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A longitudinal fMRI study of working memory in severe TBI patients with diffuse axonal injury

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ABSTRACT

Traumatic brain injury (TBI) patients have working memory deficits and altered patterns of brain activation during this function. The evolution of the impairment has not been examined to date. This study investigated longitudinal changes in brain activation during a working memory task. Twelve patients with severe and diffuse TBI and ten healthy matched controls were fMRI scanned twice at a 6-month interval during an *n*-back task (0-, 2- and 3-back). All the TBI patients selected presented signs of diffuse axonal injury on CT but had no evidence of focal lesions on MRI clinical examination. Significant changes in brain activation over time were observed in patients, but not in controls. During the first examination, though both groups engaged bilateral fronto-parietal regions known to be involved in working memory, activation of the right superior frontal gyrus was low in the TBI group. However, the difference between TBI and controls had decreased significantly after 6 months. A factor analysis confirmed the greater increase in activation in the right superior frontal cortex in the TBI group than in healthy controls, leading to normalization of the brain activation pattern. In conclusion, this longitudinal study provides evidence of a progressive normalization of the working memory activation pattern after diffuse axonal injury in severe TBI, coinciding with an improvement in performance on this function.

Introduction

Little is known about the neural substrates of recovery from cognitive dysfunctions acquired after brain injury. With the application of functional neuroimaging techniques, the specific changes in the brain that accompany the re-emergence of previously lost abilities can be investigated, at least at the macroscopic level. In addition, the ability to measure activity in multiple brain areas facilitates assessment of recovery in the context of brain networks (Grady and Kapur, 1999).

Changes in brain activation are interpreted as adaptive cortical reorganizations. They support the hypothesis of processes of plasticity in patients recovering from focal brain lesions caused by stroke (Weiller, 1992, 1998) or tumours (Caramia et al., 1998; Seitz et al., 1995) and in patients with diffuse tissue destruction such as multiple sclerosis (Penner et al., 2006) or traumatic brain injury (TBI) (Laatsch et al., 2004; Strangman et al., 2005).

Cortical motor reorganization, with increased utilization of ipsilateral motor pathways, has frequently been described (Roux et al., 2000; Schlosser et al., 1997; Pantano et al., 2005). In aphasic patients, some imaging studies have linked recovery to the recruitment of homologous sites in the non-dominant hemisphere (Weiller et al., 1995; Ohyama et al., 1996), while others suggest instead that improvement is achieved by the activation of residual left hemispheric language areas (Heiss et al., 1993, 1997).

Working memory deficit is a core feature of traumatic brain injury. Behavioural and functional neuroimaging studies have demonstrated poorer working memory performance (Cicerone 2002; Levin et al., 2004) together with alterations in the bilateral prefrontal and parietal activation patterns (Jonides et al., 1998; Braver et al., 1997). In patients tested one month after sustaining a mild TBI, McAllister et al. (1999, 2001) observed a significant increase in cerebral activation, though their performance was similar to that of the control group.

In a sample of moderate-to-severe TBI patients with focal and diffuse lesions, Christodoulou et al. (2001) reported that activation was more regionally dispersed and more lateralized towards the right hemisphere in the TBI group compared to controls. On the other hand,

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severe and diffuse TBI patients have previously shown a pattern of frontal hypoactivation (Sanchez-Carrion et al., 2008).

Although the improvement of cognitive functions in TBI patients has been attributed to the reorganization of cortical networks, research of brain activation changes through time is limited (Laatsch et al., 1997, 1999, 2004). Longitudinal fMRI studies can help to provide information about the cerebral mechanisms associated to cognitive recovery in TBI. An important advantage of using longitudinal within-subject designs is that within-subject comparison eliminates many of the methodological problems inherent in between-subjects designs (Hillary, 2008).

We hypothesized that the pattern of frontal hypoactivation observed in TBI patients (Sanchez-Carrion et al., 2008) could be partially reversible due to cerebral reorganization. To our knowledge, this is the first study that investigates changes over time in brain activation during a working memory task in a group of severe and diffuse TBI patients.

Methods

Twelve patients who had sustained a severe TBI were recruited from the Head Injury Unit of the Institut de Neurorehabilitació Guttmann. All TBIs were secondary to a motor vehicle accident: five subjects had been involved in a car collision, 5 in motorbike crashes and two patients had been run over. All patients had recovered from post-traumatic amnesia by the time of the fMRI and had scores of 76 or greater on the Galveston Orientation and Amnesia Test (GOAT; Levin et al., 1979). Subjects presented no aphasic, sensory or motor deficits that might interfere with the cognitive task.

To avoid focal brain injury effects on brain activation and reorganization, we have only included those subjects with diffuse damage according the clinical MRI data of the rehabilitation hospital. On MRI clinical examination, there was no evidence of focal lesion in any of the cases. A second structural MRI, axial FLAIR (TR=9000; TE=133; TI=2200) and gradient echo T2* (TR=760; TE=15; α=15) of the whole brain images, was performed in the Neuroradiological Unity of our University in order to evaluate brain damage.

All patients were involved in the neurorehabilitation program of our hospital which includes the standard treatments involving physiotherapy, occupational therapy and neuropsychological intervention. The later consisted of individualized cognitive rehabilitation sessions using both computer programs and non-computer tasks of increasing difficulty, following an individualized treatment plan which was established based on each patient's neuropsychological assessment.

To control for practice effects, a group of 10 healthy subjects was recruited from relatives or friends of the TBI group. This control group, matched for age, years of education and estimation of premorbid intellectual function, was exposed to repeated administration of an *n*-back task during fMRI acquisition with the same interval as the patients. All subjects were right-handed, Caucasian-Mediterranean and had no previous history of neurological or psychiatric diseases. Demographic and clinical characteristics for both groups are given in Table 1. In each group, one subject was a student, two had qualified jobs and the rest were non-qualified workers.

All participants gave written informed consent. This study was approved by the Ethical and Research Committee of the Institut de Neurorehabilitació Guttmann.

Neuropsychological assessment

The following protocol was used to assess working memory: 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).

Table 1
Demographic and clinical characteristics of TBI and control groups

	TBI (n=12) Mean (SD)	Control (n=10) Mean (SD)	p
Gender (m/f)	8/4	6/4	
Age	24.42 (4.78)	24.0 (4.88)	ns
Education (years)	11.58 (2.81)	11.92 (2.81)	ns
Vocabulary (WAIS)	9.92 (2.07)	10.5 (2.32)	ns
GCS	4.91 (1.58)		
PTA duration (days)	84.33 (42.3)		
Time since injury (days)	263.9 (123.2)		

Non statistical differences between both groups were found in any demographic variables. GCS: Glasgow Coma Scale. PTA: posttraumatic amnesia period.

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

All subjects from both TBI and control groups were assessed twice, with a mean interval of 6 months between tests.

fMRI working memory task

A visual *n*-back task was used to investigate working memory during fMRI acquisition. We used a block design with four cycles of alternation between three conditions (0-, 2- 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 target that had been presented two numbers previously in the sequence. During the 3-back condition the task was to decide whether the current number matched the target presented three numbers previously.

White numbers appeared on the screen for 500 ms against a black background, followed by a fixation cross for 1500 ms. 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 on a *Hewlett Packard* computer by *Presentation* software (*Neurobehavioral Systems, USA*).

Participants were instructed to press a button (*Fiber Optic Response*, *Current Designs*, *Philadelphia*) with their right thumb when the currently presented number was a target. Accuracy and reaction time were recorded.

Prior to the scan, participants rehearsed the task without the scanner to ensure they understood the task requirements.

Image acquisition

fMRI studies were performed with a 1.5-T MR unit (Signa-Lx, General Electric, Milwaukee, WI) using blood–oxygen level-dependent (BOLD) fMRI. Care was taken to minimize the effect of movement by instructing subjects to remain still and by placing foam padding around the head. The functional images were acquired using a gradient echo single-shot echoplanar imaging sequence (EPI): TR (repetition time)=2000 ms; TE (echo time)=40 ms; 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).

Analysis of behavioural measures

Participants' responses were analysed for accuracy (percentage of correct answers) and reaction time to the target stimuli, using SPSS software. Only reaction times to correct responses were included. Percentage of change between working memory measures on both assessments was calculated [((fMRI-2−fMRI-1)/fMRI-1)*100] for each group. The Mann–Whitney test was used for between-group analyses and the Wilcoxon test for within-group analyses.

fMRI data analysis

Statistical Parametric Mapping (SPM5) running in Matlab 6.5.0 was used for data analysis with the following preprocessing steps: realignment to correct subjects' motion, coregistration of the functional and structural data sets, resizing of the anatomical and functional images in the Z axis (by a factor of 1.3) to avoid the interslice gap, reorientation according to the anterior–posterior commissure line, spatial normalizing into T1 and EPI templates (for 3D and functional images, respectively), and smoothing of the data with a 10 mm Gaussian Kernel.

Statistical parametric map calculation was based on the voxel-by-voxel method, using a general linear model (Friston et al., 1995). Motion parameters used in the realignment were entered into the statistical analysis as regression parameters (Jones and Callan, 2003; Poldrack et al., 2002). Contrast images for each working memory condition (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 0.005 uncorrected and a minimum cluster extent (k) of 100 contiguous voxels.

Activation differences between healthy controls and patients (1st and 2nd scanning sessions) were analysed by full-factorial analysis using an explicit mask created in the one-sample t-test analysis of each group. For group-by-condition interactions we calculated the following contrasts: $[(2b>0b)_{TBI}>(2b>0b)_{Control}]$ and $[(3b>0b)_{TBI}>(3b>0b)_{Control}]$ and vice versa. Group comparisons between controls and TBI patients were computed for the 1st and 2nd scanning session respectively.

To assess cerebral activation changes over time, we performed the following contrasts $[(2b>0b)_{fMRI\ 1}>(2b>0b)_{fMRI\ 2}]$ and $[(3b>0b)_{fMRI\ 1}>(3b>0b)_{fMRI\ 2}]$ and vice versa, independently for healthy subjects and TBI patients. Finally, interaction between group and time was calculated by a t contrast of the positive and negative interaction effect. The probability threshold was set at 0.005 uncorrected (k>100). The anatomical location of the cerebral areas activated was presented by the MNI (Montreal Neurological Institute) and was qualitatively described following a visual inspection using the Talairach and Tournaux atlas (1988).

Voxel-based morphometry analysis

In order to determine if possible gray matter reductions could explain frontal hypoactivation we performed a voxel-based morphometry (VBM) analysis. We used SPM5 running in Matlab 7.0 (Mathworks, Natick, MA). Images were firstly segmented into grey matter (GM), white matter (WM) and cerebro-spinal fluid. Then, GM images were further normalized to a population template generated from the complete image set using DARTEL (Diffeomorphic Anatomical Registration Through Exponentiated Lie algebral) tool for SPM5 (Ashburner, 2007). We created the Jacobian scaled ("modulated") warped tissue class images to ensure that the overall amount of each tissue class was not altered by the spatial normalization procedure. Modulated GM images were then smoothed with an 8-mm full-width at half-maximum isotropic Gaussian kernel. Finally, we normalized the images to MNI space using an affine spatial normalization. The pre-processed GM images were analyzed in a full-factorial design with the group as one factor with two levels (TBI and healthy subjects) and the scanning session as the second factor with two levels (1st scanning session and 2nd scanning session).

We firstly performed a whole brain analysis with the same contrasts calculated in the fMRI analysis. Afterwards we performed a region of interest (ROI) analysis comprising those areas that showed significant differences in the same contrast of the fMRI analysis. ROIs mask were created using the MarsBaR toolbox for SPM (Brett et al., 2002) and applied into the analysis using the WFU Pickatlas SPM toolbox (Wake Forest University School of Medicine, Winston-Salem, NC) (Maldjian et al., 2003). The statistical threshold was set at $p<0.05$ FDR — corrected. Nevertheless, in order to explore weaker differences that might have been neglected because of this threshold we also set the statistical threshold at $p<0.005$ uncorrected because it is less strict and has been previously used by fMRI studies.

Results

Working memory performance

At the first assessment, TBI patients performed significantly worse in Digit backwards ($p=0.017$), Letter-Number Sequencing (LNS; $p=0.003$) and accuracy under the 2-back condition of the n-back task (percentage of correct responses; $p=0.025$). Reaction times for TBI patients were significantly longer under all three n-back conditions (0-back and 2-back, $p<0.001$; 3-back $p=0.031$). No significant differences were obtained in the number of comission errors for each condition.

At the second assessment, after 6 months, significant differences between groups were obtained only in Digit backwards ($p=0.036$) and in reaction time on the n-back task ($p<0.001$) under all three conditions. Working memory performance for TBI and control groups is shown in Table 2.

The TBI group improved on all neuropsychological measures in the follow-up. Interestingly, the LNS and the 2-back and 3-back conditions

Table 2
Working memory performance for TBI and control groups

	TBI ($n=12$)		CONTROL ($n=10$)	
	Time 1 Mean (SD)	Time 2 Mean (SD)	Time 1 Mean (SD)	Time 2 Mean (SD)
Digits forward	6.17 (1.03)	6.75 (0.97)	7.2 (1.32)	7.1 (1.37)
Digits backward	4.25 (0.97) * [a]	4.5 (1.09) * [b]	5.5 (1.08)	5.6 (0.97)
LNS	8.33 (2.5) * [a]	10 (2.05) * [c]	11.7 (2.67)	11.1 (2.18)
n-back task				
Accuracy				
0-back	98.11 (4.31)	99.3 (1.64)	99.53 (1.4)	99.58 (1.33)
2-back	77.64 (20.52) * [a]	87.5 (9.88)	94.9 (5.43)	92.92 (7.61)
3-back	62.1 (29.31)	78.11 (16.01)	78.72 (12.04)	85.42 (12.45)
Reaction time (ms)				
0-back	5460 (1186) * [a]	4835 (560) * [b,c]	3683 (392)	3744 (434)
2-back	7060 (1807) * [a]	6105 (1565) * [b,c]	4159 (699)	3973 (699)
3-back	7067 (2245) * [a]	5978 (1452) * [b,c]	4866 (1065)	3783 (537) * [d]
Commission errors				
0-back	0.36 (0.67)	0.42 (0.67)	0.67 (0.87)	0.5 (0.7)
2-back	4.09 (3.94)	4.58 (4.54)	3.56 (2.51)	3.2 (1.75)
3-back	4.18 (6.77)	4.17 (11.02)	3.56 (2.51)	2.0 (2.2)

LNS: Letter-Number Sequencing (WAIS-III). *n*-back performance assess by accuracy (% correct responses), median reaction time (in milliseconds) and commission errors. *N*-back performance at time 1 was only available for 11 TBI and 9 controls.
*Significant differences: [a] Time 1: TBI vs. controls; [b] Time 2: TBI vs. controls; [c] TBI: time 1 vs. time 2; [d] Controls: time 1 vs. time 2.

showed increases of above 20% (LNS 29%, 2-back 23.45% and 3-back 71.87%). Although only LNS was statistically significant ($p=0.025$), 3-back presented a trend towards significance ($p=0.075$). Reaction time of patients decreased in all *n*-back conditions (0-back, $p=0.05$; 2-back, $p=0.031$; 3-back, $p=0.041$). In the control group, the only significant difference was found in the reaction time for 3-back, in which speed was reduced by around 20% ($p=0.009$).

Neuroimaging results

Structural MRI results

Structural MRI analyses showed lesions in the cortico-subcortical junction in all patients. These lesions were located in fronto-parietal regions in ten patients, with additional temporal lesions in three of them. One patient presented lesions in fronto-temporal regions and another in the temporal cortico-subcortical junction. Additional lesions were detected in eight patients in the corpus callosum, eight in the basal ganglia and in six patients in the brain stem. According to Adams' classification (Adams et al., 1989), diffuse axonal injury grade 1 was detected in two patients, grade 2 was identified in four cases, and the most severe grade 3 was observed in six patients.

fMRI results during working memory tasks

For each group, significant activations in bilateral fronto-parietal regions were observed when comparing the two working memory conditions with the control condition (2-back>0-back; 3-back>0-back) (Fig. 1).

In Table 3, we can see the contrasts that showed significant differences. During the first scan, in the 2-back and 3-back conditions, healthy controls showed greater activation in the right superior frontal gyrus (BA 10) compared to TBI patients. In the 2-back condition, controls again showed a greater activation than patients in the left frontal gyrus (BA 10). TBI patients did not present a greater activation in any region compared to controls. In the second fMRI study no significant differences between groups were found in any working memory condition.

The paired *t*-test for the TBI group showed significantly increased activation in the second fMRI compared to the first one in the left middle frontal gyrus (BA 10) for the 2-back condition. For the 3-back condition, we found two significant clusters that showed increased activation; the left inferior frontal gyrus (BA 46 and 47) and the right middle frontal gyrus (BA 9). In the inverse contrast (fMRI-1>fMRI-2) no changes were observed. In controls, no changes in the patterns of cortical activations between the first and second scans were found.

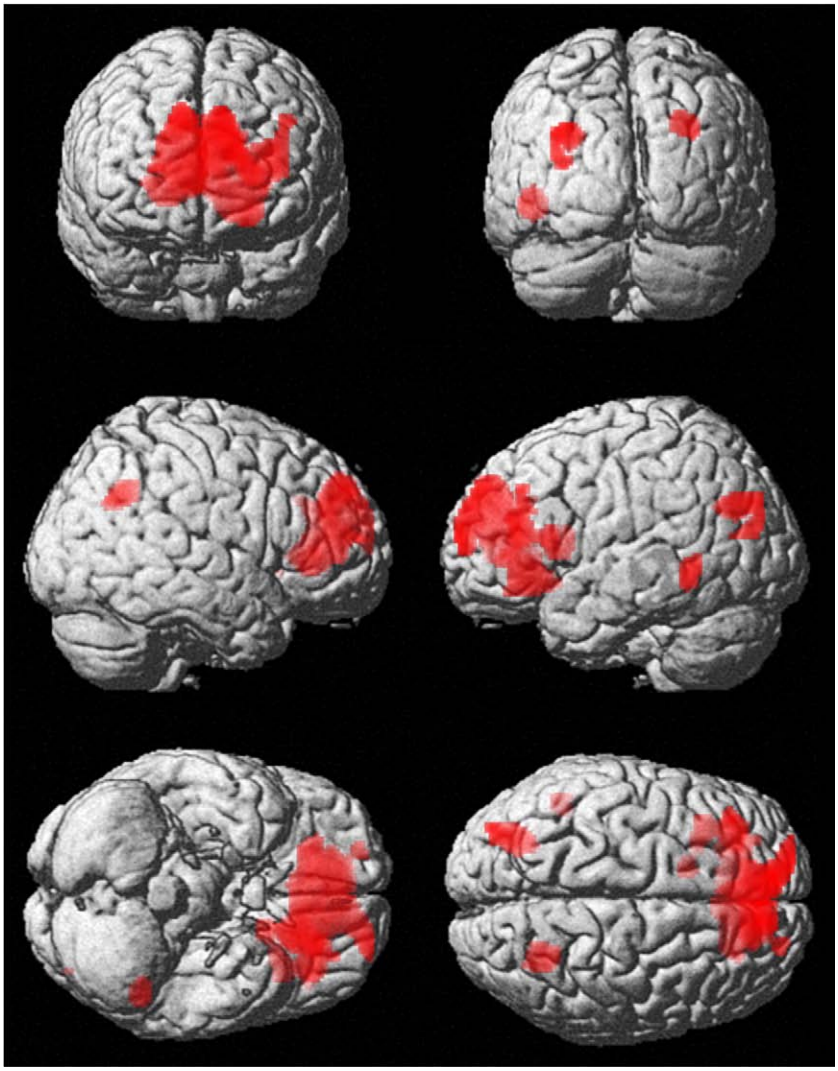

Fig. 1. Increased activation observed after 6-month evolution in TBI patients during the 3-back condition. The most striking changes were seen in the bilateral prefrontal cortex, with left hemisphere predominance. The second region that showed statistical significant changes was the biparietal posterior region. Both regions are involved in working memory processes. Statistical Parametric Maps with left as left.

Table 3
Significant results of fMRI analyses

Region	BA	K	*p*-cluster	*t*	*z*	Coordinates			*p*-voxel
						x	*y*	*z*	
fMRI-1: TBI<C (2-back)									
Right middle and superior frontal gyrus	10	4525	0.001	4.98	4.37	36	46	24	0.000
				4.57	4.08	6	62	−4	0.000
Left superior frontal gyrus	10			4.36	3.92	−22	56	−2	0.000
fMRI-1: TBI<C (3-back)									
Right middle and superior frontal gyrus	10, 9	2771	0.003	4.60	4.09	32	48	22	0.000
				4.54	4.06	6	62	−2	0.000
				4.23	3.83	40	44	30	0.000
TBI: fMRI-1<fMRI-2 (2-back)									
Middle and superior frontal gyrus	10	4013	0.001	3.82	3.50	−14	14	18	0.000
				3.79	3.48	−34	36	22	0.000
				3.55	3.29	−16	58	18	0.001
TBI: fMRI-1<fMRI-2 (3-back)									
Left inferior frontal gyrus	46,47	4734	0.000	3.72	4.43	−34	34	18	0.000
				3.68	3.39	−18	30	−4	0.000
Right middle frontal gyrus	9			3.64	3.36	10	50	38	0.000
INTERACTION TBI<C×fMRI-1>fMRI-2 (3-back)									
Right superior frontal gyrus	9, 8	1617	0.030	3.77	3.46	22	52	36	0.000
				3.54	3.28	12	48	40	0.001
				3.48	3.23	10	42	52	0.001

Coordinates refers to Montreal Neurological Institute. Results thresholded at $p<0.005$ uncorrected at voxel-level and $p<0.05$ corrected at cluster-level; BA=Brodmann areas; *k*=cluster size; fMRI-1=first scanning session; fMRI-2=second scanning session; TBI=traumatic brain injury group; C=control group.

Factor analyses (group×time) were performed to study the differential effect of time between both groups. We observed a greater activation increase in fMRI-2 for the TBI group than in controls in the right superior frontal gyrus (BA 9 and 8) for the 3-back>0-back comparison (Fig. 2). No significant group×time interactions were found in 2-back>0-back contrast.

VBM results

In order to exclude the possible effect of volumetric changes in the frontal lobes on brain activation, we performed a voxel-based morphometry (VBM) analysis. Results on grey matter volume did not show any significant difference between TBI patients and healthy control subjects, neither in the first nor in the second assessment at $p<0.05$ FDR-corrected. Comparison of grey matter volume between the first and second MRI data of the patients (paired *t*-test) did not show significant differences at $p<0.05$ FDR-corrected. The ROI analysis did not reveal significant differences in any contrast. Using a statistical threshold of $p<0.05$ corrected, we only observed significant results at voxel level.

Discussion

We observed significant changes in brain activation over time in patients with severe and diffuse traumatic brain injury (TBI). The hypofrontality observed in the TBI group compared to controls during the first scan had diminished significantly after 6 months. In contrast, no significant longitudinal changes were observed in the control group over the same interval. To our knowledge, this study is the first to obtain significant longitudinal changes in TBI patients controlling for fMRI practice effects.

TBI patients showed a clear cognitive improvement during the six months of evolution, presenting increased accuracy and faster reaction times. Moreover, whereas no changes were observed in memory span and simple vigilance task (digit forward and 0-back accuracy), the percentage of change observed in working memory suggests a selective improvement of this function. TBI patients' performance on 3-back condition improved by over 70% in the second assessment compared with the first one. Although this change was only a trend, the TBI group improved sufficiently to reach normal performance (that is, >75% accuracy). This improved performance was expected because spontaneous recovery is usually observed after TBI (Himanen et al., 2006).

Unexpectedly, improvement was also observed in healthy subjects who exhibited shorter response latencies (if only significant on the 3-back condition) whereas accuracy scores were high and stable over time. This may be because the subjects were familiar with the fMRI environment and the *n*-back paradigm and were therefore able to respond faster on the most complex task (Cardebat et al., 2003). This result is interesting because it indicates that the 3-back condition has a practice effect, which should be taken into account in longitudinal studies that do not include control groups for the second evaluation.

The general pattern of activation observed in both groups has been previously described during the *n*-back task in healthy subjects (i.e. bilateral fronto-parietal activation) (Owen et al., 2005; Cabeza and Nyberg, 2000; Braver et al., 1997). Regarding the results obtained at the first evaluation, both groups activated the fronto-parietal network, but TBI patients showed less activation in the right superior prefrontal cortex than controls. This significant hypoactivation is in accordance with previous results (Sanchez-Carrion et al., 2008; Chen et al., 2003; Chen et al., 2007; Laatsch et al., 1997). Newsome et al. (2007b) observed decreased activation in frontal structures for TBI patients under the 1-back condition, and Ricker et al. (2001) reported decreased rCBF in the frontal lobe during verbal recall.

Other authors have reported patterns of increased activation (Newsome et al., 2007a; Christodoulou et al., 2001; Levine et al., 2002; Fontaine et al., 1999). Reasons for this discrepancy might be related with the fact that those studies included TBI patients with focal lesions. The cerebral reorganization in focal and diffuse brain damages could be different. Loss of gray matter in focal regions may involve an increased role of another unimpaired region forming part of the same cognitive network. Furthermore, our sample is not directly comparable to other TBI studies which included mild TBI (McAllister et al., 1999; Perlstein et al., 2004; Chen et al., 2004). The occasional mismatches in the sign of the alteration (decrease or increase) may be related to the task or to performance among groups (Strangman et al., 2005). Whilst some authors (McAllister et al., 1999, 2001) interpreted increased right prefrontal activation as a compensatory mechanism to facilitate task performance, others (Christodoulou et al., 2001; Perlstein et al., 2004) considered that this increased activation was unlikely to be indicative of neural mechanisms, as it was associated with poorer performance.

There are few fMRI studies of recovery after TBI. In general MRI group studies of severe TBI patients are difficult to perform because these subjects tend to present both focal and diffuse brain lesions (Junqué, 1999; Bigler, 2001; Levin, 2003; Levine et al., 2006). We selected a sample of patients who had no focal brain lesions but presented diffuse white matter lesions. Several studies of brain recovery have been performed in patients suffering from multiple sclerosis, a brain pathology that mainly involves the white matter. Although multiple sclerosis is considered a degenerative illness in the initial stages, there is a clear brain reorganization after the CNS insults. Functional reorganization has been suggested in multiple sclerosis because most patients show good recovery from the symptomatic expression of new lesions (relapses) in the earlier stages of the illness, despite evidence of axonal injury with each attack (Audoin et al., 2003; Cader et al., 2006; Hillary et al., 2003; Mainero et al., 2004; Wishart et al., 2004). Abnormal patterns of brain activation may represent adaptive cortical reorganization as a compensatory mechanism that contributes to normal performance (Mainero et al., 2006; Penner et al., 2006) and consequently limits the impact of disease-

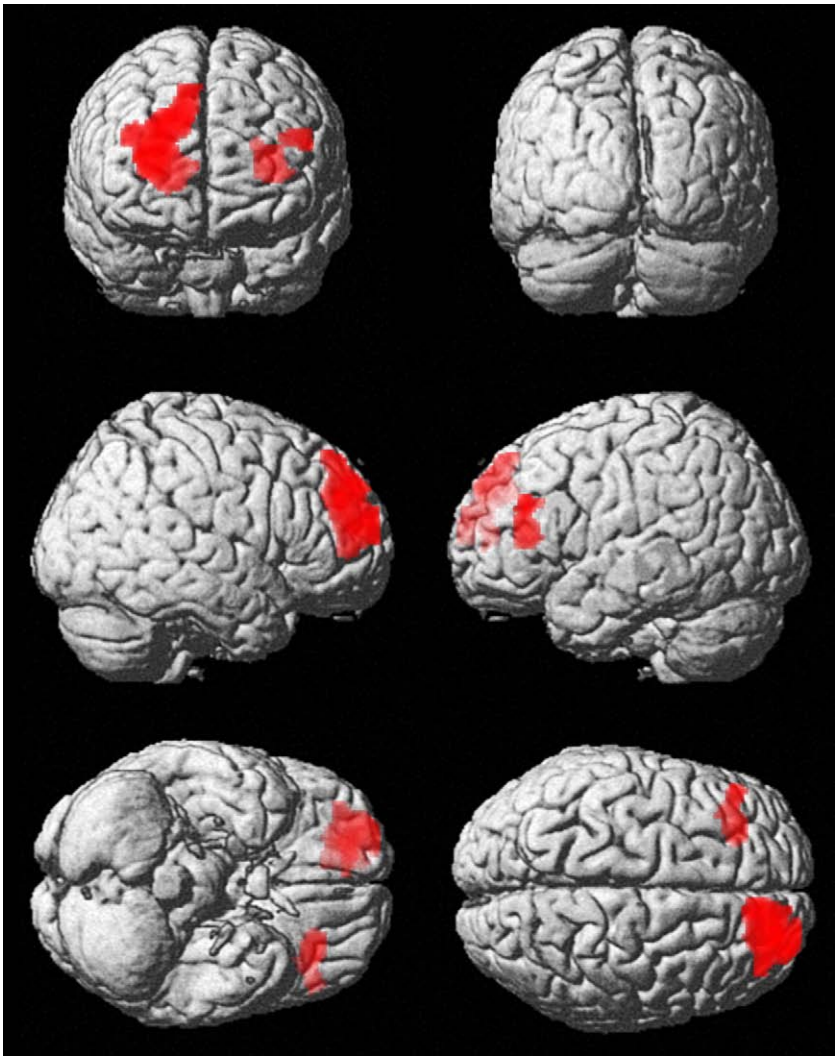

Fig. 2. Interaction group×time shows greater increases in activation in the TBI subjects than in controls (fMRI-2>fMRI-1), in the right superior frontal gyrus and left middle frontal gyrus for the 3-back>0-back comparison. Statistical Parametric Maps with left as left.

related structural damage on clinical progression and disability (Mezzapesa et al., 2007). Interestingly, these brain functional changes have been shown to be dynamic over time, not only after an acute relapse, but also in clinically stable multiple sclerosis patients (Rocca and Filippi, 2007; Reddy et al., 2000). This supports the hypothesis of spontaneous plasticity processes even in a disease characterized by multifocal lesions of cerebral white matter (Forn et al., 2006; Buckle, 2005); in this case, the results would be comparable to those found in diffuse TBI, which may produce disproportionate white matter loss (Bigler, 2001). It is well known that the fibre integrity of the white matter is essential for cognitive functioning (Penner et al., 2007) and that some consequences of axonal injury may be partially reversible and contribute to clinical recovery. Although irreversible axonal injury is substantial (Evangelou et al., 2000), other factors such as adaptive functional reorganization may also operate in the disease (Matthews et al., 2004; Cifelli and Matthews, 2002).

Spontaneous and induced functional brain reorganization reflected by changes in the intensity and regional extent of activation has also been demonstrated in studies of the motor and visual systems in stroke patients (Chollet et al., 1991; Johansen-Berg et al., 2002; Rausch et al., 2000; Weiller et al., 1992; Weiller et al., 1995). Additional recruitment of regions ipsilateral and contralateral to the lesion side after recovery was associated with cortical plasticity (Mountz, 2007). Recovery of language function may be possible by reorganization within the language network, rather than by the recruitment of new areas, in patients recovering from aphasia (Rijntjes and Weiller, 2002).

In our follow-up fMRI study, brain activation during an *n*-back task did not differ in TBI patients and healthy controls. The results for the cognitive assessment of working memory also improved. The regions that achieved statistically significant increases in activation over time in patients were the left middle and superior frontal cortex. In the 2-back condition, TBI patients showed significantly increased activation in the left middle and superior frontal cortex. In the high working memory load (3-back condition), significant enhancement of TBI patients' activation was found in the right middle frontal gyrus. These regions are core modules of the working memory circuitry (D'Esposito et al., 2000). Furthermore, the factor analysis (group×time) confirmed a greater increase in activation in the TBI group than in controls in the right superior frontal region. These changes in brain activation, which coincide with an improvement in working memory performance, may represent a brain reorganization supporting the recovery of normal performance. As expected, no significant changes were observed in the control group, suggesting that the extent and location of the activation pattern in the working memory fMRI task are stable (Laatsch and Krisky, 2006). Our results agree with the Hillary (2008) hypothesis on brain reorganization, which claims that if the recruitment of prefrontal

cortex resources represents brain organization, then recruitment of neural resources should be initiated at the outset of recovery and should increase over the course of recovery as task performance improves.

Closed head injury is often accompanied by frontal and temporal lobe lesions due to acceleration and deaceleration mechanisms (Levin et al., 1987; Bigler, 1996, 2001; Pierallini et al., 2000; Gennarelli et al., 1998). Frontal lobe changes in brain activation may be due to frontal brain damage or regional atrophy. However, in our sample we did not include any subject with focal lesions on clinical MRI. Moreover to assess whether atrophic changes in patients with TBI might account for differences in activation patterns when compared to controls, this study analyzed the integrity of the grey matter underlying the areas of activation and also in the whole brain. We did not find any significant cluster of gray matter reduction. Thus, our results agree with those reported by Prigatano et al. (2004) in the sense that differences on brain activation are not a direct consequence of gray matter focal atrophy.

Additionally, longitudinal changes in brain activation may be influenced by the reduction of anxiety or habituation to the scanner environment or task, or even by repeat administration of the same task (Laatsch et al., 2004). However, this was not the case in our study; changes in brain activation pattern were observed only in the TBI group, whereas healthy controls remained stable across both assessments.

At present it is not completely understood which neuronal mechanisms underlie functional restitution after brain damage. Recovery from brain injury is believed to be dependent on mechanisms of plasticity. Sprouting, unmasking and development of extrasynaptic receptors have been proposed as mechanisms responsible for recovery after brain injury (Bach-y-Rita, 1981). The development of functional neuroimaging research may allow identification of specific areas of the brain that have experienced changes in activation patterns. This information may greatly increase our knowledge of the gross mechanisms of brain plasticity during recovery from brain injury (Pantano et al., 1992; Laatsch et al., 1997).

Recovery of function after brain damage may take several forms (Sohlberg and Mateer, 2001). One is the reorganization or reweighting of functional interaction within an existing network of brain regions (Matthews et al., 2004). A second possibility is the recruitment of new areas inside the network or the implementation of an alternative network not normally used for task performance. This type of alteration in brain function would imply that the task is performed in a different way to prior to the injury, perhaps through the use of new strategies (Strangman et al., 2005). A third potential mechanism of functional recovery is plasticity in the region of the cortex surrounding the damaged area (Grady and Kapur, 1999). In our study, changes in brain activation coincided with working memory improvement, supporting the hypothesis of compensation.

Research suggests that when recovery of brain function is facilitated by rehabilitation techniques, it may be accompanied by neuroplastic change (Laatsch et al., 1999). In the context of motor recovery, clinical recovery after intensive rehabilitation post injury correlates with increased contralateral and decreased ipsilateral sensoriomotor activation during hand movement (Jang et al., 2003; Johansen-Berg et al., 2002). In cognition, increased activation within the language network together with improved language performance has been described in longitudinal studies on aphasic subjects after stroke (Cardebat et al., 2003; de Boissezon et al., 2005). The remission of neglect depends on the functional metabolic recovery of the intact areas of the right hemisphere and the left parietal lobe (Pantano et al., 1992; Perani et al., 1993) or on enhancement of bilateral frontal and parietal activation (Thimm et al., 2006).

Cognitive rehabilitation assists recovery from cognitive deficits after brain injury (Cicerone et al., 2000; Gianutsos, 1991; Sohlberg and Mateer, 2001), and changes after rehabilitation have been evidenced in related cerebral blood flow in PET (Laatsch et al., 1997, 1999) and in the pattern of activation using fMRI (Laatsch et al., 2004). In a case by case analysis of 5 patients by Laatsch et al. (1999), mild to moderate TBI patients presented improvement in neuropsychological abilities and changes in relative brain blood flow distribution on resting SPECT. These results suggest that, even 2 years post-injury, relative increases in rCBF may be related to improvements on neuropsychological tests. Most of the significant increases in rCBF were seen during the treatment period, though increases were also observed after a period without treatment. Laatsch et al. (2004) were the first to use fMRI to characterize activation patterns longitudinally in response to cognitive rehabilitation in subjects with neuropsychological impairment following mild TBI. Nonetheless, those authors consider that is not possible to determine whether such changes are associated with spontaneous recovery or reorganization due to cognitive rehabilitation. Further investigations should focus on longitudinal brain activation changes after therapeutic interventions, either cognitive rehabilitation or pharmacological therapy, in larger samples of TBI patients, and compare the results with those obtained in healthy subjects.

Longitudinal studies like ours allow the investigation of the pattern of neural response over time and may provide insight into the mechanisms underlying recovery after brain injury (Strangman et al., 2005). In addition, an important question in functional imaging is whether the reorganization found is also responsible for patients' functional improvement. Neuropsychological and brain changes after cognitive rehabilitation have been reported in TBI (Laatsch et al., 1997, 2004), stroke (Johansen-Berg et al., 2002) and in schizophrenic patients (Wykes et al., 2002; Wexler et al., 2000; Penadés et al., 2000, 2002). The effects of medication can be observed in improved brain activation patterns, especially in frontal activity, and in the tendency towards improvement in working memory performance. These effects have been described in schizophrenia with antipsychotic medication (Honey et al., 1999; Meisenzahl et al., 2006) and in depression following antidepressant medication (Walsh et al., 2007). Imaging techniques are likely to have a significant impact on neurorehabilitation treatment. They provide an opportunity to record the brain's reorganization and to monitor the effectiveness of rehabilitation procedures both during and on completion of training (Grady and Kapur, 1999; Matthews et al., 2004; Strangman et al., 2005). They also identify the patients most likely to benefit from rehabilitation (Mountz, 2007), detect different variables related to rehabilitation outcome, and can effectively guide the selection of different rehabilitation approaches (Ríos-Lago et al., 2004).

In conclusion, severe diffuse TBI patients with working memory impairment showed decreased activation in the right superior frontal cortex. Nevertheless, the activation of the frontal cortex increased over time. The differences between patients and controls in both working memory and brain activation disappeared in the follow-up study. Factor analysis confirmed that the TBI group showed a greater increase in activation in the right superior and left middle prefrontal cortex than healthy controls, leading to normalization of their cerebral pattern. In spite of suggestions that mechanisms of plasticity are more likely to compensate for the effect of focal lesions than for the possibly long-lasting, widespread process of diffuse axonal injury (Gale et al., 1995; Azouvi, 2000), our results provide evidence of a progressive normalization of working memory activation pattern after diffuse axonal injury.

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