◆ Human Brain Mapping 30:2789–2803 (2009) ◆

Postconcussion Syndrome After Minor Head Injury: Brain Activation of Working Memory and Attention

Marion Smits,[1]* Diederik W.J. Dippel,[2] Gavin C. Houston,[3] Piotr A. Wielopolski,[1] Peter J. Koudstaal,[2] M.G. Myriam Hunink,[1,4,5] and Aad van der Lugt[1]

[1]*Department of Radiology, Erasmus MC—University Medical Centre Rotterdam, Rotterdam, The Netherlands*
[2]*Department of Neurology, Erasmus MC—University Medical Centre Rotterdam, Rotterdam, The Netherlands*
[3]*Applied Science Lab, GE Healthcare, 's Hertogenbosch, The Netherlands*
[4]*Department of Epidemiology and Biostatistics, Erasmus MC—University Medical Centre Rotterdam, Rotterdam, The Netherlands*
[5]*Department of Health Policy and Management, Harvard School of Public Health, Boston, Massachusetts*

Abstract: After minor head injury (MHI) postconcussive symptoms (PCS) such as memory and attention deficits frequently occur. It has been hypothesised that PCS are caused by microstructural damage to the brain due to shearing injury, which is not detectable with conventional imaging, and may be responsible for a functional deficit. The purpose of this study was to correlate functional magnetic resonance imaging brain activation of working memory and selective attention with PCS. 21 MHI patients and 12 healthy controls were scanned at 3T. Stimulation paradigms were the *n*-back and Counting Stroop tasks to engage working memory and selective attention, respectively. Functional data analysis consisted of random effects group analyses, correlating brain activation patterns with the severity of PCS as evaluated with the Rivermead postconcussion symptoms questionnaire. At minimal working memory load, activation was seen in patients with greater severity of PCS in the working memory network. With an increase of working memory load, increase of activation was more pronounced in patients with greater severity of PCS. At high and increased working memory load, activation associated with the severity of PCS was seen in the posterior parietal area, parahippocampal gyrus, and posterior cingulate gyrus. Activation related to selective attention processing was increased with greater severity of PCS. The increased activity in relation to working memory and attention, and the recruitment of brain areas outside the working memory network at high working memory load, may be considered a reflection of the brain's compensatory response to microstructural injury in patients with PCS. *Hum Brain Mapp 30:2789–2803, 2009.* **© 2008 Wiley-Liss, Inc.**

Key words: postconcussion syndrome; cognitive impairment; concussion; MRI/fMRI; functional neuroimaging

INTRODUCTION

Head injury is a major health and societal burden, with an estimated incidence of 235 patients per 100,000 in Europe [Tagliaferri et al., 2006]. The vast majority of head injury patients present with a near-normal level of consciousness [Glasgow coma scale (GCS) score of 13–15] and are considered to be MHI patients [Carroll et al., 2004; Cassidy et al., 2004; Kraus and Nourjah, 1988]. Despite

*Correspondence to: Marion Smits, Department of Radiology (Hs-224), Erasmus MC—University Medical Centre Rotterdam, PO Box 2040, CA 3000, Rotterdam, The Netherlands.
E-mail: marion.smits@erasmusmc.nl

Received for publication 11 March 2008; Revised 30 October 2008; Accepted 2 November 2008
DOI: 10.1002/hbm.20709
Published online 31 December 2008 in Wiley InterScience (www.interscience.wiley.com).

being classified as minor, more than 80% of these head injury patients experience postconcussive complaints in the first week after the injury. Symptoms are generally self-limiting, and, while still present in 30% of patients 1 month after the injury, have commonly disappeared after 6 months, only to persist in a small minority of patients [Alexander, 1995; Ingebrigtsen et al., 1998; King, 2003; Lishman, 1988].

Postconcussive symptoms (PCS) comprise a wide variety of somatic, psychological, and cognitive complaints such as headache, fatigue, depression, and memory and attention deficits [Alexander, 1995, 1997; Dikmen et al., 1986; WHO, 1993]. The presence of a minimum of three symptoms for at least three months after the injury is used as a criterion for the diagnosis of the postconcussion syndrome [American Psychiatric Association, 1994; WHO, 1993], for which a neuropathological substrate is still lacking [Evans, 1992; WHO, 1993]. With conventional imaging techniques of the brain, such as computed tomography (CT) or magnetic resonance imaging (MRI), generally no structural abnormalities are found [Bigler, 2001; Hofman et al., 2001].

Despite the subjective severity of complaints in these patients, neuropsychological tests are also usually normal. If abnormal, deficits tend to be subtle, and are most commonly found in the cognitive domains of working memory and selective attention [Bohnen et al., 1992a,b; Cicerone and Azulay, 2002]. Working memory refers to the cognitive process during which a limited amount of information is kept in memory for a brief period of time for further cognitive manipulation. A common task to engage working memory is the *n*-back task, during which at least five areas of the brain have shown to be involved, namely the dorso- and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area [D'Esposito et al., 1998, 2000; Jonides et al., 1997; Owen et al., 2005; Smith and Jonides, 1998]. Selective attention concerns the process of directing attention towards a specific stimulus, and is traditionally tested with the Stroop colour word task, in which the difference in response time for a neutral stimulus (inducing an automatic response) and response time for an interference stimulus (inducing a response for which interfering information needs to be ignored) is considered a measure of selective attention [Stroop, 1935]. Brain areas involved in the processing of selective attention are the dorsolateral prefrontal cortex, the supplementary motor area, and the anterior cingulate cortex [Bush et al., 1998; Egner and Hirsch, 2005].

It has been hypothesised that PCS are caused by microstructural damage to the brain due to shearing injury, which is not detectable with conventional imaging, and may be responsible for a functional deficit [Bigler, 2001, 2003; King, 1997; Lishman, 1988; Szymanski and Linn, 1992]. A compensatory mechanism of the brain could explain the discrepancy between the subjective severity of cognitive complaints and—near—normal findings on neuropsychological testing [Audoin et al., 2003]. Previous functional MRI (fMRI) studies of MHI patients have indeed shown altered patterns of activation during the performance of working memory tasks [Chen et al., 2004; Christodoulou et al., 2001; McAllister et al., 1999, 2001], consisting of reports of both increased [McAllister et al., 1999, 2001] and decreased [Chen et al., 2004] activation in the dorsolateral prefrontal cortex and increased activation in the posterior parietal area [McAllister et al., 1999, 2001] during an *n*-back task, and more dispersed activation and the recruitment of brain regions in the contralateral hemisphere during a paced auditory serial addition task [Christodoulou et al., 2001]. Meanwhile, it is conceivable that a more global change in brain activity after MHI occurs, and that previously reported findings are not task-specific. An association of brain activation with postconcussive complaints has as yet not been assessed.

In the present study, we used fMRI to correlate PCS after MHI with neural correlates of the two cognitive domains commonly affected, i.e. working memory and selective attention. We also assessed whether PCS were associated with brain activation during a simple, noncognitive finger tapping task.

METHODS

Study Population

Patients were prospectively and consecutively included if they met the following inclusion criteria: aged 18–50 years, presentation to our emergency department with blunt head trauma, a GCS score of 13–15, a normal neurological examination, and normal CT of the head performed within 24 h of injury. As a control group, healthy volunteers were recruited from the included patients' peers and family where possible, and additionally from hospital coworkers.

Head injury patients and controls were excluded if they had a history of neurological or psychiatric disease, had previous head injury, used prescription medication other than oral contraceptives, or had contraindications for MR imaging.

The study protocol was approved by the Erasmus MC institutional review board and written informed consent was obtained from all participants.

Participant Characteristics

General demographical data were collected from all participants. Educational level was specified according the Dutch educational system, in which several levels of secondary education exist. The participants' educational level was based on their highest level of education completed and classified accordingly as follows: (1) primary education only; (2) lower-level secondary education; (3) middle-level secondary education; (4) higher-level secondary or postsecondary education. The number of years of education completed was also recorded. All participants under-

went general neurological examination and testing of crude cognitive function by means of the Mini Mental Status Examination (MMSE) [Folstein et al., 1975].

In the head injury patients, the number and severity of postconcussive complaints was assessed by means of the Rivermead postconcussion symptoms questionnaire (RPSQ) [King et al., 1995]. The RPSQ is a five point-scale of 16 symptoms that are common after head injury, and has a high test-retest and inter-rater agreement for the assessment of the presence and severity of PCS [Ingebrigtsen et al., 1998; King et al., 1995]. Patients rate severity of each symptom in comparison with preinjury levels on a scale from zero (no symptoms) to four (severe symptoms), thus adjusting for the high base-rate of (some of these) symptoms in the general population. Additional symptoms may be recorded and rated similarly. The higher the sum score, the more (severely) symptoms are present after the injury.

MRI Acquisition Protocol

Imaging was performed on a 3T MR system (HD platform, GE Healthcare, Milwaukee, WI) ~1 month after the injury. An eight-channel head coil was used for reception of the signal. For anatomical reference a high-resolution three-dimensional (3D) inversion recovery (IR) fast spoiled gradient echo (FSPGR) T1-weighted image was acquired, with the following pulse sequence parameters: repetition time (TR)/echo time (TE)/inversion time (TI) 10.7/2.2/300 ms; flip angle 18°; matrix 416 × 256 and field of view (FOV) 250 × 175 mm^2 resulting in an in-plane resolution of 0.6 × 0.7 mm^2; 192 slices with a slice thickness of 1.6 mm and 0.8 mm overlap; acquisition time: 4:57 min. For functional imaging, a single shot T2*-weighted gradient echo echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent contrast was used (TE 30 ms; flip angle 75°; acquisition matrix 64 × 96 and FOV 220 × 220 mm^2 resulting in an in-plane resolution of 3.4 × 2.3 mm^2; slice thickness 3.5 mm). TR, the number of slices (which was the maximum number that could be acquired within the given TR), and acquisition time varied according to the stimulation paradigm: for the finger tapping task TR was 3,000 ms, number of slices 39, and acquisition time 4:15 min; for the *n*-back task TR was 2,500 ms, number of slices 32, and acquisition time 6:43 min; for the Stroop task TR was 2,000 ms, number of slices 26, and acquisition time 6:10 min. Slice localisation was prescribed in the axial plane, covering at least the supratentorial brain. All functional imaging data acquisitions included five dummy scans that were discarded from further analysis.

Functional MRI Stimulation Paradigms

All tasks were presented using Presentation v9.81 software (Neurobehavioral Systems, Albany, CA) installed on a desktop PC, which was dedicated for stimulus presentation. External triggering by the MR system ensured synchronisation of the stimulus paradigms with the imaging data acquisition and precise recording of task performance and response times through fibre optic button response pads. Auditory tasks were presented binaurally through an MRI compatible headphone system; visual tasks were presented in near-darkness using a projector and a back-projection screen that was visible with a mirror mounted on the head coil. All tasks were designed according to a blocked design with 30 s block duration.

Finger tapping

The first task was a self-paced finger tapping task at an approximate rate of 1 Hz during which consecutive opposition of the thumb to each of the other fingers of the right hand only was performed. The task consisted of eight blocks (4:00 min) of alternating active (right-hand finger tapping) and rest (no finger tapping) conditions. Simple instructions indicating the start of the active and rest conditions were presented auditorily.

n-Back task: Working memory and vigilance

We used the *n*-back task to engage continuous attention (vigilance) and verbal working memory. Four different conditions with increasing levels of working memory load were presented: (1) rest, (2) 0-back, (3) 1-back, and (4) 2-back. Stimuli consisted of auditorily presented numbers (0–9), one stimulus presented every 3 s. Simple auditory instructions indicated the start of each condition. Participants responded by pressing a response button with the right thumb. During the rest condition, no stimuli were presented and the participant was instructed to do nothing. During the 0-back condition, participants were instructed to press the response button whenever the number ''0'' was presented. During the 1-back condition, a response was required when the presented number matched the previous one. During the 2-back condition, a response was required when the presented number matched the number before the previous one. The 0-back condition requires continuous attention (vigilance) and only minimal working memory; the 1-back condition represents moderate, and the 2-back condition high working memory load. A single task consisted of 13 blocks, and the task was performed twice. Conditions were counterbalanced within and across the two tasks, i.e. each condition was equally often preceded and followed by each of the other conditions [Donaldson and Buckner, 2002].

Stroop task: Selective attention

To engage selective attention, the counting Stroop task was used [Bush et al., 1998], which was presented visually. Responses were given by means of two response boxes, one held in each hand, with two buttons each to be pressed with the thumb. Simple visual instructions indicated the start of the rest, the neutral, and the interference

conditions. The task started and ended with the rest condition, during which no stimuli were presented and the participant was instructed to do nothing. A further 10 blocks were presented, alternating the neutral and the interference condition. During the neutral condition, single or multiple (up to four) animal names were presented every 2.5 s for 1.4 s, and the participant was instructed to press the response button (representing the numbers one to four) that matched the presented number of animal names. During the interference condition, single or multiple (up to four) written-out numbers (one, two, three, and four) were presented, and the participant was instructed to press the response button matching the presented number of words (i.e. ''three three'' = button no. 2). During this condition, oddballs were interspersed pseudo-randomly, during which the participant was required to press the response button matching the presented number itself (and not the number of words) when it was written in capital letters (i.e. ''THREE THREE'' = button no. 3). A single task consisted of 12 blocks, and the task was performed twice. Conditions were counterbalanced within and across the two tasks.

Statistical Analysis

Participant characteristics

The MHI patients were divided into two groups, according to their RPSQ score, to best fit the data distribution: patients with a score below the median RPSQ score were classified as having moderate PCS, whereas patients with a score of or above the median RPSQ score were classified as having severe PCS. Such labelling based on the median was chosen rather arbitrarily, as no standard methods for categorising patients based on their RPSQ score exists. Controls were classified as having no PCS. We tested differences in participant characteristics between the three groups (no, moderate, severe PCS) for significance ($P < 0.05$) using one-way analysis of variance (ANOVA) and Student's *t*-test for continuous (age, MMSE, GCS score), Pearson's chi-square test for categorical (gender), and Kruskal Wallis for ordinal (educational level) variables.

Task performance

Task performance consisted of response times and the percentage correct responses (number of correct responses divided by the number of required responses), averaged per participant and per acquisition for each condition of the *n*-back task (0-back, 1-back, 2-back) and the Stroop task (interference, neutral). Potential session effects were assessed by testing differences in task performance for each condition between the two sessions using an independent samples *t*-test for significance ($P < 0.05$). For each task, differences in performance between the conditions were assessed for significance ($P < 0.05$) using a paired *t*-test. Differences between the three groups (no, moderate, severe PCS) in task performance for each condition were assessed using one-way ANOVA for significance ($P < 0.05$).

Functional MRI

Analysis of fMRI data was performed with Statistical Parametric Mapping version 2 (SPM2, Wellcome Department, University College London, London, UK) implemented in Matlab version 6.5.1 (The Mathworks, Sherborn, MA). For individual analysis, all T2*-weighted functional images were realigned to correct for the participant's motion during data acquisition and were coregistered with the high-resolution T1-weighted anatomical image [Friston et al., 1996]. The functional and anatomical images were normalised to the standard brain space defined by the Montreal Neurological Institute (MNI) as provided within SPM2, using affine and nonlinear registration [Ashburner and Friston, 1999] and resulting in resampled voxel sizes of $2 \times 2 \times 2$ mm^3 for the functional and $1 \times 1 \times 1$ mm^3 for the anatomical images. The normalised functional images were smoothed with a 3D Gaussian filter of $6 \times 6 \times 6$ mm^3 Full Width Half Maximum (FWHM) to increase the signal-to-noise ratio, correct for interindividual anatomical variation and to normalise the data. For each task and each acquisition, individual statistical parametric maps were calculated using the general linear model by modelling the conditions as a box car function convolved with the haemodynamic response function, corrected for temporal autocorrelation and filtered with a high-pass filter of 128 s cutoff. Motion parameters were included in the model as regressors of no interest to reduce potential confounding effects due to motion. The following t-contrast images were generated: right-hand finger tapping versus rest (finger tapping task); 0-back versus rest, 1-back versus 0-back, 2-back versus 0-back and 2-back versus 1-back (*n*-back task); interference versus neutral (Stroop task).

These individual t-contrast images were then used for second-level random effects group analyses. We used 1-sample *t*-tests to assess the average activation patterns across all participants with main effect analyses, using a threshold of $P < 0.05$ with family wise error (FWE) correction for multiple comparisons and a minimum cluster size (k) of 20 voxels. We then performed multiple regression analysis to assess differences in activation between the three groups, using postconcussive complaints (categorised as no, moderate or severe PCS) as a regressor of interest, and adjusting for potential confounders (based on our analysis of group differences for participant characteristics and task performance) added to the model as regressors of no interest. Initially, we assessed brain activation changes for significance at a threshold of $P < 0.05$ with FWE correction for multiple comparisons. However, since no activation surviving this stringent threshold was observed, a more lenient threshold of $P < 0.001$ not corrected for multiple comparisons and a minimum cluster size of 20 voxels was applied.

TABLE I. Participant characteristics

	Moderate PCS (n = 10)	Severe PCS (n = 11)	Controls (n = 12)	P-value
Age, years (SD)	23.9 (4.6)	27.8 (9.8)	27.8 (10)	0.50[a]
Male gender, n (%)	7 (70)	5 (46)	8 (67)	0.45[b]
Educational level[c], mean (SD)	3.2 (1.0)	3.1 (0.9)	3.3 (1.1)	0.64[d]
Number of education years, mean (SD)	15.3 (1.9)	15.4 (2.3)	15.7 (3.1)	0.92[a]
MMSE, mean (SD)	27.5 (1.3)	27.6 (2.1)	27.5 (1.8)	1.00[a]
GCS, mean (SD)	14.7 (0.5)	14.7 (0.5)	–	0.89[a]

PCS, postconcussive symptoms; RPSQ, Rivermead postconcussion symptoms questionnaire; SD, standard deviation.
[a] One-way ANOVA/Student's t-test.
[b] Pearson's chi-square test.
[c] Educational level ranged from one (primary education only) to four (higher-level secondary or postsecondary education).
[d] Kruskal Wallis.

Anatomical labelling of significantly activated clusters was performed using the MNI Space Utility software extension to SPM2 according to the methods described by Brett on http://www.ihb.spb.ru/~pet_lab/MSU/MSU-Main.html [Calder et al., 2001; Duncan et al., 2000].

RESULTS

Study Population

Between December 2005 and November 2006, 236 patients with recent MHI presented to our emergency department who were eligible for inclusion in the study. Of these, 51 could be contacted, 36 of whom were willing to participate. Of these, six did not fulfil the study's inclusion criteria, and nine were excluded because of contraindications for MR imaging (n = 2), previous history of neurological or psychiatric disease (n = 4), and previous history of head injury (n = 3). The 21 remaining patients were imaged at an average of 30.6 days (range, 18–40 days) after MHI. None of these patients had a neurocranial traumatic finding on CT performed within 24 h of the injury.

In addition 12 healthy volunteers were included in the study. In one control subject, the n-back task was not performed because of technical difficulties. In a different control subject, the Stroop task was not performed due to the subject's poor visual acuity without spectacle correction.

Participant Characteristics

The median RPSQ score was 8.0 (mean, 14; range, 0–46). Patients with an RPSQ score below 8.0 were classified as moderate PCS (n = 10), and patients with an RPSQ of 8.0 or higher were classified as severe PCS (n = 11).

The majority of participants were male (n = 20; 61%), and the mean age was 28 years, which was not different among the three groups (P = 0.45 and P = 0.50 for gender and age respectively; Table I). Neurological examination was normal in all participants. There was also no difference between the three groups in level (P = 0.64; Table I) or number of completed years (P = 0.91; Table I) of education, nor in crude cognitive function as measured with the MMSE (P = 1.00; Table I).

All but one patient had a history of loss of consciousness or (post-traumatic) amnesia after the injury. Most patients had a GCS score of 15 upon presentation (n = 15; 71%) and six patients presented with a GCS score of 14 (29%). There was no difference in average GCS score between the group of patients with severe and moderate PCS (P = 0.89; Table I).

Task Performance

Because of technical difficulties, task performance (both for the n-back and the Stroop task) was not recorded in three participants (one control, one moderate, and one severe PCS). Imaging data from these participants were available and included in the fMRI analyses.

n-Back task (vigilance and working memory)

There was no significant session effect on n-back task performance. As expected, performance became significantly worse at the highest level of working memory load (Table II). For the 2-back versus the 0-back condition the average proportion of correct responses was significantly decreased (P = 0.02) and the average response time showed a significant increase ($P < 0.001$).

Severe PCS patients had a significantly lower percentage of correct responses than the control subjects and moderate PCS patients for the 1-back (P = 0.01 both for comparison with the control subjects and with the moderate PCS patients) and the 2-back (P = 0.01 and P = 0.02 for comparison with the control subjects and with the moderate PCS patients, respectively) conditions. The percentage correct responses was therefore adjusted for as a potential confounder in the multivariable regression analysis. There was no difference in the average response times for any of the conditions between the three groups.

TABLE II. Performance on the *n*-back task

	0-Back (SD)	1-Back (SD)	2-Back (SD)
Average proportion correct (n = 29)[a]	0.95 (0.20)	0.88 (0.27)	0.85 (0.24)
Controls (n = 10)	0.99 (0.03)	1.00 (0.00)	0.95 (0.10)
Moderate PCS (n = 9)	1.00 (0.00)	0.99 (0.03)	0.97 (0.06)
Severe PCS (n = 10)	0.86 (0.33)	0.66 (0.39)	0.65 (0.31)
Average response time (n = 29)[a] in seconds	0.75 (0.18)	0.80 (0.29)	0.95 (0.36)
Controls (n = 10)	0.70 (0.11)	0.79 (0.21)	0.84 (0.25)
Moderate PCS (n = 9)	0.78 (0.10)	0.82 (0.14)	0.88 (0.18)
Severe PCS (n = 10)	0.76 (0.29)	0.81 (0.45)	1.13 (0.51)

SD, standard deviation.
[a] The *n*-back task was not performed in one control subject. In a further three participants (one control, one moderate, and one severe PCS) task performance was not recorded.

TABLE III. Performance on the counting Stroop task

	Neutral (SD)	Interference (SD)
Average proportion correct (n = 29)[a]	0.97 (0.26)	0.89 (0.11)
Controls (n = 10)	0.98 (0.02)	0.95 (0.32)
Moderate PCS (n = 9)	0.97 (0.03)	0.92 (0.06)
Severe PCS (n = 10)	0.96 (0.03)	0.82 (0.15)
Average response time (n = 29)[a]	0.82 (0.10)	0.93 (0.11)
Controls (n = 10)	0.78 (0.11)	0.89 (0.09)
Moderate PCS (n = 9)	0.80 (0.11)	0.94 (0.14)
Severe PCS (n = 10)	0.87 (0.06)	0.97 (0.09)

SD = standard deviation.
[a] The Stroop task was not performed in one control subject. In a further three participants (one control, one moderate, and one severe PCS) task performance was not recorded.

Stroop task (selective attention)

There was no significant session effect on Stroop task performance. The average proportion of correct responses was significantly lower for the interference than for the neutral condition ($P < 0.001$), whereas the average response time was significantly longer for the interference than for the neutral condition ($P < 0.001$). Severe PCS patients had a significantly lower percentage of correct responses than the control subjects for the interference condition ($P = 0.02$; Table III). The percentage correct responses was therefore adjusted for as a potential confounder in the multivariable regression analysis.

Functional MRI

Areas of significant activation are detailed in Tables IV–XI.

Right-hand finger tapping

During right-hand finger tapping versus rest, significant activation was seen in the left pre- and postcentral gyrus (primary sensorimotor cortex), bilaterally in the medial superior frontal gyrus (supplementary motor area), bilaterally in the inferior parietal lobule, and in the left lentiform nucleus. No association with severity of PCS was seen.

n-Back task: Vigilance and working memory

0-Back versus rest: Vigilance. The 0-back condition compared with the rest condition (main effect; Table IV, Fig. 1a) yielded significant activation bilaterally in the inferior frontal gyrus and insula (ventrolateral prefrontal cortex); in the right (medial) superior frontal gyrus (supplementary motor area); and in the right middle and bilateral superior temporal gyrus (auditory cortex).

Increased activation was seen associated with increased severity of PCS (Table V, Fig. 1b) bilaterally in the inferior and middle frontal gyrus and precentral gyrus, and in the right superior frontal cortex (dorsolateral prefrontal cor-

TABLE IV. Main effect of the 0-back versus rest condition (n = 32[a]; one-sample t-test; $P_{corrected} < 0.05$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI x	MNI y	MNI z	t-value
Superior frontal gyrus (83%)	R	53	6	8	62	6.31
Medial superior frontal gyrus (17%)	R					
Insula (31%)	R	457	42	14	6	8.03
Precentral gyrus (9%)	R					
Inferior frontal gyrus (44%)	R					
Insula (61%)	L	114	−34	22	12	6.51
Inferior frontal gyrus (27%)	L					
Middle temporal gyrus (53%)	R	241	58	−24	−6	6.78
Superior temporal gyrus (47%)	R					
Superior temporal gyrus (96%)	L	281	−66	−30	10	6.43

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (x, y, and z) and statistical t-values of areas of significant activation for the main effect of the 0-back versus rest condition.
L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.
[a] The *n*-back task was not performed in one control subject.

TABLE V. Regression analysis of the 0-back versus rest condition ($n = 32$[a]; multivariable regression analysis; $P_{uncorrected} < 0.001$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			*t*-value
			x	*y*	*z*	
Precentral gyrus (%)	R	568	42	6	48	4.28
Inferior frontal gyrus (%)	R					
Middle frontal gyrus (%)	R					
Cingulate gyrus (15%)	R	354	8	24	56	4.53
Superior frontal gyrus (36%)	R					
Medial superior frontal gyrus (46%)	R					
Superior frontal gyrus (100%)	R	30	6	8	62	3.86
Middle frontal gyrus (57%)	R	187	30	50	4	5.08
Superior frontal gyrus (5%)	R					
Superior frontal gyrus (98%)	R	94	20	50	32	4.87
Middle frontal gyrus (38%)	R	24	12	−12	66	4.87
Medial superior frontal gyrus (62%)	R					
Middle frontal gyrus (77%)	R	30	34	38	36	3.58
Superior frontal gyrus (23%)	R					
Inferior frontal gyrus (53%)	R	93	38	30	16	4.05
Middle frontal gyrus (24%)	R					
Precentral gyrus (24%)	L	584	−38	14	24	4.27
Inferior frontal gyrus (17%)	L					
Middle frontal gyrus (26%)	L					
Cingulate gyrus (43%)	L	65	−10	24	42	3.95
Medial superior frontal gyrus (55%)	L					
Medial superior frontal gyrus (96%)	L	25	−8	38	34	3.61
Middle temporal gyrus (96%)	R	23	58	−48	−4	3.54
Inferior parietal lobule (55%)	R	527	50	−32	48	5.09
Postcentral gyrus (18%)	R					
Inferior parietal lobule (42%)	L	589	−34	−44	46	4.54
Superior parietal lobule (16%)	L					
Precuneus (17%)	L					
Superior parietal lobule (92%)	L	25	−30	−56	62	4.62
Inferior parietal lobule (40%)	L	40	−42	−48	62	4.26
Postcentral gyrus (40%)	L					

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (*x*, *y*, and *z*) and statistical *t*-values of areas of significant activation for the regression analysis of the 0-back versus rest condition with severity of postconcussive complaints.

L, left hemisphere; R, right hemisphere.

[a] The *n*-back task was not performed in one control subject.

tex); bilaterally in the medial superior frontal gyrus (includes the right supplementary motor area); in the cingulate gyrus bilaterally; in the right middle temporal gyrus (auditory cortex); and in the left superior parietal lobule and precuneus and bilaterally in the inferior parietal lobule (posterior parietal area).

1-Back versus 0-back: Moderate working memory load. The 1-back compared with the 0-back condition (main effect; Fig. 2a) yielded significant activation in the right supramarginal gyrus and inferior parietal lobule (posterior parietal area). No association with severity of PCS was seen.

2-Back versus 0-back: High working memory load. The 2-back compared with the 0-back condition (main effect; Table VI, Fig. 2b) yielded significant activation bilaterally in the inferior and middle frontal gyrus and the precentral gyrus (dorsolateral prefrontal cortex and premotor area); bilaterally in the insula and inferior frontal gyrus (ventrolateral prefrontal cortex), and in the (medial) superior frontal gyrus (supplementary motor area); and bilaterally in the supramarginal gyrus, the inferior and superior parietal lobule, and the precuneus (posterior parietal area).

Increased activation was seen associated with increased severity of PCS (Table VII, Fig. 3) in the left (medial) superior frontal gyrus (supplementary motor area); bilaterally in the parahippocampal gyrus, the (posterior) cingulate gyrus; and in the precuneus (posterior parietal area).

2-Back versus 1-back: Differential working memory load. The comparison of the 2-back with the 1-back condition (main effect; Table VIII, Fig. 2c) yielded significant activation in the right middle and superior frontal gyrus (dorsolateral prefrontal cortex and premotor area); the left (medial) superior frontal gyrus (supplementary motor area); and in the supramarginal gyrus, the inferior and superior parietal lobule, and precuneus bilaterally (posterior parietal area).

Increased activation, associated with increased severity of PCS was seen (Table IX) in the right supramarginal

TABLE VI. Main effect of the 2-back versus 0-back condition ($n = 32$[a]; one-sample *t*-test; $P_{corrected} < 0.05$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			*t*-value
			x	*y*	*z*	
Precentral gyrus (6%)	R	1387	28	0	62	8.60
Inferior frontal gyrus (8%)	R					
Middle frontal gyrus (76%)	R					
Precentral gyrus (9%)	L	1161	−46	12	34	8.36
Inferior frontal gyrus (16%)	L					
Middle frontal gyrus (65%)	L					
Anterior cingulate gyrus (4%)	L + R	566	2	18	52	8.61
Medial superior frontal gyrus (47%)	L + R					
Superior frontal gyrus (31%)	L + R					
Insula (29%)	R	111	32	22	4	6.74
Inferior frontal gyrus (47%)	R					
Insula (31%)	L	35	−34	24	0	6.13
Inferior frontal gyrus (40%)	L					
Supramarginal gyrus (11%)	R	1465	46	−44	46	9.65
Inferior parietal lobule (51%)	R					
Superior parietal lobule (12%)	R					
Precuneus (14%)	R					
Precuneus (84%)	R	79	4	−68	50	6.21
Superior parietal lobule (6%)	R					
Supramarginal gyrus (4%)	L	1055	−32	−64	42	9.50
Inferior parietal lobule (41%)	L					
Superior parietal lobule (21%)	L					
Precuneus (13%)	L					

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (*x*, *y*, and *z*) and statistical *t*-values of areas of significant activation for the main effect of the 2-back versus 0-back condition.
L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.
[a] The *n*-back task was not performed in one control subject.

gyrus and inferior parietal lobule and bilaterally in the paracentral lobule and precuneus (posterior parietal area); the right posterior cingulate gyrus and parahippocampal gyrus; and the middle and superior temporal gyrus bilaterally (auditory cortex).

Stroop task (selective attention). The comparison of the interference with the neutral condition (main effect; Fig. 4a; Table X) yielded significant activation in the right inferior and bilateral middle frontal gyrus (dorsolateral and ventrolateral prefrontal cortex), in the (medial) superior frontal gyrus (supplementary motor area), and in the right inferior and superior parietal lobule and bilateral precuneus (posterior parietal area).

Increased activation, associated with increased severity of PCS was seen (Table XI, Fig. 4b) in the left insula, infe-

TABLE VII. Regression analysis of the 2-back versus 0-back condition ($n = 32$[a]; multivariable regression analysis; $P_{uncorrected} < 0.001$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			*t*-value
			x	*y*	*z*	
Superior frontal gyrus (14%)	L	21	−6	62	24	3.83
Medial superior frontal gyrus (86%)						
Parahippocampal gyrus (80%)	R	88	16	−36	−4	4.33
Posterior cingulate gyrus (54%)	L + R	251	−6	−48	4	4.67
Parahippocampal gyrus (1%)	L					
Cingulate gyrus (25%)	L + R					
Precuneus (14%)	L + R					
Precuneus (76%)	R	37	12	−68	18	3.68

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (*x*, *y*, and *z*) and statistical *t*-values of areas of significant activation for the regression analysis of the 2-back versus 0-back condition with severity of postconcussive complaints.
L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.
[a] The *n*-back task was not performed in one control subject.

TABLE VIII. Main effect of the 2-back versus 1-back condition ($n = 32$[a]; one-sample *t*-test; $P_{corrected} < 0.05$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			*t*-value
			x	*y*	*z*	
Middle frontal gyrus (46%)	R	83	24	−4	54	5.96
Superior frontal gyrus (5%)	R					
Superior frontal gyrus (82%)	L	44	−4	16	54	5.77
Medial superior frontal gyrus (16%)	L					
Inferior parietal lobule (21%)	R	85	30	−54	38	6.51
Supramarginal gyrus (6%)	R					
Precuneus (87%)	R	91	32	−72	38	6.45
Superior parietal lobule (5%)	R					
Inferior parietal lobule (65%)	L	48	−36	−56	40	5.57
Supramarginal gyrus (10%)	L					
Precuneus (61%)	L	75	−26	−68	42	5.85
Superior parietal lobule (32%)	L					

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (*x*, *y*, and *z*) and statistical *t*-values of areas of significant activation for the main effect of the 2-back versus 1-back condition.
L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.
[a] The *n*-back task was not performed in one control subject.

rior frontal gyrus and precentral gyrus (ventrolateral prefrontal cortex); bilaterally in the anterior cingulate and posterior cingulate cortex; and bilaterally in the precuneus (posterior parietal area).

DISCUSSION

In this study, we examined the neural correlates of PCS after MHI. A positive correlation was found between the

TABLE IX. Regression analysis of the 2-back versus 1-back condition ($n = 32$[a]; multivariable regression analysis; $P_{uncorrected} < 0.001$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			*t*-value
			x	*y*	*z*	
Insula (24%)	R	21	40	−24	6	3.89
Superior temporal gyrus (76%)	R					
Insula (30%)	R	30	56	−34	16	4.21
Superior temporal gyrus (70%)	R					
Middle temporal gyrus (85%)	L	119	−58	−30	−6	4.74
Superior temporal gyrus (15%)	L					
Middle temporal gyrus (7%)	L	58	−54	32	10	3.72
Superior temporal gyrus (90%)	L					
Insula (26%)	L	27	−44	−22	4	4.28
Superior temporal gyrus (74%)	L					
Superior temporal gyrus (18%)	L	44	−54	8	4	4.11
Precuneus (72%)	R	32	6	−50	54	3.55
Paracentral lobule (28%)	R					
Precuneus (65%)	R	20	20	−74	22	3.60
Supramarginal gyrus (53%)	R	51	52	−44	28	4.33
Inferior parietal lobule (47%)	R					
Precuneus (87%)	L + R	23	6	−56	62	3.70
Paracentral lobule (4%)	L					
Postcentral gyrus (80%)	L	20	−52	−20	20	3.79
Parahippocampal gyrus (22%)	R	109	18	−16	−12	4.72
Lentiform nucleus (11%)	R					
Posterior cingulate gyrus (40%)	R	43	6	−40	8	3.75
Parahippocampal gyrus (14%)	R					
Lingual gyrus (9%)	R					
Culmen (12%)	R					

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (*x*, *y*, and *z*) and statistical *t*-values of areas of significant activation for the regression analysis of the 2-back versus 1-back condition with severity of postconcussive complaints.
L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.
[a] The *n*-back task was not performed in one control subject.

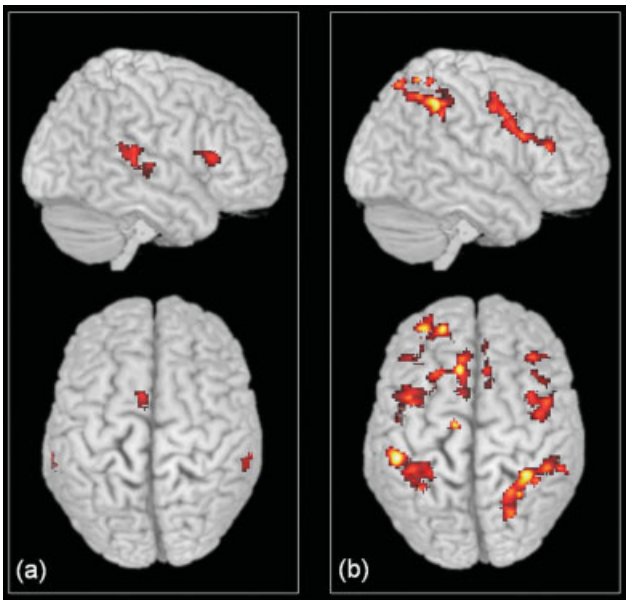

Figure 1.
Three-dimensional brain rendering with right lateral (upper row) and top views (lower row), showing significant activation for the 0-back versus rest comparison. (**a**) Main effect ($P_{corrected} < 0.05$; $k \geq 20$; $n = 32$); (**b**) activation associated with severity of postconcussive complaints (regression analysis, $P_{uncorrected} < 0.001$; $k \geq 20$; $n = 32$).

severity of postconcussive complaints and brain activation in relation to the two cognitive domains most commonly affected after MHI: working memory and selective attention. Additionally, at high working memory load, activation outside the working memory network positively correlated with the severity of PCS was observed. These findings indicate a manifestation of underlying neurophysiological damage after MHI.

Working memory and selective attention, essential for normal functioning in everyday life, are commonly affected in patients after MHI [Bohnen et al., 1992a,b; Cicerone and Azulay, 2002]. This is reflected in the time course of postconcussive complaints, which, after an initial spontaneous decrease over the course of several weeks after the injury, typically aggravate when patients resume their normal activities, such as return to work or school [Bohnen et al., 1992a]. To probe these cognitive domains after MHI, we used the *n*-back and Stroop tasks to evaluate brain activation changes.

Our study confirms involvement of the areas previously reported during performance of the *n*-back task of verbal working memory, namely the dorsolateral and ventrolateral prefrontal cortex, the supplementary motor and premotor areas, and the posterior parietal area [D'Esposito et al., 1998, 2000; Jonides et al., 1997; Owen et al., 2005, 1998; Smith and Jonides, 1998]. In accordance with previous studies, activation increased with increasing working memory demands [Jonides et al., 1997; Manoach et al.,

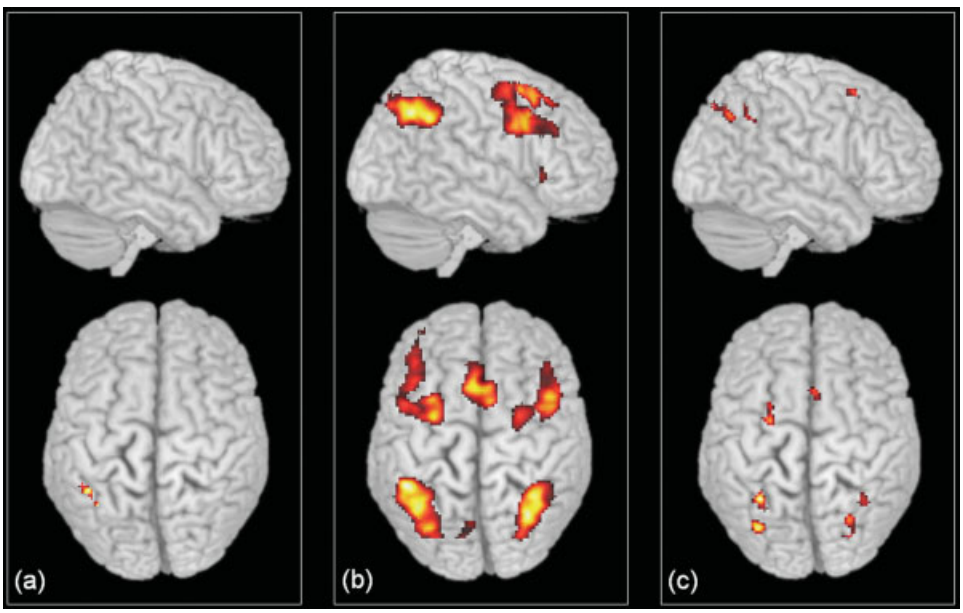

Figure 2.
Three dimensional brain rendering with right lateral (upper row) and top views (lower row), showing significant ($P_{corrected} < 0.05$; $k \geq 20$; $n = 32$) main effect activation for (**a**) the 1-back versus 0-back, (**b**) the 2-back versus 0-back, and (**c**) the 2-back versus 1-back comparisons.

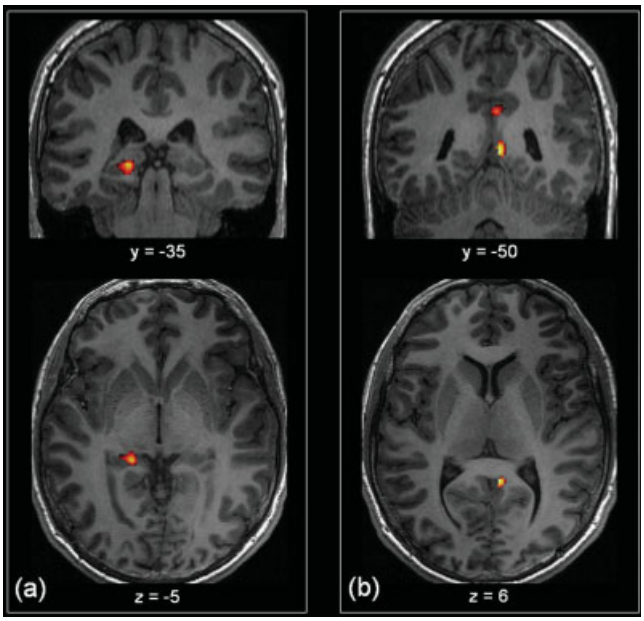

Figure 3.

Coronal (upper row) and axial (lower row) T1 weighted sections of the brain showing significant ($P_{uncorrected} < 0.001$; $k \geq 20$) activation associated with severity of postconcussive complaints for the 2-back versus 0-back comparison in (**a**) the parahippocampal and (**b**) posterior cingulate gyrus (regression analysis; $n = 32$).

1997; McAllister et al., 2001; Newsome et al., 2007], both in the prefrontal cortex and in the posterior parietal cortex, due to the higher demands placed on attentional and short-term storage components of working memory. Likewise, during performance of the Stroop task activation was found in the dorsolateral prefrontal cortex and the supplementary motor area, as reported in previous studies. [Bush et al., 1998; Egner and Hirsch, 2005]. In the anterior cingulate cortex however, which is also reported to be involved in selective attention processing, no activation was seen surviving our significance threshold, which was more stringent than thresholds used in previous reports [Bush et al., 1998; Egner and Hirsch, 2005].

In this study, we found that the severity of PCS was associated with differences in activation related to verbal working memory processing and selective attention. In contrast to previous fMRI studies of MHI patients, patients were not simply compared with healthy controls, but the presence and severity of PCS was correlated with the neural correlates of verbal working memory and selective attention. Thus, the activation is not just correlated with MHI in general, but with the severity of PCS explicitly.

Specifically, at minimal working memory load, activation was not only observed in brain areas involved in vigilance (inferior frontal gyrus) [Eyler et al., 2004], but also in areas involved in working memory processing (dorsolateral prefrontal cortex, supplementary motor area and posterior parietal area). Such activation may be explained by increased attentional and short-term memory demands in patients with postconcussive complaints, providing evidence of an elevated resting state of the ''working memory network'' in patients exhibiting PCS. With an increase of working memory load, differential activation in the posterior parietal area was more pronounced in patients reporting a greater severity of PCS. Our findings support previous work by McAllister et al. [1999, 2001], who also found increased activation in the working memory network with increasing working memory load in patients 1 month after MHI, when compared with healthy controls. In our study, additional activation was seen in the superior and middle temporal cortex bilaterally, which are involved in the articulatory loop of working memory and related to verbal rehearsal [Christodoulou et al., 2001]. Furthermore, at high working memory load contrasted with either minimal or moderate working memory load, activation associated with PCS was seen in areas outside the working memory network, most notably in the parahippocampal gyrus and the posterior cingulate gyrus. Both these areas are involved in memory processing: the parahippocampal gyrus in the consolidation of episodic information into memory, and the posterior cingulate gyrus in memory retrieval [Qin et al., 2007; Sweet et al., 2006]. Involvement of the parahippocampal and posterior cingulate gyrus in rela-

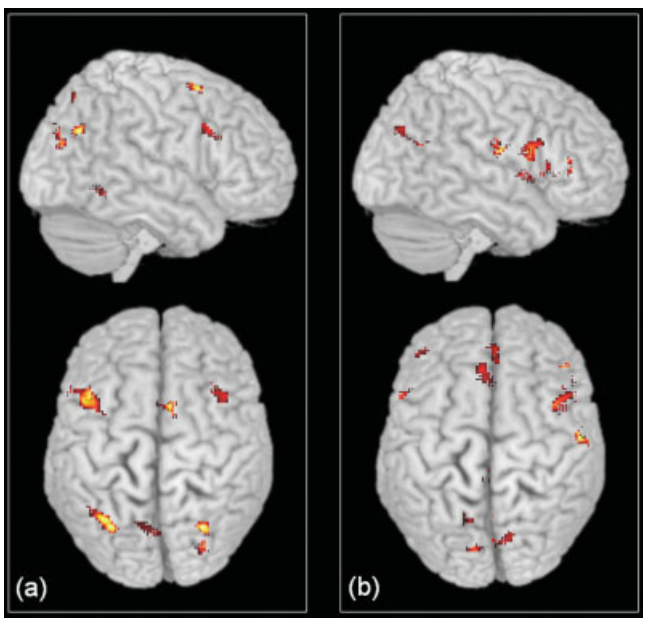

Figure 4.

Three-dimensional brain rendering with right lateral (upper row) and top views (lower row), showing significant activation for the Stroop interference versus neutral comparison. (**a**) Main effect ($P_{corrected} < 0.05$; $k \geq 20$; $n = 32$); (**b**) activation associated with severity of postconcussive complaints (regression analysis, $P_{uncorrected} < 0.001$; $k \geq 20$; $n = 32$).

TABLE X. Main effect of the Stroop interference versus neutral condition ($n = 32$[a]; one-sample t-test; $P_{corrected} < 0.05$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			t-value
			x	y	z	
Inferior frontal gyrus (100%)	R	47	42	18	−6	6.82
Inferior frontal gyrus (84%)	R	31	54	20	30	6.84
Middle frontal gyrus (13%)	R					
Inferior frontal gyrus (14%)	R	135	42	16	36	8.39
Middle frontal gyrus (81%)	R					
Middle frontal gyrus (39%)	L	61	−44	16	32	6.75
Superior frontal gyrus (95%)	L + R	37	−8	10	58	8.56
Medial superior frontal gyrus (5%)	L					
Inferior parietal lobule (46%)	R	87	30	−66	46	8.36
Superior parietal lobule (49%)	R					
Precuneus (76%)	L + R	46	2	−70	54	6.76
Superior parietal lobule (2%)	R					
Cuneus (33%)	L	42	−30	−78	24	7.37
Precuneus (12%)	L					
Precuneus (32%)	L	44	−28	−66	32	8.45

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (x, y, and z) and statistical t-values of areas of significant activation for the main effect of the Stroop interference versus neutral condition.

L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.

[a] The Stroop task was not performed in one control subject.

tion to working memory has been previously reported, albeit inconsistently. Typically, both regions are implicated in relation to long-term, rather than short-term or working memory processing. Involvement in working memory has been observed, however, both in healthy controls at very high working memory challenges, and in patients with other cognitive syndromes, such as minor cognitive impairment and probable Alzheimer disease [Yetkin et al., 2006], multiple sclerosis [Sweet et al., 2006] and depression [Walsh et al., 2007]. Although the relationship of these regions with verbal working memory remains to be established, our findings together with previous reports indicate that these regions may subserve strategies for dealing with very high working memory demands, possibly when the

TABLE XI. Regression analysis of Stroop interference versus neutral condition ($n = 32$[a]; multivariable regression analysis; $P_{uncorrected} < 0.001$, $k \geq 20$)

Anatomical location	Side	Cluster size	MNI			t-value
			x	y	z	
Insula (30%)	L	80	−38	8	18	4.36
Precentral gyrus (4%)	L					
Inferior frontal gyrus (9%)	L					
Precentral gyrus (10%)	L	29	−56	−10	18	4.90
Postcentral gyrus (90%)	L					
Anterior cingulate gyrus (97%)	L + R	33	−4	44	10	3.84
Anterior cingulate gyrus (67%)	R	30	4	32	26	3.78
Cingulated gyrus (20%)	R					
Posterior cingulate gyrus (4%)	R	52	−4	−26	24	4.17
Cingulated gyrus (56%)	L + R					
Posterior cingulate gyrus (63%)	L + R	144	−12	−60	−18	4.36
Cingulate gyrus (5%)	L					
Precuneus (23%)	L + R					
Cuneus (100%)	R	26	10	−80	20	4.03
Cuneus (31%)	L	51	−20	−58	22	4.22
Precuneus (35%)	L					

Anatomical location (and the percentage of activated voxels within the anatomical area), cluster sizes (number of voxels), MNI coordinates (x, y, and z) and statistical t-values of areas of significant activation for the regression analysis of the Stroop interference versus neutral condition with severity of postconcussive complaints.

L, left hemisphere; R, right hemisphere; MNI, Montreal Neurological Institute.

[a] The Stroop task was not performed in one control subject.

working memory network itself is exhausted [McAllister et al., 2001]. Using the Counting Stroop task [Bush et al., 1998] we were also able to show a positive correlation between the severity of PCS and increased activation in areas involved in selective attention, namely the ventrolateral prefrontal cortex, the posterior parietal area, and the cingulate gyrus [Bush et al., 1998; Egner and Hirsch, 2005]. The Stroop colour word task is known to be very sensitive to subtle deficits of selective attention in MHI patients. As far as we are aware, we are the first to report on the use of the Counting Stroop task in MHI patients, and to find a positive correlation between the severity of PCS and the neural correlates of selective attention.

It is also conceivable that increases in activation after MHI are a result of more widespread alterations in brain functioning. As no association of PCS with activation during a simple noncognitive finger tapping task was observed, changes in brain activation after MHI seem to be task-specific rather than global, suggesting that specific neural pathways are selectively vulnerable to neurophysiological damage, which is not detectable with conventional structural imaging.

Despite more widespread and additional brain activation, task performance was slightly worse in MHI patients with severe PCS. Theoretically, poorer task performance, inducing some form of error monitoring, could also be underlying the differences in activation. Because no feedback was given on task performance, it seems unlikely that participants were aware of the missed responses.

As increases in fMRI signal are generally accepted to be correlated with increased brain activity [Audoin et al., 2003; Lange et al., 2005; Levine et al., 2002; McAllister et al., 2001], our finding of increased activation in areas of the brain related to working memory and selective attention most likely reflects increased brain activity in these regions in patients with PCS. Such increases in activation only become apparent with increased task difficulty, which is consistent with the aggravation of PCS in demanding situations, such as upon return to work or school. Additionally, our findings provide evidence that patients with PCS recruit brain areas outside of the normal working memory network, reflecting altered or multiple strategies used for working memory processing to counterbalance functional deficits in working memory processing. Thus, the recruitment of these additional brain areas reflects both the brain's response to microstructural injury and a neuropathological correlate of the postconcussion syndrome.

Such observations have significant clinical importance. Identifying brain areas associated with PCS after MHI is not only important for an understanding of the underlying neuropathology of postconcussion syndrome, but it may also have implications for future diagnostic and therapeutic strategies. Early intervention, such as neurocognitive training, has shown to be effective in reducing cognitive symptoms and risk of chronicity [Bohnen and Jolles, 1992; Wade et al., 1998], but diagnosis and patient selection for intervention is problematic [Bazarian et al., 1999; Bordini et al., 2002]. Early detection and subsequent intervention is important, since chronic postconcussion syndrome is difficult to treat, and treatment results are often not satisfactory [King, 2003]. Because of the nonspecific nature of the symptoms and their high base-rate in the general and other trauma populations, early diagnosis is challenging. To account for spontaneous resolution of symptoms, persistence of symptoms for more than 3 months is commonly used as a diagnostic criterion, even though earlier diagnosis would be desirable [American Psychiatric Association, 1994]. Additionally, many confounding factors for the development of postconcussion syndrome have been identified, such as litigation, psychological distress or anxiety due to the traumatic event, premorbid levels of complaints, and female gender [Alexander, 1997; Bazarian et al., 1999; Bohnen et al., 1994; King, 2003]. At an individual level, the use of cognitive fMRI may make early and reliable diagnosis possible and facilitate the identification of patients suitable for therapeutic intervention. Furthermore, such imaging techniques may be used to evaluate and guide treatment strategies, specifically targeting brain areas involved in recovery of brain injury [Laatsch et al., 2004; Strangman et al., 2005].

We acknowledge that our study had some limitations. Firstly, the statistical power of our study was limited by a relatively small sample size. As far as we are aware, however, our study represents the largest published cognitive fMRI study of MHI patients, as previously published study populations ranged from 5 to 18 patients [Chen et al., 2004; Christodoulou et al., 2001; McAllister et al., 1999, 2001; Soeda et al., 2005; Strangman et al., 2005]. Although the statistical power of our study may not be as great as would be desired, we did control for false positive errors by applying a minimum cluster size threshold equivalent to 160 mm^3. Furthermore, the statistical threshold we applied is commonly used in exploratory fMRI studies. Secondly, only limited testing of cognitive function was performed. Testing cognition in the present study served solely to assess potential heterogeneity, and thus confounding across subgroups, and not to evaluate neuropsychological deficits after MHI, studies of which are already numerous [Bohnen et al., 1992a,b; Cicerone and Azulay, 2002]. We feel that using MMSE and educational level as crude measures of cognitive function were sufficient for the purpose of this study.

CONCLUSION

We found that the severity of PCS after MHI was significantly associated with an increase in brain activation during verbal working memory and selective attention processing. Additionally, activation outside the working memory network was found at high working memory load in patients with greater severity of PCS. These brain activation changes were detectable as early as 1 month after MHI. Our observation that the severity of PCS was associated with increased and additional activation suggests a

causal relationship and potentially represents a manifestation of a neuropathological correlate of the postconcussion syndrome.

ACKNOWLEDGMENTS

The authors thank the trial nurses of the department of Radiology, Mrs. W.J. van Leeuwen and Mrs. C. van Bavel-van Hamburg for their contribution to participant recruitment; and Dr. F. van der Veen, Dr. C. Roeder, and Dr. I. Franken for their critical review of the task design. The figures were created with the free software MRIcro version 1.39, available from http://www.mricro.com.

REFERENCES

Alexander MP (1995): Mild traumatic brain injury: Pathophysiology, natural history, and clinical management. Neurology 45:1253–1260.

Alexander MP (1997): Minor traumatic brain injury: A review of physiogenesis and psychogenesis. Semin Clin Neuropsychiatry 2:177–187.

Ashburner J, Friston KJ (1999): Nonlinear spatial normalization using basis functions. Hum Brain Mapp 7:254–266.

Association AP (1994): Diagnostic and Statistical Manual of Mental Disorders, 4th edition. Washington: American Psychiatric Association.

Audoin B, Ibarrola D, Ranjeva J-P, Confort-Gouny S, Malikova I, Ali-Chérif A, Pelletier J, Cozzone P (2003): Compensatory cortical activation observed by fMRI during a cognitive task at the earliest stage of MS. Hum Brain Mapp 20:51–58.

Bazarian JJ, Wong T, Harris M, Leahey N, Mookerjee S, Dombovy M (1999): Epidemiology and predictors of post-concussive syndrome after minor head injury in an emergency population. Brain Inj 13:173–189.

Bigler ED (2001): Distinguished Neuropsychologist Award Lecture 1999. The lesion(s) in traumatic brain injury: Implications for clinical neuropsychology. Arch Clin Neuropsychol 16:95–131.

Bigler ED (2003): Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury. Arch Clin Neuropsychol 18:595–621; discussion 623–627.

Bohnen N, Jolles J (1992): Neurobehavioral aspects of postconcussive symptoms after mild head injury. J Nerv Ment Dis 180:683–692.

Bohnen N, Jolles J, Twijnstra A (1992a): Neuropsychological deficits in patients with persistent symptoms six months after mild head injury. Neurosurgery 30:692–696.

Bohnen N, Twijnstra A, Jolles J (1992b): Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. Acta Neurol Scand 85:116–121.

Bohnen N, Van Zutphen W, Twijnstra A, Wijnen G, Bongers J, Jolles J (1994): Late outcome of mild head injury: Results from a controlled postal survey. Brain Inj 8:701–708.

Bordini EJ, Chaknis MM, Ekman-Turner RM, Perna RB (2002): Advances and issues in the diagnostic differential of malingering versus brain injury. NeuroRehabilitation 17:93–104.

Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL (1998): The Counting Stroop: An interference task specialized for functional neuroimaging—Validation study with functional MRI. Hum Brain Mapp 6:270–282.

Calder AJ, Lawrence AD, Young AW (2001): Neuropsychology of fear and loathing. Nat Rev Neurosci 2:352–363.

Carroll LJ, Cassidy JD, Holm L, Kraus J, Coronado VG (2004): Methodological issues and research recommendations for mild traumatic brain injury: The WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med (43 Suppl):113–125.

Cassidy J, Carroll L, Peloso P, Borg J, von Holst H, Holm L, Kraus J, Coronado V (2004): Incidence, risk factors and prevention of mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. J Rehabil Med(43 Suppl):28–60.

Chen JK, Johnston KM, Frey S, Petrides M, Worsley K, Ptito A (2004): Functional abnormalities in symptomatic concussed athletes: An fMRI study. Neuroimage 22:68–82.

Christodoulou C, DeLuca J, Ricker JH, Madigan NK, Bly BM, Lange G, Kalnin AJ, Liu W-C, Steffener J, Diamond BJ, Ni AC (2001): Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. J Neurol Neurosurg Psychiatr 71:161–168.

Cicerone KD, Azulay J (2002): Diagnostic utility of attention measures in postconcussion syndrome. Clin Neuropsychol 16:280–289.

D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J (1998): Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res 7:1–13.

D'Esposito M, Postle BR, Rypma B (2000): Prefrontal cortical contributions to working memory: Evidence from event-related fMRI studies. Exp Brain Res 133:3–11.

Dikmen S, McLean A, Temkin N (1986): Neuropsychological and psychosocial consequences of minor head injury. J Neurol Neurosurg Psychiatr 49:1227–1232.

Donaldson DI, Buckner RL (2002): Effective paradigm design. In: Jezzard P, Matthews PM, Smith SM, editors. Functional MRI: An Introduction to Methods. Oxford: Oxford University Press. pp 177–195.

Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, Newell FN, Emslie H (2000): A neural basis for general intelligence. Science 289:457–460.

Egner T, Hirsch J (2005): The neural correlates and functional integration of cognitive control in a Stroop task. Neuroimage 24: 539–547.

Evans RW (1992): The postconcussion syndrome and the sequelae of mild head injury. Neurol Clin 10:815–847.

Eyler LT, Olsen RK, Jeste DV, Brown GG (2004): Abnormal brain response of chronic schizophrenia patients despite normal performance during a visual vigilance task. Psychiatry Res 130: 245–257.

Folstein MF, Folstein SE, McHugh PR (1975): ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189–198.

Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R (1996): Movement-related effects in fMRI time-series. Magn Reson Med 35:346–355.

Hofman PAM, Stapert SZ, van Kroonenburgh MJPG, Jolles J, Kruijk JD, Wilmink JT (2001): MR imaging, single-photon emission CT, and neurocognitive performance after mild traumatic brain injury. Am J Neuroradiol 22:441–449.

Ingebrigtsen T, Waterloo K, Marup-Jendsen S, Attner E, Romner B (1998): Quantification of post-concussion symptoms 3 months after minor head injury in 100 consecutive patients. J Neurol 245:609–612.

Jonides J, Schumacher EH, Smith EE, Lauber EJ, Awh E, Minoshima S, Koeppe RA (1997): Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 9:462–475.

King N (1997): Mild head injury: Neuropathology, sequelae, measurement and recovery. Br J Clin Psychol 36(Part 2):161–184.

King NS (2003): Post-concussion syndrome: Clarity amid the controversy? Br J Psychiatry 183:276–278.

King NS, Crawford S, Wenden FJ, Moss NEG, Wade DT (1995): The rivermead post concussion symptoms questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. J Neurol 242:587–592.

Kraus JF, Nourjah P (1988): The epidemiology of mild, uncomplicated brain injury. J Trauma 28:1637–1643.

Laatsch LK, Thulborn KR, Krisky CM, Shobat DM, Sweeney JA (2004): Investigating the neurobiological basis of cognitive rehabilitation therapy with fMRI. Brain Inj 18:957–974.

Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, Deluca J, Natelson BH (2005): Objective evidence of cognitive complaints in chronic fatigue syndrome: A BOLD fMRI study of verbal working memory. Neuroimage 26:513–524.

Levine B, Cabeza R, McIntosh AR, Black SE, Grady CL, stuss DT (2002): Functional reorganisation of memory after traumatic brain injury: A study with H(2)-(15)O positron emission tomography. J Neurol Neurosurg Psychiatr 73:173–181.

Lishman WA (1988): Physiogenesis and psychogenesis in the 'post-concussional syndrome'. Br J Psychiatry 153:460–469.

Manoach DS, Schlaug G, Siewert B, Darby DG, Bly BM, Benfield A, Edelman RR, Warach S (1997): Prefrontal cortex fMRI signal changes are correlated with working memory load. Neuroreport 8:545–549.

McAllister TW, Saykin AJ, Flashman LA, Sparling MB, Johnson SC, Guerin SJ, Mamourian AC, Weaver JB, Yanofsky N (1999): Brain activation during working memory 1 month after mild traumatic brain injury. A functional MRI study. Neurology 53:1300–1308.

McAllister TW, Sparling MB, Flashman LA, Guerin SJ, Mamourian AC, Saykin AJ (2001): Differential working memory load effects after mild traumatic brain injury. Neuroimage 14:1004–1012.

Newsome MR, Scheibel RS, Steinberg JL, Troyanskaya M, Sharma RG, Rauch RA, Li X, Levin HS (2007): Working memory brain activation following severe traumatic brain injury. Cortex 43:95–111.

Owen AM, McMillan KM, Laird AR, Bullmore E (2005): N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 25:46–59.

Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M (1998): Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. Proc Natl Acad Sci USA 95:7721–7726.

Qin S, Piekema C, Petersson KM, Han B, Luo J, Fernandez G (2007): Probing the transformation of discontinuous associations into episodic memory: An event-related fMRI study. Neuroimage 38:212–222.

Smith EE, Jonides J (1998): Neuroimaging analyses of human working memory. Proc Natl Acad Sci USA 95:12061–12068.

Soeda A, Nakashima T, Okumura A, Kuwata K, Shinoda J, Iwama T (2005): Cognitive impairment after traumatic brain injury: A functional magnetic resonance imaging study using the Stroop task. Neuroradiology 47:501–506.

Strangman G, O'Neil-Pirozzi TM, Burke D, Cristina D, Goldstein R, Rauch SL, Savage CR, Glenn MB (2005): Functional neuroimaging and cognitive rehabilitation for people with traumatic brain injury. Am J Phys Med Rehabil 84:62–75.

Stroop J (1935): Studies of interference in serial verbal reactions. J Exp Psychol 28:643–662.

Sweet LH, Rao SM, Primeau M, Durgerian S, Cohen RA (2006): Functional magnetic resonance imaging response to increased verbal working memory demands among patients with multiple sclerosis. Hum Brain Mapp 27:28–36.

Szymanski HV, Linn R (1992): A review of the postconcussion syndrome. Int J Psychiatry Med 22:357–375.

Tagliaferri F, Compagnone C, Korsic M, Servadei F, Kraus J (2006). A systematic review of brain injury epidemiology in Europe. Acta Neurochir (Wien) 148:255–268; discussion 268.

Wade DT, King NS, Wenden FJ, Crawford S, Caldwell FE (1998): Routine follow up after head injury: A second randomised controlled trial. J Neurol Neurosurg Psychiatr 65:177–183.

Walsh ND, Williams SC, Brammer MJ, Bullmore ET, Kim J, Suckling J, Mitterschiffthaler MT, Cleare AJ, Pich EM, Mehta MA, Fu CH (2007): A longitudinal functional magnetic resonance imaging study of verbal working memory in depression after antidepressant therapy. Biol Psychiatry 62:1236-1243.

WHO (1993): The ICD-10 classification of mental and behavioural disorders. Diagnostic criteria for research. Geneva: WHO.

Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM (2006): FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol 16:193–206.