPATIBLE CONDITIONS) WITH GCS COMPONENT SCORES AND DEMOGRAPHIC VARIABLES^a

Corrected ^b cluster p≤	k ^c	x ^d	Y	Z (mm)	Location
4a. Negative regression of GCS verbal score with arrows activation					
0.015	1525	−14	42	18	Left medial frontal gyrus
		−2	22	15	Left corpus callosum
		14	20	8	Right caudate (body)
		2	40	20	Right medial frontal gyrus
0.005	1932	−6	−30	16	Left corpus callosum
		−12	−13	8	Left thalamus (ventral lateral nucleus)
		4	−7	8	Right thalamus
		18	3	29	Right frontal lobe (white matter)
		12	−36	17	Right corpus callosum
		−24	−44	21	Left parietal lobe (white matter)
		8	−12	26	Right cingulate gyrus
Height threshold ^e : p = 0.006 (T = 2.74, degrees of freedom = 22). Smoothness FWHM = 9.0 9.5 8.9 {voxels}. Search volume = 93545 voxels = 110.8 resolution elements (resels).					
4b. Positive regression of age with arrows activation					
0.023	1956	6	3	16	Near right caudate nucleus (body)
		−16	9	31	Left cingulate gyrus
		−10	1	15	Left caudate nucleus (body)
		22	24	15	Right frontal lobe (white matter)
		24	7	16	Near right putamen
0.025	1920	34	−4	30	Right frontal lobe (white matter)
		−30	−38	30	Near left insula
		−26	−69	15	Left cuneus
		−32	−53	19	Temporal lobe (white matter)
		−22	−85	4	Left lingual gyrus
Height threshold ^e : p = 0.010 (T = 2.51, degrees of freedom = 22). Smoothness FWHM = 9.0 9.5 8.9 {voxels}. Search volume = 93545 voxels = 110.8 resolution elements (resels).					
4c. Negative regression of BEPIQ with arrows activation					
0.015	1369	−46	2	9	Left precentral gyrus
		−48	−37	28	Left inferior parietal lobule
		−48	−33	44	Left inferior parietal lobule (BA40)
		−48	−16	23	Left postcentral gyrus
0.050	968	−10	−28	22	Left corpus callosum
		−9	−25	26	Left cingulate gyrus
		−23	−29	15	Near left caudate nucleus (tail)
Height threshold ^e : p = 0.005 (T = 2.82, degrees of freedom = 22). Smoothness FWHM = 9.0 9.5 8.9 {voxels}. Search volume = 93545 voxels = 110.8 resolution elements (resels).					
4d. Positive regression of red arrows accuracy with arrows activation					
0.025	1917	−51	−39	26	Left inferior parietal lobule
		−36	−51	21	Left temporal lobe (white matter)
		−14	−34	26	Left cingulate gyrus
		−26	−76	26	Left occipital lobe (white matter)

Height threshold^e: $p = 0.010$ ($T = 2.51$, degrees of freedom = 22).

Smoothness FWHM = 9.0 9.5 8.9 [voxels].

Search volume = 93545 voxels = 110.8 resolution elements (resels).

Brodmann areas are reported within parentheses. BA, Brodmann area; BEPIQ, Barona estimated preinjury IQ; FWHM, full width at half maximum; GCS, Glasgow Coma Scale; OI, orthopedic injury; TBI, traumatic brain injury.

^aRelative maxima shown are greater than 16 mm apart.

^bProbability at the cluster level of significance after random field theory correction over the whole brain search volume.

^cNumber of voxels within a cluster.

^dNegative values along the x-axis are defined to be in the patient's left hemisphere.

^eCluster defining threshold (see text for cluster defining procedures).

FIG. 2. Three-plane maximum intensity projections for selected group contrasts. Procedures for determining the height threshold are specified within the text.

score. The OI subjects were also included as a separate group. As expected, there were no areas where the OI group had significantly greater activation than any of the TBI groups.

The moderate TBI group did not have any brain areas with significantly greater activation than the OI group. However, the severe TBI group had a higher level of activation than the OI patients within a large ($k = 3357$) posterior cluster that was significant when the height threshold was $p = 0.020$, but not when the threshold was reduced to decrease the cluster's size. This cluster included portions of the cerebellum, the right parietal lobe, bilateral posterior cingulate gyri (bilateral BA23, BA29, BA30), subcortical brain structures (e.g., left thalamus), and areas within the right temporal and both occipital lobes (Fig. 2 and Table 5a). Patients with very severe TBI also had

greater activation than the OI group and this analysis produced five significant clusters, including a bilateral cluster ($k = 1932$), which included midline cortical and subcortical tissue such as the cingulate gyri (bilateral BA23, BA31) and both thalami (Table 5b). There was another cluster that was predominantly within the right frontal lobe (precentral, medial, and middle frontal gyri) and cingulate gyrus (BA24), one that included mostly medial frontal structures (e.g., bilateral medial frontal gyri) and anterior cingulate gyri (bilateral BA24, left BA32), a right-sided cluster within the insula (BA13) and temporal lobe (e.g., middle and superior temporal gyri), and a cluster that included mostly right parietal cortex (BA5, BA7, BA40).

Comparisons among the TBI groups indicated no instances where a less severely injured group had significantly greater

TABLE 5. STATISTICAL PARAMETRIC MAPPING SUMMARY FOR ANALYSIS OF COVARIANCE COMPARING THE PATIENT GROUPS ON ARROWS ACTIVATION (INCOMPATIBLE MINUS COMPATIBLE CONDITIONS)^a

<i>Corrected^b cluster p≤</i>	<i>k^c</i>	<i>x^d</i>	<i>Y</i>	<i>Z (mm)</i>	<i>Location</i>
5a. OI < severe TBI					
0.047	3357	-8	-26	22	Left corpus callosum
		10	-34	22	Right corpus callosum
		-26	-24	23	Near left insula
		55	-29	11	Right superior temporal gyrus
		-8	-49	1	Left cerebellum (culmen)
		42	-19	3	Right insula (BA13)
		44	-40	9	Right superior temporal gyrus
		-24	-50	6	Near left parahippocampal gyrus
		30	-38	22	Right parietal lobe (white matter)
		18	-48	10	Near right posterior cingulate gyrus
		0	-62	3	Cerebellum (vermis)
Height threshold ^c : $p = 0.020$ ($T = 2.14$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5b. OI < very severe TBI					
0.000	1932	-8	-26	22	Left corpus callosum
		6	-3	15	Near right thalamus
		-22	-40	24	Left frontal lobe (white matter)
		-26	-24	23	Near left insula
0.010	683	34	-1	52	Right middle frontal gyrus
		18	-15	43	Right cingulate gyrus (BA24)
0.000	1704	-32	-6	57	Left middle frontal gyrus (BA6)
		-16	8	50	Left medial frontal gyrus (BA6)
		-43	-4	38	Left precentral gyrus (BA6)
0.024	516	42	-38	9	Right superior temporal gyrus
0.011	670	10	-46	54	Right precuneus (BA7)
Height threshold ^c : $p = 0.001$ ($T = 3.40$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5c. Moderate TBI < severe TBI					
0.018	1984	0	-26	22	Corpus callosum
		-18	-46	6	Near left parahippocampal gyrus
		14	-25	7	Right thalamus (pulvinar)
		-6	-19	8	Left thalamus (medial dorsal nucleus)
		2	-62	3	Cerebellum (vermis)
Height threshold ^c : $p = 0.007$ ($T = 2.60$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5d. Severe TBI < very severe TBI					
0.012	3418	-32	-5	52	Left precentral gyrus
		-26	-39	30	Left parietal lobe (white matter)
		-53	-35	42	Left inferior parietal lobule
		-40	2	35	Left precentral gyrus
		-34	-47	41	Left parietal lobe (white matter)
		-34	-55	21	Left temporal lobe (white matter)
Height threshold ^c : $p = 0.013$ ($T = 2.33$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5e. Moderate TBI < very severe TBI					
0.001	1846	2	-26	22	Right corpus callosum
		4	-3	13	Near right thalamus
		-8	8	14	Left caudate (body)
		12	-25	9	Right thalamus (pulvinar)
Height threshold ^c : $p = 0.002$ ($T = 3.10$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					

(Continued)

TABLE 5. (CONTINUED)

Corrected ^b cluster $p \leq$	k^c	x^d	Y	Z (mm)	Location
5f. Positive regression of age with arrows activation					
0.013	2388	2	-26	22	Right corpus callosum
		-34	-52	15	Left temporal lobe
		-28	-64	3	Left middle occipital gyrus
		-28	-36	18	Left temporal lobe (white matter)
		-50	-52	4	Left middle temporal gyrus
Height threshold ^e : $p = 0.008$ ($T = 2.54$). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5g. Positive regression of education with arrows activation					
0.029	3832	-34	-3	52	Left middle frontal gyrus (BA6)
		-32	-52	52	Left superior parietal lobule (BA7)
		-51	-33	40	Left inferior parietal lobule
		-42	0	30	Left inferior frontal gyrus
		-50	15	31	Left middle frontal gyrus
Height threshold ^e : $p = 0.020$ ($T = 2.14$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5h. Negative regression of BEPIQ with arrows activation					
0.039	1266	8	-22	25	Right corpus callosum
		-10	-24	21	Left corpus callosum
		8	-5	11	Right thalamus (anterior nucleus)
		-24	-30	16	Near left caudate nucleus (tail)
Height threshold ^e : $p = 0.005$ ($T = 2.74$, degrees of freedom = 32). Smoothness FWHM = 9.5 10.2 9.4 {voxels}. Search volume = 92104 voxels = 89.5 resolution elements (resels).					
5i. Positive regression of red arrows accuracy with arrows activation					
0.045	5074	-18	-51	58	Left superior lobule (BA7)
		12	-39	28	Right cingulate gyrus
		-14	-34	27	Left cingulate gyrus
		8	-48	58	Right precuneus (BA7)
		-14	-5	11	Left thalamus (ventral anterior nucleus)
		26	-57	32	Right parietal lobe (white matter)
		-38	-37	46	Left inferior parietal lobe
		26	-54	54	Right parietal lobe (white matter)
		-14	-16	63	Left precentral gyrus (BA6)
		-22	-11	45	Left frontal lobe (white matter)
		12	-66	46	Right precuneus
		51	-27	44	Right inferior parietal lobule
		42	-40	48	Right inferior parietal lobule
		-34	-5	56	Left middle frontal gyrus (BA6)

Height threshold^e: $p = 0.031$ ($T = 1.93$, degrees of freedom = 32).

Smoothness FWHM = 9.5 10.2 9.4 {voxels}.

Search volume = 92104 voxels = 89.5 resolution elements (resels).

Brodman areas are reported within parentheses. BA, Brodmann area; BEPIQ, Barona estimated preinjury IQ; FWHM, full width at half maximum; GCS, Glasgow Coma Scale; OI, orthopedic injury; TBI, traumatic brain injury.

^aRelative maxima shown are greater than 16 mm apart.^bProbability at the cluster level of significance after random field theory correction over the whole brain search volume.^cNumber of voxels within a cluster.^dNegative values along the x -axis are defined to be in the patient's left hemisphere.^eCluster defining threshold (see text for cluster defining procedures).

activation than a group with a more severe TBI, whereas groups with more severe TBI had higher levels of activation. The severe TBI group had greater activation than the moderate TBI group within a posterior, midline region that extended bilaterally into the posterior cingulate gyri (bilateral BA23, BA29, BA30), the cerebellum, and the thalami and occipital lobes of both cerebral hemispheres (Fig. 2 and Table 5c). Relative to the moderate TBI group, patients with very severe TBI had significantly greater activation within a midline area that included bilateral posterior cingulate gyri (bilateral BA23, BA29) and thalami, as well as the right precuneus (BA31; Table 5e). Finally, the very severe TBI group had greater activation than the severe TBI group in a large, left-sided cluster that could not be reduced in size and that was located mostly within the frontal (precentral, medial frontal, inferior frontal, and middle frontal gyri) and parietal lobes (postcentral gyrus, precuneus, inferior and superior parietal lobules; Table 5d). This cluster also included a portion of the left cingulate gyrus (BA24, BA31).

Relation of age and education to brain activation

The multiple regression models (i.e., total GCS, GCS component scores) produced two clusters where older age was associated with a higher level of brain activation (i.e., significant positive regression coefficient). For both models the results included an anterior cluster that was midline and included bilateral anterior cingulate gyri (bilateral BA24 and BA33, left BA32), bilateral thalami, and parts of the basal ganglia (bilateral putamen, left globus pallidus; Tables 3b and 4b). There was some extension into the right precentral (BA6) and inferior frontal gyri. Both models also produced a second cluster on the left that included the posterior cingulate gyrus (BA30, BA31), part of the insula (BA13), and portions of the occipital (cuneus, precuneus, and the lingual, inferior occipital, and middle occipital gyri) and temporal lobes (middle and superior temporal gyri). The results from the ANCOVA, which included both OI and TBI patients, differed from those of the two multiple regression analyses. With the ANCOVA there was a significant positive relation between age and activation within a single cluster that included bilateral posterior cingulate gyri (bilateral BA23, left BA30), as well as the left parahippocampal gyrus (BA30) and parts of the left occipital (cuneus and the lingual and middle occipital gyri) and temporal (middle and superior temporal gyri) lobes (Table 5f). This cluster also extended into the left insula (BA13) and thalamus.

Education was not related to brain activation within multiple regression models with either total GCS or the GCS component scores. However, when included in the ANCOVA as a covariate, higher levels of education were associated with greater activation within a large, left-sided cluster that included the cingulate gyrus (BA24) and areas of the frontal (precentral, medial frontal, inferior frontal, and middle frontal gyri) and parietal lobes (postcentral and supramarginal gyri, precuneus, inferior and superior parietal lobules; Table 5g).

Relation of estimated pre-injury IQ to brain activation

All three statistical models revealed an association between lower estimated pre-injury IQ and higher levels of brain activation within midline cerebral structures. However, there were differences in the distribution and extent of the clusters.

The multiple regression analysis with GCS component scores indicated a negative relation between activation and IQ within two clusters, including a midline cluster in bilateral portions of the posterior cingulate gyri (BA23) and thalami (Table 4c). A second, left-sided cluster was located within the frontal (inferior frontal gyrus, BA9, BA44; precentral gyrus, BA4, BA6), parietal (postcentral gyrus; inferior parietal lobule, BA40; supramarginal gyrus, BA40), and temporal lobes (superior temporal gyrus, BA22) and included the insula (BA13). In contrast, the regression model with total GCS produced a single large cluster with many of the same midline structures (e.g., posterior cingulate gyrus and thalamus), but also with greater extension into the right hemisphere (Table 3c). This cluster included part of the right parietal (postcentral gyrus, paracentral lobule, inferior and superior parietal lobules, precuneus) and right posterior frontal lobes (precentral and inferior frontal gyri). Results from the ANCOVA indicated a negative relation between IQ and activation within a smaller cluster that included both thalami and the posterior cingulate gyri (bilateral BA23; Table 5h).

Relation of task performance to brain activation

Each of the three analyses produced a single cluster where better task accuracy was associated with higher levels of brain activation, but the distribution of the cluster differed some depending upon the model. For the regression model with GCS component scores (Table 4d), this cluster was located entirely within the left hemisphere and included the cingulate gyrus (BA23, BA31) and structures within the occipital (cuneus, precuneus, and middle occipital gyri), temporal (middle and superior temporal gyri), and parietal (precuneus, inferior parietal lobule, supramarginal gyrus) lobes. However, the ANCOVA and the regression model with the total GCS score each produced a large bilateral cluster ($k > 5000$) that did not survive additional reductions in the cluster-defining threshold. Therefore, for these two analyses the positive relation between accuracy and activation is reported here as a cluster within an extensive area of the posterior cerebrum (Tables 3d and 5i), including parts of both parietal lobes and bilateral posterior cingulate gyri (BA23). The cluster from the regression model with total GCS score also included structures within both temporal lobes and much of the left occipital lobe, while the cluster produced by the ANCOVA had some anterior extension into a posterior and medial portion of the left frontal lobe (e.g., precentral gyrus, medial frontal gyri) and included parts of the right temporal lobe (middle and superior temporal gyri), left thalamus, and globus pallidus.

Discussion

Relation of GCS component scores to brain activation

During a condition of stimulus-response incompatibility designed to engage cognitive control, lower total GCS score was related to increased brain activation within midline structures that included the left anterior cingulate gyrus and both thalami. However, when the regression model included separate GCS component scores only the verbal score had a significant relation with brain activation. Lower verbal scores were associated with higher activation levels within the anterior and posterior cingulate gyri, the medial frontal cortex, and deep midline structures that included the thalamus and

basal ganglia. A number of these brain areas have been reported to have a role in visual attention, conflict monitoring, error detection, and response inhibition (Garavan et al., 2002; Kim et al., 1999). Thus, we found that the GCS verbal component was related to brain activity within neural networks that are likely to be involved in visual attention and the inhibition of pre-potent responses. Although the GCS motor component has often been reported to have a stronger relation with survival or overall level of disability (Al-Salamah, et al., 2004), other studies have found that the eye and verbal components are good predictors when they can be reliably obtained (Haukoos et al., 2007). Our finding that the GCS verbal score was specifically related to cognitive control induced brain activation may reflect that the transition to normal consciousness is graded on the verbal component of the GCS by resolution of confusion, a relatively late stage of the initial hospitalization when sedation has been lifted and patients are beginning to consistently follow commands, i.e., their motor scores have already approached a normal level. This delayed recovery of the verbal component of the GCS was confirmed by serial observations of 135 severe TBI patients (Bricolo et al., 1980). In contrast, the effects of pharmacologic management during more acute phases of injury may mask the predictive value of motor scores, at least in relation to later brain activation during cognitive performance.

TBI severity between-group comparisons

Between-group comparisons revealed increased cognitive-control related activation in TBI patients with a total GCS score of 8 or less. During the stimulus-response incompatibility condition, patients with severe (GCS = 5–8) or very severe TBI (GCS = 3–4) had greater activation within the thalamus and posterior cingulate gyrus (BA23) than either moderate TBI or OI patients. Relative to the OI control group, patients with severe TBI also increased activation within a large portion of the right temporal lobe while the very severe TBI group had diffusely increased activation within both parietal lobes, as well as the right temporal lobe and a smaller area of the posterior frontal lobes. These findings are consistent with previous studies of cognitive control that have reported increased, diffuse activation in patients with severe TBI (Christodoulou et al., 2001; Scheibel et al., 2003).

Previous functional imaging investigations of TBI have not examined activation differences in relation to severity of acute injury. We found that patients who sustained worse than moderate TBI had greater task-related activation within a midline region that included the posterior cingulate gyrus and thalamus. Moreover, very severe TBI (i.e., GCS of 4 or less) resulted in additional activation relative to severe TBI within a more lateral region that included the left posterior frontal lobe and much of the left parietal lobe. This finding may reflect the allocation of more extensive neural resources to allow patients with the most severe injuries to maintain adequate task performance. Interpretations that have been proposed to explain the over-activation that is frequently observed in populations with neuropathology include disinhibition of duplicate neural systems, learning-related neuroplasticity, and cognitive reorganization (Price and Friston, 2001). When task performance is equated this over-activation may reflect a higher level of effort, perhaps as a consequence of inefficient processing or as a form of compensation with additional

cognitive and neural resources brought online in an attempt to maintain adequate performance (Price and Friston, 2002; Ricker et al., 2001). The mechanisms underlying over-activation are not mutually exclusive and individuals may rely upon different neural resources to perform the same task (Price and Friston, 2002).

Both the thalamus and cingulate gyrus were identified as having increased task-related activation following TBI, a finding that may reflect the participation of these areas in an attention network (Kim et al., 1999). The posterior region of the cingulate gyrus may be involved in responses to attention directing cues (Mesulam et al., 2001), in the allocation of spatial attention (Small et al., 2003), and in modulating effort during attention demanding tasks (Kim et al., 1999). The anterior cingulate gyrus has been reported to mediate other aspects of attention deployment such as performance monitoring, response selection, and target identification (Mesulam et al., 2001). Although the anterior cingulate was related to TBI severity within the overall regression models, the posterior cingulate gyrus and the thalamus were the brain areas that most consistently exhibited increased activation in the group comparisons.

Yount et al. (2002) found decreases in thalamic volume following TBI, as well as atrophy within the posterior cingulate gyrus that was related to injury severity. Kim et al. (2008) also identified localized tissue loss within the cingulate gyrus, including its posterior region, and they reported that the pulvinar and medial dorsal nucleus were the brain areas with greatest volume loss following TBI. These thalamic nuclei were among the structures where we observed increased task-related activation following TBI. Consistent with previous volumetric MRI studies (Kim et al., 2008; Yount et al., 2002) and our fMRI data, there are strong anatomical connections between the thalamus and cingulate gyrus (Shibata and Yukie, 2003). In addition, following TBI there are alterations in resting state metabolism within the posterior cingulate gyrus, including hypometabolism on positron emission tomography (PET) that is related to decreased verbal memory (Fontaine et al., 1999). These structural and metabolic findings suggest that the thalamus and the cingulate gyrus, including its posterior sector, are areas with vulnerability to damage in diffuse TBI.

Nakashima et al. (2007) suggested that axotomy of neurons connecting the posterior cingulate gyrus with other brain regions is the mechanism of injury for this structure. Deafferentation is likely to produce degeneration within the cingulate gyrus and thalamus (Yount et al., 2002), and in relation to findings from the current study, diffuse axonal injury may contribute to decreased neural efficiency and the need for over-activation within networks that mediate performance on the stimulus response compatibility task. However, additional elevations in thalamic and posterior cingulate activation were not found with an increase in severity level from severe to very severe. There is the possibility that engagement of these particular midline structures had already reached maximal levels, or was no longer effective for improving performance, and that patients with the most severe injuries then accessed an additional neural network to maintain accurate responding. Over-activation of structures within the left lateral frontal and parietal lobes may reflect reliance upon different or additional cognitive strategies to perform the task, such as verbal mediation.

Task performance and demographic variables

Training procedures were used to establish equivalent performance levels among the groups and, as suggested by Price and Friston (2001), performance accuracy was included within the statistical models as an additional correction for this factor. The findings for accuracy should be interpreted with caution, however, because pre-scan training probably did more to increase the performance of impaired TBI subjects and this is also likely to have reduced the range. Despite this limitation, all three statistical models indicated a relation between better accuracy and elevated brain activation within the posterior cingulate gyrus and other structures throughout the brain. These results differ from those of Scheibel et al. (2007), who did not find a significant relation between accuracy and activation in patients with TBI. The previous study had examined a smaller TBI sample, however, and the statistical model did not include demographic variables that might also relate to activation. The present findings are consistent with the interpretation that over-activation is at least partially effective for improving performance and is thus compensatory, rather than merely a reflection of pathological processes. A similar explanation has been offered for the increased extent of task-related activation that is often noted with normal aging (Cabeza, 2002).

All three statistical models indicated an association between older age and increased activation within midline structures and the left posterior cerebrum, including the left temporal and occipital lobes. The location of the age-related activation increases differed, however, depending upon the particular model. When the model was restricted to TBI patients the age-related increase in midline activation included the anterior cingulate gyrus, but when OI controls were also included (i.e., ANCOVA) the midline portion of the cluster was centered within the posterior cingulate region. There is the possibility that TBI pathology in combination with older age may cause an anterior shift in the location of this midline activation, perhaps as a form of compensation. Possible interactions between age and injury severity may be an issue to examine with future research.

Findings for education level and estimated pre-injury IQ were less consistent. Higher education was associated with greater task-related activation, but only for the ANCOVA. This analysis produced a large, left-sided cluster located primarily within the parietal lobe and posterior frontal lobe. The distribution of this cluster was similar to the pattern of left-sided over-activation we observed for the contrast between the severe and very severe TBI groups. There is thus the possibility that education may facilitate the ability of individuals with neuropathology to engage a left-sided neural network for verbal guidance or mediation while performing the task, perhaps as an alternative mechanism or a type of compensation. A similar explanation was provided by Solé-Padullés et al. (2009) for elevated brain activation in Alzheimer's disease patients with high cognitive reserve scores. In contrast to education, lower estimated preinjury IQ was associated with greater task-related activation within all three models. The thalamus and posterior cingulate gyrus were identified as areas where there was an association between activation and IQ, but there was considerable variation among the models with regards to other brain areas that exhibited this rela-

tion. As with age, the influence of IQ and education may be interesting topics for future research.

Limitations

The current study has a number of limitations. Unlike event-related fMRI, block design fMRI methodology does not permit the extraction of data associated with specific responses or events, such as the separation of brain activity associated with correct and incorrect responses. However, the greater sensitivity of block design fMRI permits data collection with relatively brief runs, and it is often more tolerable for patients with limited endurance (Price and Friston, 2002). Within our current sample, there was also an imbalance among the groups for age, with older subjects in the moderate TBI group. Although this is a limitation of the study, age was included within the statistical models and contrasts which did not include the moderate TBI group produced results that were consistent with those that did (i.e., increasing levels of activation with increasing TBI severity).

Other limitations reflect the nature of the TBI population under study. Imaging was performed approximately three months post-injury, a time when many patients with moderate to severe TBI have recovered sufficiently to cooperate with fMRI, but before the trajectory of cognitive recovery has reached a plateau. Functional imaging at this time is most likely to be sensitive to TBI severity and, eventually, early assessments may be prognostic for long-term outcome or response to later interventions. Results obtained on fMRI at a later point may differ from those reported here and longitudinal research is needed to elucidate changes during recovery. In addition, although many patients with severe TBI can participate in functional imaging at 3 months post-injury, others cannot. Thus there are some biases within the sample for our severe and very severe TBI groups that should be considered while generalizing these findings. For example, patients with lower GOS-E scores might have been included and their imaging results would have differed if we had not required that all patients perform to criterion on the cognitive task. Finally, patients with GCS scores of 13–15 were excluded if they did not have a lesion visible on acute imaging. However, previous studies of mild TBI (McAllister et al., 2001) have revealed activation patterns that differ from those reported in patients with more severe injury (Levin and Scheibel, 2005). The purpose of the present investigation was to examine injuries within the moderate to severe spectrum and, within that range, differences between TBI and OI subjects were statistically significant only when comparisons were made using TBI patients with an initial GCS score of 8 or less.

Conclusion

Acute TBI severity was related to increased, diffuse brain activation during a visuospatial cognitive control task that included elevated activity within areas thought to mediate cognitive functions such as visual attention and the ability to inhibit pre-potent responses. The cingulate gyrus and thalamus were among those regions showing the greatest activation increases and this finding is consistent with vulnerability of these midline structures in severe, diffuse TBI. In addition, better task performance was related to elevated activation and there were differences in the pattern of over-activation that varied with TBI severity, including greater

utilization of left hemisphere structures in patients with the most severe injuries. Overall, these findings are consistent with the interpretation that increased activation following TBI is at least partially effective for improving performance and may be compensatory.

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Address correspondence to:
 Randall S. Scheibel, Ph.D.
 Cognitive Neuroscience Laboratory
 Baylor College of Medicine
 1709 Dryden Road, Suite 725
 Houston, TX 77030
 E-mail: scheibel@bcm.tmc.edu