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Frontal Hypoactivation on Functional Magnetic Resonance Imaging in Working Memory after Severe Diffuse Traumatic Brain Injury

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ABSTRACT

Working memory is frequently impaired after traumatic brain injury (TBI). The present study aimed to investigate working memory deficits in patients with diffuse axonal injury and to determine the contribution of cerebral activation dysfunctions to them. Eighteen patients with severe TBI and 14 healthy controls matched for age and gender were included in the study. TBI patients were selected according to signs of diffuse axonal injury on computed tomography (CT) and without any evidence of focal lesions on MRI clinical examination. Functional magnetic resonance (fMRI) was used to assess brain activation during n-back tasks (0-, 2-, and 3-back). Compared to controls, the TBI group showed significant working memory impairment on the Digits Backwards ($p = 0.022$) and Letter-Number Sequencing subtests from the WAIS-III ($p < 0.001$) under the 2-back ($p = 0.008$) and 3-back ($p = 0.017$) conditions. Both groups engaged bilateral fronto-parietal regions known to be involved in working memory, although patients showed less cerebral activation than did controls. Decreased activation in TBI patients compared to controls was observed mainly in the right superior and middle frontal cortex. The correlation patterns differed between patients and controls: while the control group showed a negative correlation between performance and activation in prefrontal cortex (PFC), TBI patients presented a positive correlation in right parietal and left parahippocampus for the low and high working memory load, respectively. In conclusion, severe TBI patients with diffuse brain damage show a pattern of cerebral hypoactivation in the right middle and superior frontal regions during working memory tasks, and also present an impaired pattern of performance correlations.

Key words: diffuse axonal injury; functional MRI; traumatic brain injury; working memory

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INTRODUCTION

Neuropsychological deficits following traumatic brain injury (TBI) involve impairments in attention, memory, executive functions, and slowed information processing, as well as changes in personality and behavior (Levin et al., 1990; Junqué, 1999; Salmond et al., 2005). These deficits have an important impact on quality of life and compromise patient's psychosocial and vocational functioning (Fontaine et al., 1999; Bernabeu and Roig, 1999).

Memory and learning are frequently impaired after brain damage, and this is particularly so for working memory. Working memory refers to the maintenance and manipulation of information across a temporal delay (Baddeley, 1992), and deficits in it are a core feature of various neurological conditions such as Alzheimer's disease (Baddeley et al., 1999; Germano and Kinsella, 2005), Parkinson's disease (Higginson et al., 2003), schizophrenia (Wexler et al., 2000; Perlstein et al., 2003), alcoholism (Desmond et al., 2003; Pfefferbaum et al., 2001), multiple sclerosis (Wishart et al., 2004; Mainero et al., 2004; Lazeron et al., 2003; Hillary et al., 2003), and TBI (Cicerone, 2002; Levin et al., 2004).

The neural network of working memory involves prefrontal (PFC), temporal, and parietal cortex, depending on the specific task (Cabeza and Nyberg, 2000). Within the prefrontal cortex (PFC), the ventrolateral region (VLPFC) is activated while maintaining information, whereas the dorsolateral portion (DLPFC) is involved in both maintenance and manipulation (Smith and Jonides, 1998; D'Esposito et al., 1999; D'Esposito et al., 2000; Na et al., 2000; Owen, 2000). Fletcher and Henson (2001) go further as regards functional prefrontal organization and consider that three regions in the lateral frontal cortex (ventrolateral, dorsolateral, and anterior) are consistently activated in working memory; they attribute these activations to the updating/maintenance of information, the selection/manipulation/monitoring of that information, and the selection of processes/subgoals, respectively.

The n-back paradigm has been widely used to investigate the neural basis of working memory (Owen et al., 2005; Cabeza and Nyberg, 2000). This task involves monitoring a continuous sequence of stimuli and individuals are required to indicate when the current stimulus matches the stimulus shown n positions before. Bilateral prefrontal and parietal activation has been demonstrated in healthy subjects using functional neuroimaging (Jonides et al., 1998; Braver et al., 1997).

Although structural changes following TBI are well known, functional impairments have been studied in less detail (Levine et al., 2006). Functional magnetic resonance (fMRI) is a non-invasive technique of proven utility in characterizing neurofunctional correlates of cognitive impairment following TBI (Hillary et al., 2002).

McAllister et al. (1999, 2001) found that the pattern of frontal activation according to working memory load on an *n*-back task was altered in patients tested one month after having sustained a mild TBI. They observed a significant increase of cerebral activation (mainly in right dorsolateral PFC and right parietal cortex) in the TBI group in relation to high cognitive load during a verbal working memory task, although performance was similar to the control group.

Alterations in brain activation have also been described in patients with moderate-to-severe TBI during performance of a working memory task. Using a serial addition task, Christodoulou et al. (2001) observed that a distributed network, including the middle medial frontal gyrus, was activated in TBI patients and a group of healthy controls, although activation in the TBI patients was more regionally dispersed and more lateralized towards the right hemisphere, particularly in the frontal lobes. In a single case studied 1 year after severe diffuse TBI, Scheibel et al. (2003) found more bilaterally dispersed activation in a severely injured TBI patient than in controls using an *n*-back task for identity of faces.

The present research aimed to investigate the working memory deficits in patients with diffuse brain injury and to determine the contribution of cerebral activation dysfunctions to them. Given that working memory is a core deficit in TBI, we predicted that severe TBI patients, in the absence of a focal lesion on structural MRI, would exhibit deficits in an *n*-back task. Furthermore, based on the findings of previous studies we postulated that the cerebral network involved in working memory would be disrupted in TBI patients and the pattern of correlations between blood-oxygen-level-dependent (BOLD) signal activity and performance would differ between groups.

To our knowledge, this study is the first to investigate cerebral activation patterns during an *n*-back task in a group of severe, diffuse TBI patients with working memory impairment, and to compare them with a matched control group.

METHODS

Eighteen adult patients (12 male, six females) who had sustained a severe TBI were recruited from the Institut de Neurorehabilitació Guttmann. Severe TBI is defined as a Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) score of <9, loss of consciousness for >6 h, and/or duration of post-traumatic amnesia (PTA) for >6 h (Lezak et al., 2004). Acute computed tomography (CT) scans

showed intraparenchymal hemorrhages (smaller than 2 cm) in eight patients, subarachnoid hemorrhage in seven cases, intraventricular hemorrhage in five patients, and subdural hematoma in one patient. Three acute CT scans were reported normal. All structural MRI scans were suggestive of diffuse axonal injury (DAI). Gennarelli's DAI grading system was used: type I DAI involved the convexity gray-white matter junction; type II involved the corpus callosum in addition to the gray-white junction; and type III also involved the rostral brainstem (Gennarelli et al., 1982). In our sample, five patients presented type I DAI, eight had type II, and five presented the most severe type (type III). There was no evidence of focal lesion on MRI clinical examination in any case.

The cause of TBI was a motor vehicle accident in all cases: eight were involved in a car collision, eight in motorbike crashes, and two patients were run over. Time since injury was 6–18 months (mean, 224.9 [SD, 125.1] days). All patients had recovered from PTA by the time of the fMRI and had a score of 76 or greater on the Galveston Orientation and Amnesia Test (GOAT) (Levin et al., 1979). The duration of PTA was 20–171 days (mean, 84.7 [SD, 43.2] days). Subjects presented no aphasic, sensory, or motor deficits that could interfere with results.

A group of 18 healthy subjects (11 males, seven females) were recruited from relatives or friends of the TBI group. This control group was matched for age, years of education and estimation of premorbid intellectual function. Four participants of the control group were excluded due to acquisition problems: three of them presented a movement pattern synchronized with activation blocks and one of them had anomalous global intensity changes across the time series, resulting in an activation of 100% of the voxels in the brain. Demographic characteristics for both groups are given in Table 1. All subjects were right handed and had no previous history of neurological or psychiatric diseases.

Written informed consent was obtained from all participants. This study was approved by the Ethical and Research Committee of the Institut de Neurorehabilitació Guttmann.

Neuropsychological Assessment

All participants were evaluated by the same neuropsychologist (R.S.C.) using the following protocol: Galveston Orientation and Amnesia Test (GOAT) (Levin et al., 1979), Digit Span and Letter-Number Sequencing (LNS) subtests from the Wechsler Adult Intelligence Scale (WAIS-III) (Wechsler, 1999), and the *n*-back task (Cohen et al., 1997).

Digit span was measured as the series length correctly reproduced at least once in the same order (forwards) and in reverse order (backwards). In LNS, subjects hear lists of randomized numbers and letters (in alternating order) of increasing lengths, and are asked to reproduce the numbers and letters from the lowest in each series, always with numbers first. The Vocabulary subtest of the WAIS-III (Wechsler, 1999) was also administered as it is a well-regarded method for estimating general intelligence (Lezak et al., 2004).

The neuropsychological assessment was carried out on the same day as fMRI acquisition for the control group. Most TBI patients needed at least two sessions, within the same week, to complete testing.

Working Memory Task

A visual *n*-back task was used to investigate working memory. Three conditions were presented: 0-back, 2-back, and 3-back. In the 0-back condition, individuals were asked to decide whether the current number matched a single target number that was specified before the epoch began. During the 2-back condition, they were asked to decide whether the number currently presented matched the number that had been presented two back in the sequence. During the 3-back condition, the task was to decide whether the current number matched the number presented three numbers before (Fig. 1).

Each *n*-back condition was presented in a 58-sec epoch, preceded by a 2-sec short written instruction. There were 12 epochs during the scan. All conditions were matched for number of target numbers presented per epoch = 6 (target stimulus: 25%). We used a block

Table 1. Demographic Characteristics from TBI and Control Groups

	TBI (n = 18)		*Control (n = 14)*		
	Mean	*SD*	*Mean*	*SD*	p
Age (years)	23.6	4.7	24.2	4.7	ns
Education (years)	11.3	2.5	12.6	2.5	ns
Vocabulary (WAIS)	10.1	1.9	10.8	2.0	ns

Nonstatistical differences between both groups were found in any demographic variables.

TBI, traumatic brain injury; SD, standard deviation; WAIS, Wechsler Adults Intelligence Scale.

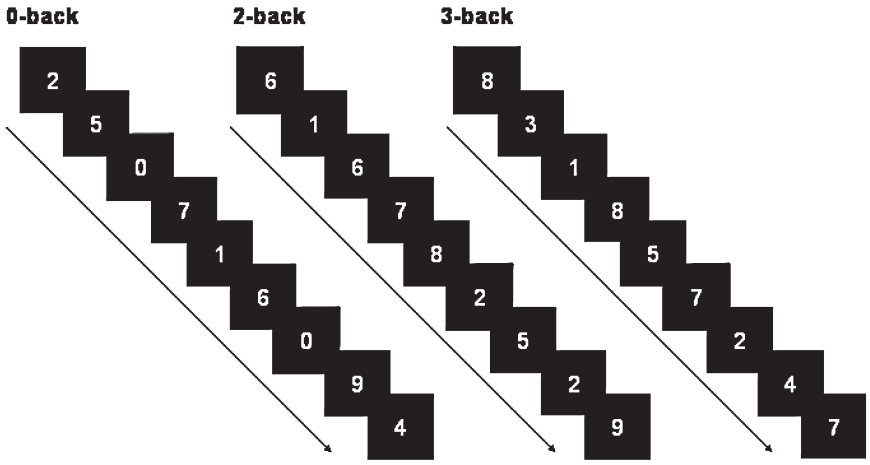

FIG. 1. The figure illustrates the design of the n-back task. A block design was applied, alternating 0-back, 2-back, and 3-back. Each block was repeated four times.

design where four cycles of alternation between conditions were presented in the course of the 12-min experiment. The order of presentation was as follows: 0, 2, 3, 0, 2, 3, 0, 2, 3, 0, 2, 3. Both 2- and 3-back conditions were considered as working memory conditions, whereas 0-back was the control task.

White numbers appeared on the screen for 500 msec against a black background, which was followed by a fixation cross for 1500 msec. Numbers presented were 0–9 for the control condition, and 1–9 for working memory tasks. All the stimuli were back-projected (by a Sanyo Multimedia Prox-III) onto a screen which subjects viewed through a mirror located on the scanner's head coil. Stimuli were generated in a Hewlett Packard computer by Presentation software (Neurobehavioral Systems).

Participants were required to press a button (Fiber Optic Response; Current Designs, Philadelphia, PA) with their right thumb when the currently presented number was a target. Hits, misses, correct rejects, false alarms, and reaction times were registered.

Prior to scan, participants rehearsed the task outside the scanner to ensure they understood the task requirements.

Image Acquisition

The MRI protocol was administered with a 1.5-Tesla (T) MR unit (Signa-Lx, General Electric, Milwaukee, WI) using the blood–oxygen-level-dependent (BOLD) fMRI signal; this unit was located in the Centre for Image Diagnosis (CDI) of the Hospital Clínic in Barcelona. Care was taken to minimize the effect of movement by instructing subjects to remain still; foam padding was also placed around their head. The functional images were acquired using a gradient echo single-shot echoplanar imaging sequence (EPI): TR (repetition time) = 2000 msec; TE (echo time) = 40 msec; FOV (field of view) = 24 × 24 cm, 64 × 64 pixel matrix; flip angle = 90°; slice thickness 5 mm; gap 1.5 mm; and 20 axial slices per scan.

During fMRI, subjects performed the working memory task described above, which resulted in 360 volumes of 20 slices each. Following fMRI scans, high-resolution T1-weighted images were acquired using axial three-dimensional (3D) fast spoiled gradient recalled acquisitions for anatomic localization (FSPGR) (TR/TE = 12/5.2; TI 300 = 1 nex; FOV = 24 × 24 cm; 192 × 256 pixel matrix, continuous axial 1.5-mm slices).

Preprocessing Procedures

All image processing was performed using SPM2 (Statistical Parametric Mapping; Wellcome Department of Imaging, Institute of Neurology, University College London, UK), running in Matlab 6 (MathWorks, Natick, MA). The fMRI protocol was administered as follows. In order to remove head movement effects, the 360 scans were first realigned. Following realignment, we resized the anatomical and functional images to avoid the interslice gap (volumes of 20 slices) in the z axis (by a factor of 1.3). Next, a single investigator determined the anterior commissure manually and reoriented all the images according to the anterior–posterior commissure line. 3D and functional images were normalized to T1 and EPI templates, respectively. The normalized images were then smoothed with an isotropic Gaussian kernel (full width at half-maximum [FWHM] = 10 mm) to create a local weighted average of the surrounding pixels.

Statistical Analysis

Between-groups comparisons of demographic and neuropsychological variables were examined using the Mann-Whitney test for independent samples. All statistical analyses were carried out with SPSS 13.0. To determine accuracy of performance, we used d′ signal detection measure, a bias-free measure of discrimintaion of signal from noise. The d′ provides a means of assessing discriminative power since, in general, the greater the difference between the signal and noise distribution, the better the ability to distinguish and detect target and non-target stimuli.

fMRI analyses included statistical parametric mapping using a general linear model (Friston et al., 1995), as implemented in SPM2. A high-pass temporal filter with cut-off of 360 sec was used to reduce low-frequency noise. To further reduce any motion related to the task, the motion parameters used in the realignment were entered into the statistical analysis as regression parameters (Jones and Callan, 2003; Poldrack et al., 2002). Smoothed normalized scans for all subjects were entered into a model and contrast images for the blocked design conditions ($2 > 0$ back, $3 > 0$ back) were created for each subject. These contrast images were then used for within-group (one-sample *t*-test) comparisons in order to obtain the brain activation pattern for each group. The probability threshold was set at 0.001 FDR corrected and a minimum cluster extent (k) of 100 contiguous voxels.

To investigate group differences for each contrast, between-group (two-sample *t*-test) comparisons were carried out in those areas in which activation was observed in the within-group test, using an explicit mask. The probability threshold was set at 0.001 uncorrected ($k > 100$). The anatomical location of the activated cerebral areas was determined by the MNI (Montreal Neurological Institute) global maxima coordinates.

Finally, we performed a simple regression analysis of activation with clinical variables and accuracy scores on the two working memory conditions during fMRI scan, for patients and controls separately.

Table 2. Working Memory Performance for TBI and Control Groups

	TBI (n = *18*)		*Control* (n = *14*)		
	Mean	*SD*	*Mean*	*SD*	p
Digits forward	6.11	0.96	6.97	1.27	ns
Digits backwards	4.39	0.97	5.36	1.01	0.022*
LNS	8.11	2.37	11.57	2.53	<0.001**
n-back task					
% Correct					
0-back	97.8	5.13	99.68	1.16	ns
2-back	76.7	24.74	95.19	4.77	0.008*
3-back	60.3	28.87	84.30	13.3	0.017*
Discrimination (d′)					
0-back	3.89	0.44	3.96	0.018	ns
2-back	2.51	1.07	3.38	0.44	0.017*
3-back	2.05	1.27	2.94	0.77	0.035*
Reaction time (msec)					
0-back	5442	1134	3842	558	<0.001**
2-back	6953	1859	4397	897	<0.001**
3-back	8344	2404	5041	1248	<0.001**
Commission errors					
0-back	0.59	1.3	0.69	0.9	ns
2-back	4.71	4.2	2.85	2.4	ns
3-back	4.59	5.7	2.92	2.7	ns

Back performance assess by accuracy (% correct responses), median reaction time (in milliseconds) and commission errors. N-back performance was available only for 17 TBI and 13 controls.

*$p < 0.05$; **$p \leq 0.001$.

ns, nonsignificant; TBI, traumatic brain injury; SD, standard deviation; LNS, Letter-Number Sequencing (WAIS-III).

RESULTS

Working Memory Performance

Statistical differences in working memory were observed between groups (Table 2). TBI patients performed poorer on Digits backwards ($p = 0.022$), Letter-Number Sequencing ($p < 0.001$) and in terms of accuracy under the 2- and 3-back conditions from the *n*-back task (number of correct answers; $p = 0.008$ and $p = 0.017$, respectively). Reaction times for TBI patients were significantly longer under all three *n*-back conditions (0-back and 2-back, $p < 0.001$; 3-back $p = 0.009$). No differences were observed between groups in Digits Forward ($p = 0.077$), 0-back correct answers ($p = 0.62$), or in terms of errors in any of the *n-back* conditions ($p = 0.457$; $p = 0.213$; $p = 0.51$, respectively). Figure 2 shows the performance for each group on the *n*-back task.

Neuroimaging

Significant activation in bilateral fronto-parietal regions was observed in both groups when comparing the low working memory condition with the control task (2-back > 0-back). Frontal lobe activation was observed in the left inferior and superior frontal cortex and bilateral middle fontal gyrus for the control group, whereas TBI subjects only showed significant activation in left middle frontal cortex and right precentral gyrus. Bilateral activation in superior and inferior parietal lobes was significant in both groups. Additional activation of left precuneus and bilateral cerebellum was observed in controls. To control for the effect of impaired performance in TBI patients an analysis of covariance were performed using d′ as a covariate. We observed similar results, but we lost the significcance of the bilateral superior parietal lobe, but remained the bilateral middle frontal and inferior parietal significances. Table 3 summarizes the coordinates, cluster size and probability levels of significant clusters of activation observed in the 2-back condition.

When increasing working memory load (3-back > 0-back comparison), a bilateral fronto-parietal pattern of significant activation was once again observed in both groups. Although the bilateral middle frontal region was activated in both groups, controls showed a higher number of activated regions and larger clusters with greater statistical significance. Bilateral inferior parietal and precuneus activation was found in both groups, but TBI patients also activated the right superior parietal cortex. In addition, the control group showed significant bilateral cerebellar activation. After covariation between brain activation and working memory performance, the TBI group showed significant activation only in the right middle frontal gyrus (Table 4).

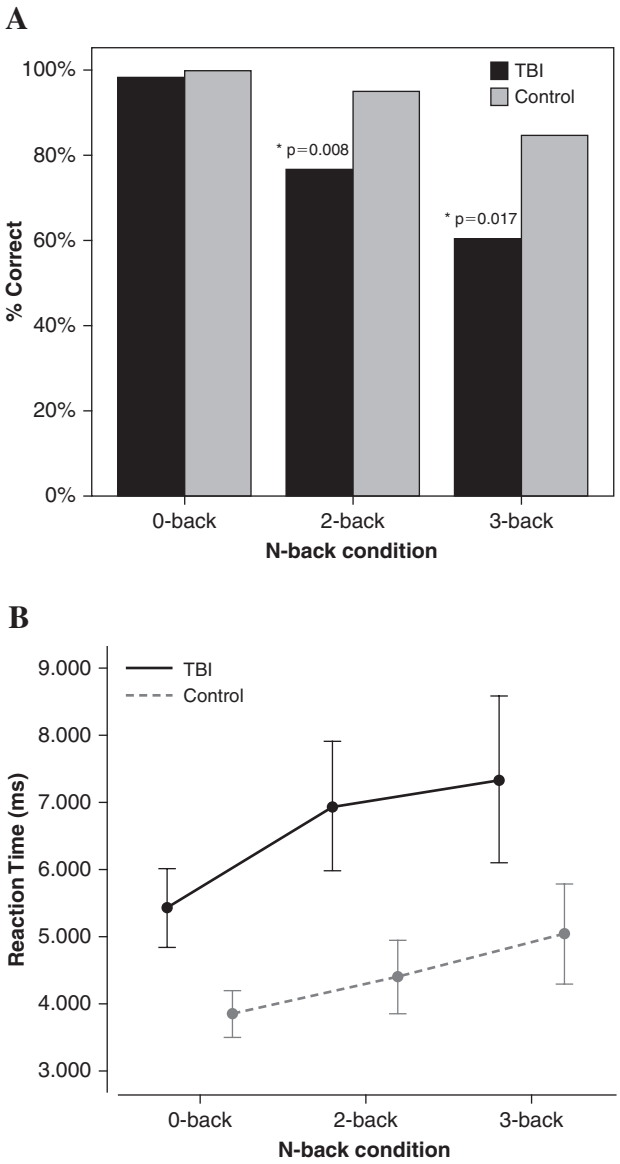

FIG. 2. Performance on the n-back task during functional magnetic resonance imaging (fMRI) acquisition was only available for 17 TBI patients and 13 healthy controls. (**A**) Significant differences between groups are observed in the percentage of correct answers under the 2-back ($p = 0.008$) and 3-back ($p = 0.017$) conditions. (**B**) Reaction time (msec) for correct answers. Reaction time for the traumatic brain injury (TBI) group was significantly longer than for controls under the 0-back ($p < 0.001$), 2-back ($p < 0.001$), and 3-back ($p = 0.009$) conditions.

The two-sample *t*-test in the 2-back versus 0-back pattern of activation showed decreased activation in TBI patients compared to controls mainly in the right superior and middle frontal cortex ($p = 0.019$; cluster size = 591 voxels) and left sub-gyral regions ($p = 0.032$; cluster size = 321 voxels). The results after covariation for

Table 3. Local Maxima of Differences between 2-Back and 0-Back by Subtraction Analyses for the TBI and Control Group

	CLUSTER-level		*Voxel-level*		*MNI*		
Region	$P_{corrected}$[a]	K_E[b]	$P_{FDR\text{-}cor}$	*T*	*X*	*Y*	*Z*
TBI patients							
Frontal							
R precentral gyrus	<0.001	10241	0.003	7.95	34	−6	56
L middle frontal gyrus			0.003	7.73	−28	2	54
L middle frontal gyrus			0.003	7.37	−50	12	30
Parietal							
L inferior parietal lobule	0.009	1259	0.003	5.88	−34	−52	42
L superior parietal lobule			0.013	4.06	−28	−68	46
R inferior parietal lobule	<0.001	1811	0.004	5.76	44	−48	44
R superior parietal lobule			0.005	4.91	34	−62	44
Healthy controls							
Frontal							
R middle frontal gyrus	<0.001	8967	<0.001	16.67	24	4	62
L superior frontal gyrus			<0.001	15.97	−4	6	60
L inferior frontal gyrus			<0.001	11.82	−52	12	26
L inferior frontal gyrus	<0.001	372	<0.001	12.04	−34	24	2
L middle frontal gyrus	<0.001	333	<0.001	6.82	−36	44	24
L sub-lobar			<0.001	6.80	−40	50	8
Insula	0.001	226	<0.001	8.84	34	22	4
Parietal							
L inferior parietal lobule	<0.001	8277	<0.001	9.51	−42	−46	46
Left precuneus			<0.001	9.12	−22	−66	42
L superior parietal lobule			<0.001	8.15	−32	−56	48
R inferior parietal lobule	<0.001	2394	<0.001	8.50	40	−54	52
R inferior parietal lobule			<0.001	8.18	44	−46	44
R superior parietal lobule			<0.001	7.86	16	−68	56
Cerebellum							
R cerebellum	<0.001	1889	<0.001	9.09	8	−76	−26
R cerebellum			<0.001	9.07	32	−56	−38
L cerebellum			<0.001	8.74	−34	−56	−38

[a]*P* corrected at voxel level (FDR = 0.001).
[b]Minimum cluster size: 100 voxels.
Only significant clusters at $p < 0.001$ corrected are shown.
R, right hemisphere; L, left hemisphere; TBI, traumatic brain injury; MNI, Montreal Neurological Institute coordinates.

d′score are shown in Figure 3. Significant differences were seen in the right superior frontal cortex ($p = 0.040$; cluster size = 1226) and in left middle frontal gyrus ($p = 0.042$; cluster size = 1215 voxels). Similarly, in the higher working memory load condition (3-back > 0-back) patients showed significantly lower activation than did controls in the right superior and middle frontal regions ($p = 0.032$; cluster size = 563 voxels). After covariation, significant differences between groups were observed in the right middle and inferior frontal cortex ($p = 0.043$; cluster size = 493) and in the left middle frontal cortex ($p = 0.043$; cluster size = 491 voxels; Fig. 4).

The TBI group did not show any brain region with greater activation than controls on any working memory condition. Correlations between brain activation and task performance (percentage of correct answers) were calculated for each group separately. While the TBI group showed a significant positive correlation localized in the superior parietal lobe ($p = 0.016$), the control group showed a negative correlation in the inferior frontal lobe ($p = 0.028$). For the 3-back condition, the TBI group had a positive correlation in parahippocampus ($p = 0.001$) and cerebellum ($p = 0.30$), while no correlation was found in the control group (Fig. 5). No significant correlation was found between brain activation in the TBI

Table 4. Local Maxima of Differences between 3-Back and 0-Back by Subtraction Analyses for the TBI and Control Group

	CLUSTER-level		*Voxel-level*		*MNI*		
Region	$P_{corrected}$[a]	K_E[b]	$P_{FDR\text{-}cor}$	*T*	*X*	*Y*	*Z*
TBI patients							
Frontal							
R middle frontal gyrus	0.013	1033	0.026	5.74	32	−6	56
R middle frontal gyrus			0.026	5.74	46	2	54
L middle frontal gyrus	0.006	1247	0.026	5.11	−52	12	38
L precentral gyrus			0.026	4.80	−50	−2	48
L inferior frontal gyrus			0.026	4.73	−60	8	16
Parietal							
L inferior parietal lobule	0.005	1291	0.026	5.50	−34	−56	46
L precuneus			0.026	4.65	−24	−80	46
L precuneus			0.026	4.49	−28	−76	40
R inferior parietal lobule	0.002	1614	0.026	5.17	44	−52	48
R superior parietal lobule			0.026	5.04	34	−66	44
R inferior parietal lobule			0.026	4.83	44	−44	38
Healthy controls							
Frontal							
L inferior frontal gyrus	<0.001	2083	<0.001	12.62	−52	10	24
L middle frontal gyrus			<0.001	7.78	−30	−2	46
L middle frontal gyrus			<0.001	7.65	−32	−2	56
R middle frontal gyrus	<0.001	1974	<0.001	12.31	24	2	62
R middle frontal gyrus			<0.001	8.16	4	20	44
L inferior frontal gyrus	<0.001	283	<0.001	10.79	−34	26	6
R middle frontal gyrus	<0.001	1861	<0.001	10.68	42	32	34
R middle frontal gyrus			<0.001	8.63	40	46	20
R middle frontal gyrus			<0.001	7.85	52	10	30
L middle frontal gyrus			<0.001	7.20	−42	50	10
L middle frontal gyrus	<0.001	342	<0.001	6.62	−34	42	20
Insula	<0.001	300	<0.001	8.94	34	22	4
Parietal							
L precuneus	<0.001	1738	<0.001	9.68	−20	−68	40
L inferior parietal lobule			<0.001	8.02	−38	−48	44
R inferior parietal lobule	<0.001	1388	<0.001	8.08	44	−46	46
R precuneus					34	−74	36
Cerebellum							
R cerebellum	0.005	116	<0.001	7.55	14	−82	−26
R cerebellum	0.004	127	<0.001	6.55	38	−66	−32

[a]*P* corrected at voxel level (FDR = 0.001).
[b]Minimum cluster size: 100 voxels.
Only significant clusters at $p < 0.001$ corrected are shown.
R, right hemisphere; L, left hemisphere; TBI, traumatic brain injury; MNI, Montreal Neurological Institute coordinates.

group and any clinical variable (GCS, PTA duration, time since injury, or severity of DAI).

DISCUSSION

Our results show that severe TBI patients with diffuse brain damage have a pattern of cerebral hypoactivation during working memory tasks in the right middle and superior frontal regions. Interestingly, the pattern of correlations between working memory performance and brain activation differed between patients and controls.

Our neuropsychological results confirm working memory impairment in patients with severe TBI (Bublak et al., 2000; McDowell et al., 1997; Christodoulou et al., 2001; Kinsella et al., 1996). Performance on Digits Back-

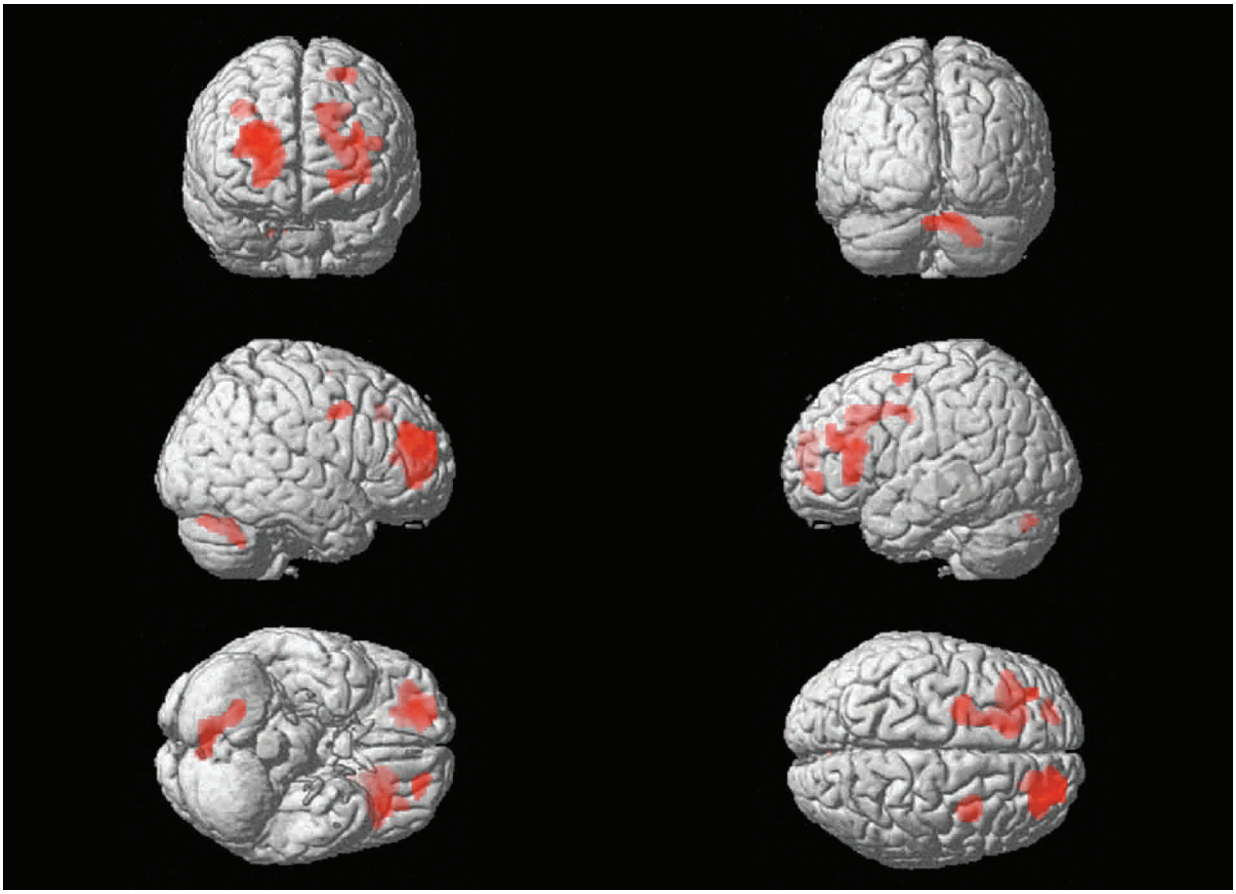

FIG. 3. Areas where patients showed significantly lower activation than did controls for the 2-back > 0-back comparison after covariation for performance. Significant differences are observed in right superior and left middle frontal regions ($p = 0.005$). Statistical Parametric Maps with left as left, according to neurological convention.

wards, LNS, and under the 2-back and 3-back conditions was significantly poorer for the TBI group and, as expected, no differences were observed on Digits forwards or under the 0-back condition, suggesting that TBI patients were not impaired on memory span or tasks of simple vigilance.

In addition to the *n*-back paradigm, different tasks have been used to examine working memory in TBI, for example, the modified Paced Auditory Serial Addition Task (PASAT) (Christodoulou et al., 2001; Park et al., 1999), the action-sequencing task (Bublak et al., 2000), and the dual-task paradigm (McDowell et al., 1997; Leclercq et al., 2000). However, the *n*-back task is particularly interesting because it involves not only short-term maintenance but also constant updating (Cabeza and Nyberg, 2000).

Depending upon the load level, the *n*-back task requires monitoring and coding of incoming information, maintaining the appropriate number of items in a "buffer," temporally tagging, sequencing and updating the information held in the buffer, and replacing no-longer relevant information with newer, more relevant information (Smith and Jonides, 1997). Although our results are consistent with working memory impairment in the TBI group in terms of accuracy (McDowell et al., 1997; Azouvi et al., 1996) and discriminability assessed by d′ value (Perlstein et al., 2004) on the *n*-back task.

In the fMRI study, the bilateral fronto-parietal pattern observed during the n-back task in our control group is consistent with previous studies of working memory in healthy adults (Cabeza and Nyberg, 2000). As previously reported, we observed that in addition to the bilateral frontal activations seen in all the working memory tasks, there was also activation of Brodmann areas 9 and 46, which are usually seen in *n*-back tasks (Braver et al., 1997; Cohen et al., 1997). This was probably due to the extra demands on monitoring and updating. Our results agree with the findings of Petrides et al. (1993), who re-

port a two-stage neuroanatomical model of working memory in which information from the posterior association cortex is received initially in the lateral PFC and held online while comparisons are made with information currently available in working memory. Areas of dorsolateral PFC are recruited when modulation or manipulation of this information is required. In support of this model, Owen et al. (1996) found that working memory tasks requiring high monitoring activated dorsal regions of the PFC, whereas those tasks with minimal monitoring requirements activated only ventral areas of the PFC. In addition to the fronto-parietal network, the additional activation in cerebellar regions found in our control group is consistent with previous studies (Cabeza and Nyberg, 2000; Owen, 2000; Ranganath and D'Esposito, 2005).

Although the TBI group activates an identically distributed fronto-parietal network, it is important to note the smaller cluster sizes for those regions and the lower t values; this suggests decreased cerebral activation of the working memory network, similar to the results obtained by Chen et al. (2003) with mild TBI patients without focal lesions.

The comparison between patients and controls indicated a significantly decreased activation during working memory tasks in TBI patients. For the low working memory load condition (2-back), patients showed a decreased activation in the right middle and superior frontal and in left sub-gyral regions as compared to controls. For the high working memory load condition (3-back), patients again showed a decreased activation localized in the right superior and middle frontal cortex. Our sample is not directly comparable to other TBI studies that have investigated fMRI on *n*-back tasks because previous research has been conducted in mild TBI (McAllister et al., 1999; Perlstein et al., 2004) or has included focal lesions in the samples of moderate and severe TBI (Newsome et al., 2007a,b; Perlstein et al., 2004). However, similar findings to our own were reported by Newsome et al. (2007b), who observed decreased activation in frontal structures for TBI patients under the 1-back condition, and Ricker et al. (2001), who reported decreased rCBF during free recall in the frontal lobe.

In children, impaired working memory was accompanied by hypoactivation of prefrontal and extrafrontal regions in four of the eight subjects studied following moderate to severe TBI. In contrast, patients with normal working memory performance on *n*-back displayed more extensive brain activation than did controls (Newsome et al., 2007a). When adult TBI subjects show normal performance after training, the fMRI pattern was also one of increased activation (Scheibel et al., 2007). The effect of performance on the pattern of cerebral activation has also been investigated in schizophrenia. Callicott et al. (2003) found that schizophrenic patients only showed decreased frontal activity when they performed poorly and that high performance was correlated with increased activity. They sought to integrate these discrepant findings into one model, proposing an inverted U-shaped curve that represented the signal responses of the DLPFC to increasing working memory load, which indicates greater activation in high-performing patients and less activation in low-performing ones.

In contrast to our findings, there are some positron emission tomography (PET) studies in moderate to severe TBI that show increased cerebral activation in patients compared to controls. Levine et al. (2002) described larger and additional areas of activation in patients, and Ricker et al. (2001) observed a decreased activation in posterior brain regions. Furthermore, patterns of increased activation have also been reported in fMRI studies (Newsome et al., 2007a; Scheibel et al., 2007; Christodoulou et al., 2001), but all of them included patients with focal lesions.

There is strong evidence that focal cerebral lesions induced ipsilateral and contralateral regions of increased activation following stroke (Rosen et al., 2000; Riecker et al., 2002; Rossini et al., 2007) and mesial temporal epilepsy (Pataraia et al., 2004, 2005). This idea is reinforced by findings from fMRI patterns of patients with multiple sclerosis. Increased and additional functional activation described in mild to moderate impairment has been interpreted as a compensatory mechanism, while severely impaired patients showed less extensive brain activation (Penner et al., 2006). Although some studies found hypoactivation in superior medial frontal gyrus (Cader et al., 2006), others reported hyperactivation, mainly in frontal regions (Audoin et al., 2003; Forn et al., 2006). These discrepancies may be explained by the presence of focal and diffuse white matter lesions. Mainero et al. (2004) suggest that the extent of activation in some cerebral areas increases with increasing lesion burden on conventional MRI.

Simple regression analyses between 2-back activation and performance revealed different pattern of correlations in the two groups. We found a significant negative correlation between prefrontal activity and performance in our control group, this being consistent with previous reports (Mattay et al., 2000; Mehta et al., 2000; Otten and Rugg, 2001; Daselaar et al., 2004; Hampson et al., 2006). In contrast, the TBI group showed a positive correlation between performance and right parietal activation, supporting the idea that high performers have hyperactivation and low performers hypoactivation. This greater parietal activation in high performers can be interpreted

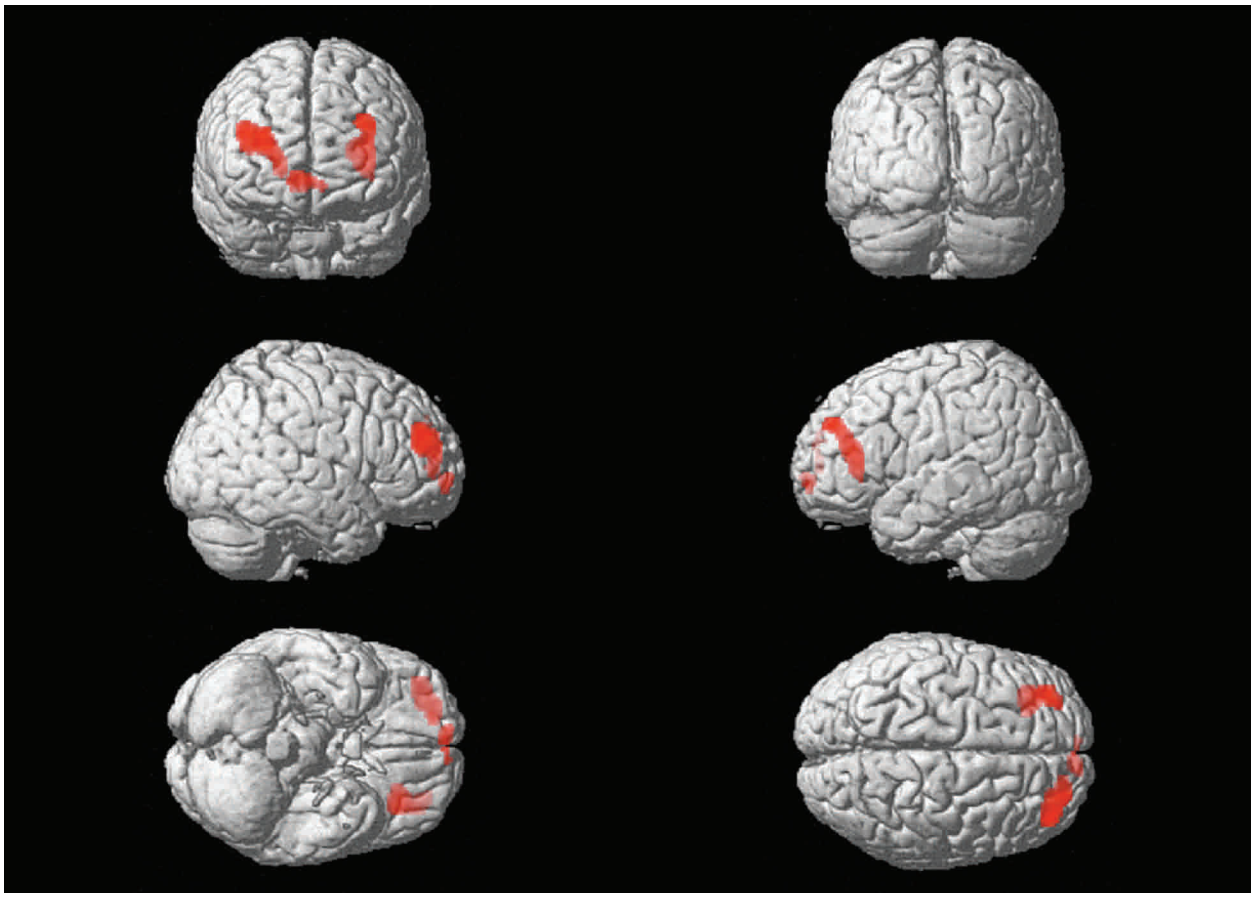

FIG. 4. Areas where patients showed significantly lower activation than did controls for the 3-back > 0-back comparison after covariation for performance. Significant differences are located in the bilateral middle frontal and right inferior frontal cortex ($p = 0.001$). Statistical Parametric Maps with left as left, according to neurological convention.

as a result of greater involvement of posterior attentional mechanisms (Posner and Petersen, 1990) or storage of verbal information (Jonides et al., 1998a).

For the higher working memory load condition (3-back) the negative correlation between parahippocampal activation and performance may indicate that in order to achieve better performance, TBI patients need to activate additional regions. Although medial-temporal lobe activation has been widely studied for episodic memory encoding and retrieval (Cabeza and Nybert, 2000), Cohen et al. (1999) suggested that parahippocampal activity may at times be more related to high-level stimulus analysis or manipulation than to the declarative memory process itself; in this regard, it should be noted that the medial temporal lobe is part of the network for visual working memory functions (Ranganath and D'Esposito, 2005).

Given the critical role of the PFC in working memory (Cohen et al., 1997; Perlstein et al., 2003) and the susceptibility of the PFC to insult in TBI (Adams et al., 1980), the *n*-back impairment is to be expected after moderate to severe TBI. Perhaps of more importance than focal lesions, injury to subcortical white matter (Gennarelli and Graham, 1998) can disrupt the integrity of the widely distributed neural circuitry involved in working memory. Thus, it is not surprising that impairment in working memory is a common if not a core deficit in individuals who have sustained a TBI (McAllister et al., 2004). The white matter damage may also be responsible for the pattern of decreased cerebral activation seen in our sample.

Unfortunately, previous studies of working memory activation in severe or moderate TBI included patients with either focal lesions alone (Newsome et al., 2007b) or focal lesions in addition to diffuse injury (Christodoulou et al., 2001; Newsome et al., 2007a; Scheibel et al., 2007). Another explanation for working memory deficits and the pattern of cerebral hypoactivation could

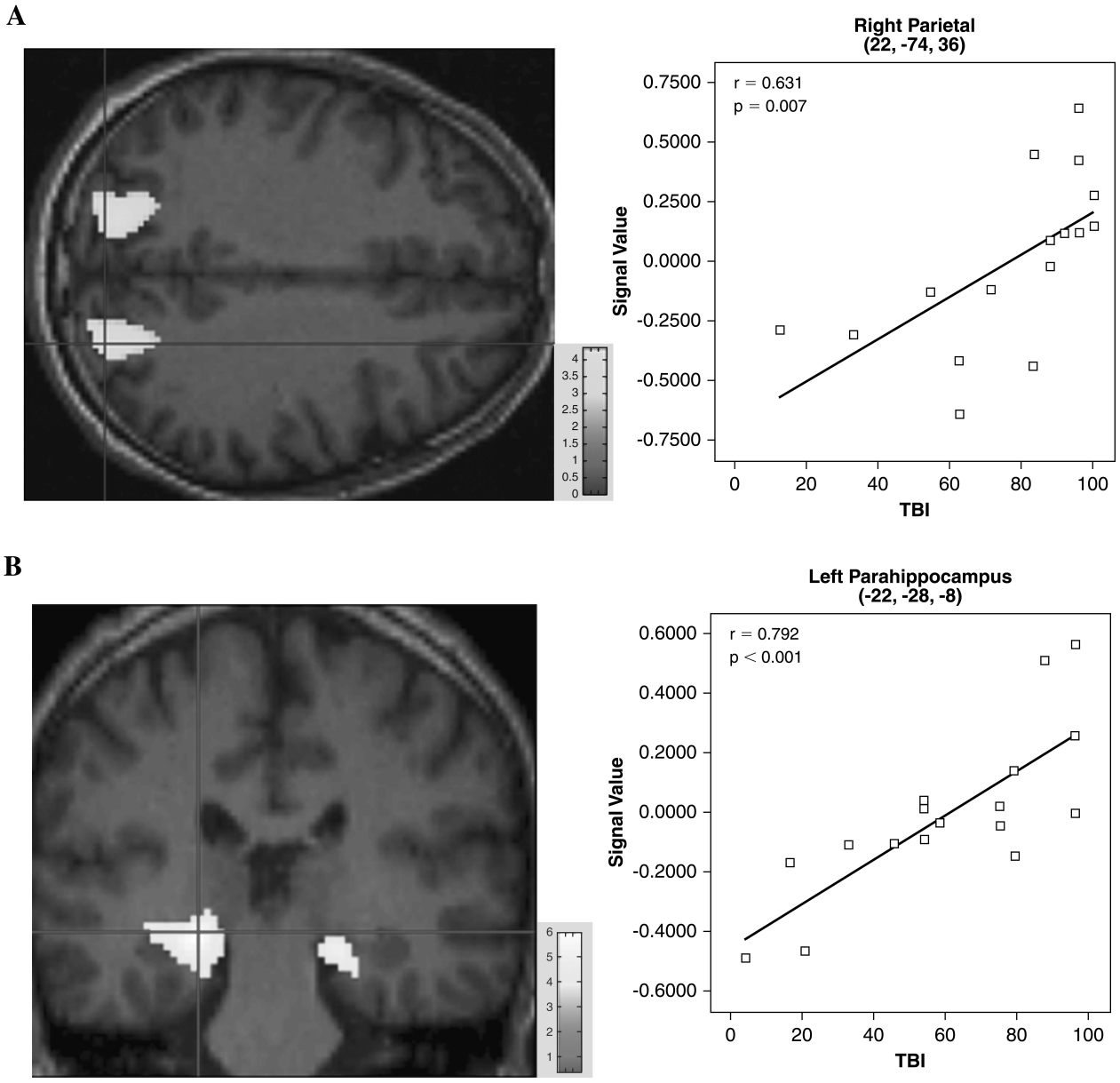

FIG. 5. Significant correlations between working memory performance and brain activation, expressed as signal in arbitrary units (AU): activation map on the left, plots on the right. Significant positive correlations in superior parietal for 2-back > 0-back comparison (**A**); and in left parahippocampus for the 3-back > 0-back comparison (**B**). Statistical Parametric Maps with left as left, according to neurological convention. Scales reflect *t* values.

be the catecholaminergic deficits associated with TBI (McAllister et al., 2004).

As regards the potential limitations of the fMRI study, several aspects must be borne in mind. First, fMRI in TBI faces a number of inherent interpretational challenges. Observed differences in activation between TBI and control groups could be due to several factors that are not directly related to impairments in task performance. These include (1) possible fundamental anomalies in cerebral vasculature in patients with TBI; (2) some alteration in the relationship between neuronal activity and the blood flow response induced by the brain injury; (3) alterations in apparent blood flow or volume due to alterations in the ratio of gray to white matter, resulting in cortical atrophy which can cause partial volume effects that can artefactually reduce signal intensity; and (4) some unanticipated artefact of the experimental design (Price and Friston, 1999; Price et al., 2001).

Even if an event-related design for fMRI acquisition had been applied in order to examine the temporal course of the hemodynamic response during the series of trials (Perlstein et al., 2004), most studies with severe TBI have used block-design fMRI due to its simplicity, the ease of implementation, and high statistical power in relation to the scanning time (Scheibel et al., 2007).

While in some *n*-back fMRI studies, subjects were asked to respond to different buttons when identifying target and non-target stimulus (Perlstein et al., 2004; Wishart et al., 2004; Newsome et al., 2007b), we have used a single response button, in line with other researches (McAllister et al., 2001; Forn et al., 2006). However, our results are in agreement with the brain activation observed bilaterally in prefrontal and parietal cortices observed in all the previous *n*-back studies, suggesting that the response procedure does not influence on the overall pattern of cerebral activation during an *n*-back task.

The present sample of TBI survivors may not be representative of those encountered in some clinical settings. Functional activation studies can only be performed with highly cooperative participants who can tolerate a constraining environment without head movement while complying with cognitive tasks (Ricker et al., 2001).

In line with the comments of Levine et al. (2002), it is possible that our findings are simply an artefact of impaired performance. However, the prefrontal hypoactivation found in the TBI group remained when controlling for performance, for prefrontal and inferior parietal lobe. Previous fMRI studies in TBI using *n*-back paradigm and comparing controls with non-impaired TBI subjects reported similar results to those obtained in our study (McAllister et al., 1999; Newsome et al., 2007b; Scheibel et al., 2007). However, the lack of performance criterion to include the TBI patients in the fMRI study can be considered a limitation of the study. The covariation analyses involves lack of some signifficant results indicating the relationship between activation and performance.

Further research is needed to evaluate the effect of rehabilitative intervention on working memory performance and related brain activation. Diffusion tensor imaging (DTI) concurrent with fMRI could elucidate changes in the microstructure of cerebral white matter in working memory-related regions.

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DISCLOSURE STATEMENT

No conflicting financial interests exist.

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