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# Functional abnormalities in symptomatic concussed athletes: an fMRI study

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**Our aim was to quantify with functional magnetic resonance imaging (fMRI) changes in brain activity in concussed athletes and compare the results with those of normal control subjects. Regional brain activations associated with a working memory task were obtained from a group of concussed athletes (15 symptomatic, 1 asymptomatic) and eight matched control subjects, using blood oxygen level dependent (BOLD) fMRI. The average percent signal change from baseline to working memory condition in each region of interest was computed. Symptomatic concussed athletes demonstrated task-related activations in some but not all the regions of interest, even when they performed as well as the control subjects. Furthermore, several concussed athletes had additional increases in activity outside the regions of interest, not seen in the control group. Quantitative analysis of BOLD signals within regions of interest revealed that, in general, concussed athletes had different BOLD responses compared to the control subjects. The task-related activation pattern of the one symptom-free athlete was comparable to that of the control group. We also repeated the study in one athlete whose symptoms had resolved. On the first study, when he was still symptomatic, less task-related activations were observed. On follow-up, once his symptoms had disappeared, the task-related activations became comparable to those of the control group. These results demonstrate the potential of fMRI, in conjunction with the working memory task, to identify an underlying pathology in symptomatic concussed individuals with normal structural imaging results.**

*Keywords:* Athlete; Concussion; fMRI

## Introduction

Most studies agree that, of all cases of head trauma, approximately 80% to 90% fall within the category of mild head injury (MHI) or concussion (Kraus and Nourjah, 1988; Nell and Brown, 1991; Vazquez-Barquero et al., 1992). Concussion used to be considered as a temporary fluctuation in consciousness without enduring effects on cognition. As such, no long-term sequelae were believed to ensue. Recent cases of athletes and individuals with persistent cognitive deficits following concussion (the post-concussion syndrome) suggest that this is not always the case. Despite being considered as ‘mildly’ injured, individuals who sustain a concussion often exhibit diverse symptomatology and abnormal neuropsychological profiles, such as deficits in working memory, attention, information processing speed, and more generally, in executive function, known to be linked to the frontal lobe (Bohnen et al., 1992; Collins et al., 1999; Hinton-Bayre et al., 1997; Leininger et al., 1990; Matser et al., 1999; Newcombe and Briggs, 1994).

Although the exact pathophysiological changes after concussion are not known, there is now increased acceptance of the idea that concussion results mainly in functional disturbance rather than structural damage. This view is reflected in a more comprehensive definition of concussion that was recently proposed by the Concussion in Sport Group (Aubry et al., 2002). According to this updated definition, concussion may be caused either by a direct blow to the head or elsewhere on the body with an ‘impulsive’ force transmitted to the head. Such injury typically results in the rapid onset of short-lived impairment of neurological function that usually resolves spontaneously. Importantly, although concussion may result in neuropathological changes, it is typically associated with grossly normal structural neuroimaging examinations and the acute clinical symptoms largely reflect a functional deficit rather than a structural injury. Thus, functional neuroimaging techniques that examine the metabolic/physiological state of the brain may have great potential for demonstrating brain abnormalities that may be undetectable by morphological imaging methods.

Existing functional imaging studies of individuals with head trauma are mainly based on resting metabolic measurements using positron emission tomography (PET) and single-photon emission computerized tomography (SPECT). Data acquired from these studies have shown perfusion deficits that extend beyond any structural damage shown by CT or MRI (Abdel-Dayem et al., 1987; Alavi et al., 1987; Jansen et al., 1996; Langfitt et al., 1986; Newton et al., 1992). The most commonly reported finding is frontal hypometabolism or a decrease in frontal cerebral blood flow. One major disadvantage of these imaging techniques, however, is the requirement of a radioactive tracer, which greatly

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limits their clinical application. This limitation can be overcome by the relatively new method of functional magnetic resonance imaging (fMRI) which holds great potential for widespread research and clinical use because it does not require exposure to any radioactive substance, has temporal resolution limited only by brain hemodynamics, and spatial resolution comparable to that of conventional MRI. Thus, fMRI can be used both in within and across subjects designs. In a recent fMRI prospective study that used an auditory *n*-back working memory task with a varying degree of processing load (McAllister et al., 1999, 2001), individuals with mild traumatic brain injury showed a disproportionate increase in activation in right frontal and parietal cortex in response to a moderate working memory demand, but relatively few increases in activation when the working memory load was high.

In the present study, we have used fMRI and a verbal and visual working memory task to test concussed athletes with persisting post concussive symptoms. Our goal was to explore the feasibility of employing functional MRI as a potential diagnostic tool in detecting the effects of concussion and to provide a way to quantify concussive injury. Thus, unlike other functional imaging studies on mild head injury, in which only group comparisons were made, we have examined and quantified the effect of concussion on brain activation patterns at the individual level.

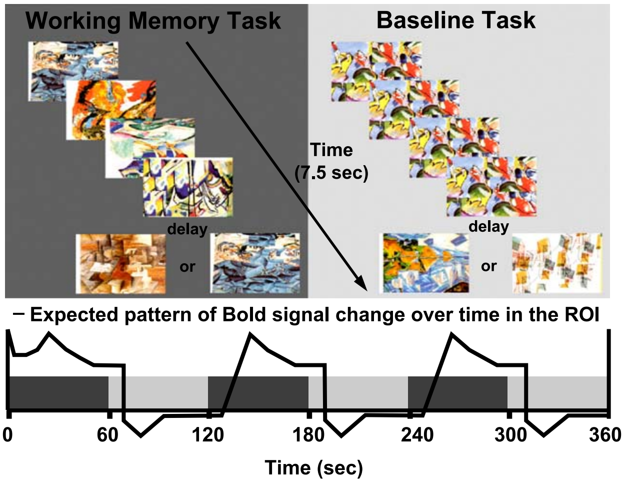

Fig. 1. Schematic representation of the experimental design and the expected pattern of BOLD signal change across time.

## Methods

### *Subjects*

Sixteen male athletes (mean age 26.9, SD = 7.2) who had sustained a concussion, ranging from 1 to 14 months before the study (mean = 4.7), and eight normal male control subjects matched in age (mean age 27.6, SD = 5.2) participated in the study. The concussed subjects were elite athletes referred to one of the co-authors (Johnston) at the McGill University Health Center. Data regarding the number of past concussions, the presence/absence of loss of consciousness (LOC) during the last concussion, the presence/absence of post-concussive symptoms (PCS) at the time of study, as well as the outcome of standard anatomic neuroimaging (T1, T2, and Flair MRI) are summarized in Table 1. Except for athlete 16, all had post-concussive symptoms at the time of the study. The control subjects were university students recruited from McGill University. None had a history of head

Table 1
Information on athletes

| | Sport | No. of concussions | Time since last injury (months) | Standard MRI (T1, T2, FLAIR) | LOC | PCS at time of study | Estimated severity of PCS* |
|---|---|---|---|---|---|---|---|
| Athlete 1 | Wrestling | >5 | 8 | Normal | No | Yes: headache, visual disturbances, neurocognitive complaints | 2 |
| Athlete 2 | Hockey | >5 | 6 | Normal | No | Yes: headache, neurocognitive complaints, dizzy | 2 |
| Athlete 3 | Snowboarding | 3 | 1 | Normal | No | Yes: headache, fatigue, insomnia | 2 |
| Athlete 4 | Wrestling | >5 | 6 | Normal | No | Yes: headache, neurocognitive complaints, balance | 1 |
| Athlete 5 | Hockey | >5 | 14 | Normal | No | Yes: fatigue, insomnia, irritability | 1 |
| Athlete 6 | Hockey | >5 | 10 | Normal | Yes | Yes: headache, neurocognitive complaints | 1 |
| Athlete 7 | Hockey | 5 | 12 | Normal | No | Yes: headache | 2 |
| Athlete 8 | Hockey | 3 | 3 | Normal | No | Yes: headache, dizzy | 1 |
| Athlete 9 | Hockey | 3 | 3 | Normal | No | Yes: headache, neurocognitive complaints, photophobia, fatigue | 2 |
| Athlete 10 | Hockey | 5 | 2 | Normal | No | Yes: headache | 2 |
| Athlete 11 | Hockey | 1 | 2 | Normal | No | Yes: head “pressure”, fatigue | 2 |
| Athlete 12 | Hockey | >5 | 1 | Normal | No | Yes: headache, neurocognitive complaints, insomnia | 2 |
| Athlete 13 | Hockey | >5 | 1 | Normal | No | Yes: headache, neurocognitive complaints | 2 |
| Athlete 14 | Hockey | 2 | 1 | Normal | No | Yes: headache, balance, dizzy | 2 |
| Athlete 15 | Hockey | 3 | 2 | Normal | No | Yes: fatigue, head “pressure”, insomnia | 2 |
| Athlete 16 | Hockey | 2 | 3 | Abnormal | Yes | No | 0 |

* Based on clinical judgment by the neurosurgeon at the time of study (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe).

trauma or other neurological and/or psychiatric disorders. All participants gave informed, written consent for their participation in the study which was approved by the Ethics Committee of the Montreal Neurological Institute.

### Task description

We used the externally ordered task, one of the working memory tasks devised by Petrides and validated in neuropsychological studies of patients with lateral frontal lesions (Petrides, 2000a), monkeys with lesions restricted to the mid-dorsolateral prefrontal cortex (Petrides, 1991, 1995, 2000b), and functional neuroimaging work with PET (Petrides et al., 1993) and fMRI (Stern et al., 2000). There were two versions of the task: one uses verbal stimuli and the other visual abstract designs as material. In each version, subjects were familiarized with a set of five items that were going to be used throughout the test (five abstract drawings or five abstract words for the visual and verbal versions, respectively). During each trial, four out of these five items were presented successively in random order at the center of a computer screen and the subject had to monitor their occurrence so as to identify the one item from the set that would not be presented (Fig. 1). The four items presented were randomly selected from the five items. After the presentation of the fourth item, a delay of 1 s was introduced. Immediately after this delay, a test item was presented and the subject had to indicate whether this test item was one of the four items presented before the delay or whether it was the item from the set of five that had not been presented. The subjects indicated their response by pressing a mouse button (yes = right button, no = left button). The subject had 1.5 s to respond after which a new trial began. In the baseline control condition, the format and type of stimulus presentation, mode of response (pressing a left or a right mouse button), and the timing of events were identical to those of the experimental working memory conditions. The stimuli used in this baseline condition were unrelated to those used in the verbal and visual design working memory conditions. The control condition was introduced to obtain baseline activation to “subtract out” any activation related to the motor and perceptual components of the working memory task. During stimulus presentation in each trial, a single item (visual abstract design or verbal for the visual and verbal conditions, respectively) was presented four times in succession at the center of the screen, followed by a delay of 1 s. After the delay, one of two items associated with either a left or a right mouse button press was presented at the center of the screen and the subject had 1.5 s to respond. The subjects had learned before scanning which one of these two items (two abstract designs or two abstract words for the visual and verbal versions of the task, respectively) was associated with a left mouse button press and which one with a right button press. Thus, in the baseline control condition, the subject was making identical responses (i.e., press left or right) as in the working memory experimental conditions, but these motor responses were based on particular conditional associations learned before scanning rather than on a decision based on the monitoring of information in working memory (i.e., whether a particular item from the expected set of five had or had not been presented during the trial). The subjects practiced the working memory task extensively before the beginning of the fMRI session so that the sets of target items (the five designs and the five words in the visual and verbal versions, respectively) were very familiar. Similarly, in the control task, the conditional associations between the designs and the words indicating right or left pressing responses were very well learned before scanning.

### Functional imaging procedure

The fMRI scanning was carried out using a 1.5 Tesla Siemens Magneton Vision scanner. Each scanning session started with the acquisition of high-resolution T1-weighted 3D anatomical images (voxel size 1 mm$^3$) for anatomical localization of the functional data, followed by acquisitions of T2* weighted gradient echo (GE) echo-planar images (EPI) with BOLD contrast (TR: 3000 ms, TE: 51 ms, FA: 90). Six functional scans (three for the verbal working memory condition and its control and three for the visual design working memory condition and its control) were acquired in a single session. Each functional scan lasted 6 min, with working memory and baseline conditions alternating every eight trials (60 s). Fig. 1 provides a schematic representation of the experimental paradigm and the expected pattern of signal change in the regions of interest (ROI). A total volume of 120 acquisitions was obtained during each functional scan, with 12 T2*-weighted, 7-mm-thick contiguous oblique slices taken during each acquisition. This covered all of the brain, except for the topmost part of the parietal region and the most rostral part of the ventral temporal lobe. Before entering the scanner, all participants were introduced to the tasks and were trained extensively until they reached their performance plateau. This was defined as a change in behavioral score (in percentage correct) of less than 5% in two consecutive runs (48 trials). All the stimuli were presented via a projector to a screen placed at the back of the scanner, then to the subject with a mirror mounted on the head coil.

### Functional MRI data processing and analysis

The images were analyzed using an in-house package (available at http://www.bic.mni.mcgill.ca/users/keith/). The anatomical

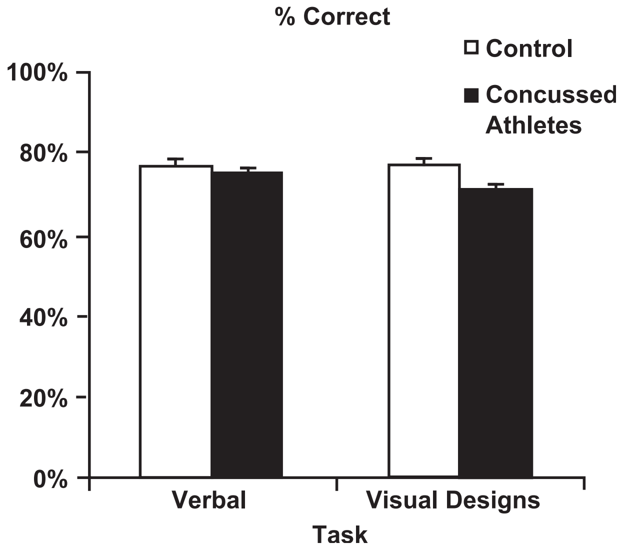

Fig. 2. Performance on the working memory task for the control group ($N$ = 8) and the concussed athlete group ($N$ = 16). There was no significant difference in performance between these two groups. The mean percent correct and the SE are shown.

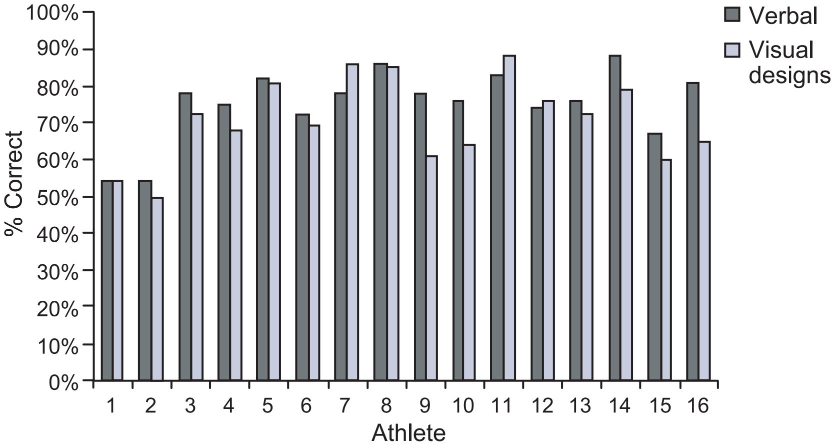

Fig. 3. Individual performance of the athletes on the working memory task.

MRI scans were corrected for intensity non-uniformity and mapped into the common standard proportional space of Talairach and Tournoux (1988). The functional data were first corrected for motion by registering all image frames in each dynamic file to the fourth frame in that run and smoothed with a 6-mm full-width at half-maximum Gaussian filter to increase the signal-to-noise ratio of the data, the tolerance of the subsequent analysis steps to residual motion in the scans, and to minimize resampling artifacts. The motion corrected data were then analyzed statistically at each voxel, based on a linear model with correlated errors. The fMRI time series data from the verbal and visual tasks were analyzed separately. For both tasks, a working memory minus baseline control task subtraction was performed and the mean parametric t-maps were constructed for each individual by averaging functional data across scans using linear regression analyses (Worsley et al., 2002). To obtain the average group t-maps, all individual data were first transformed into the common standard space of Talairach and Tournoux as described by Evans et al. (1992) then combined using a mixed effects linear model. The resulting T statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory (Worsley et al., 1996) to correct for multiple comparisons. A directed search method was employed to calculate the threshold for significance within the lateral prefrontal cortex, using an estimated gray matter volume of 64000 mm$^3$ of the dorsal prefrontal area. This yielded a threshold for significance within the lateral prefrontal cortex, value of $t = 4.2$, $P < 0.05$. Each set of fMRI data was then co-registered to the corresponding anatomical MRI.

To quantify the level of activation, regions of interest were identified based on the location of the activation peaks and their surrounding voxels that reached the significance threshold ($t = 4.2$) based on the control group average t-map in Talairach space. Once identified, these regions were labeled using an in-house software tool that allows simultaneous viewing of MRI volumes in coronal, sagittal, and horizontal orientations. A mask of the labeled regions of interest was then created and the BOLD signal intensity within

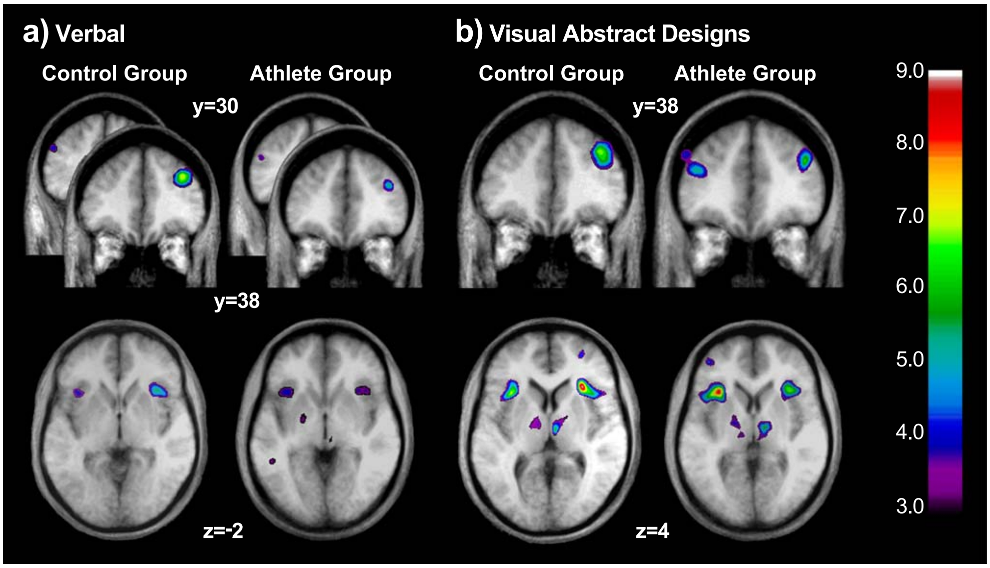

Fig. 4. (a) fMRI activation pattern for the verbal condition and (b) for the visual abstract designs condition of working memory task.

these defined regions was extracted using another in-house program. Finally, the average percent signal change from baseline to working memory condition in each of the regions of interest was computed.

## Results

### *Behavioral results*

Fig. 2 compares the performance of the control and concussed athlete groups on the working memory task. Mixed design ANOVA revealed that the mean performance of the concussed athletes did not differ significantly from that of the control group ($F_{(1,22)} = 1.12$, $P > 0.05$). The same analysis indicated that the performance of the two groups was not significantly different on the verbal and visual design versions of the task ($F_{(1,22)} = 3.02$, $P > 0.05$), although the concussed athletes seemed to have more difficulty with the visual design version of the task. Planned comparisons that compared the tasks for each group revealed that while the control subjects did not differ in their performance on the two versions of the task, the athletes had a significantly better performance on the verbal than the visual design version of the task ($F_{(1,22)} = 7.33$, $P < 0.01$). The individual scores for the athlete group are also shown in Fig. 3. There was great variability in performance across athletes, ranging from chance to performance as good as that of the control group. There were only three athletes (athletes 1, 2, and 15) who showed below normal performance for both versions of the task. Athletes 9, 10, and 16 had below normal performance only on the visual version of the task.

### *fMRI results*

#### *Group Analysis*

Analysis of the fMRI data from the control group revealed various task-related activation foci. The anatomical location of the activation peaks was identified by superimposing activation maps onto the high-resolution anatomical MRI. Table 2 summarizes the location of the activation peaks, expressed in standardized stereotaxic coordinates of Talairach and Tournoux, their *t* values, as well as their anatomical loci. Almost identical prefrontal activation patterns were found for both versions of the task. In both tasks, clusters of activations were observed in the mid-dorsolateral prefrontal cortex and in the anterior insula, bilaterally. Regions of interest were defined using the clusters of activation, which consisted of the maximum peaks summarized in Table 2, combined with the surrounding voxels that reached the threshold value ($t$ threshold = 4.2).

As a group, the concussed athletes also showed frontal activation peaks within the regions of interest. Figs. 4a and 4b compare the activation patterns of the control and the athlete groups during the verbal and visual tasks, respectively. Despite the overall similarity in the topographical activation patterns of these two groups, visual inspection of the peaks suggested that the concussed athletes had less task-related activation in the mid-dorsolateral prefrontal cortex, an area that plays a key role in the monitoring of information in working memory. Fig. 5 compares the time course of the BOLD signal and the mean percentage signal change in the right dorsolateral prefrontal cortex (DLPC) for both the control and the concussed athlete groups. For the control group, the BOLD signal across time in the right mid-dorsolateral prefrontal cortex (peak coordinates: verbal version, $x = 36$, $y = 38$, $z = 30$; visual design version, $x = 36$, $y = 38$, $z = 32$) compared favorably to our predictions

Table 2
Significant task-related activation peaks of the control group ($P < 0.01$)

| Stereotaxic coordinate | | | | Brain region |
|---|---|---|---|---|
| *x* | *y* | *z* | *t* | |
| *Verbal working memory* | | | | |
| Left hemisphere | | | | |
| −48 | 30 | 30 | 3.9[a] | middle frontal gyrus (area 9/46) |
| −56 | 20 | 30 | 4.9 | middle frontal gyrus |
| −56 | 6 | 4 | 3.9[a] | precentral gyrus (area 6—premotor cortex) |
| −50 | 0 | 32 | 6.0 | precentral gyrus (area 6—premotor cortex) |
| −52 | −36 | 2 | 3.9[a] | middle temporal gyrus (area 21) |
| −36 | 16 | 0 | 4.9 | rostral insula |
| −20 | −12 | 10 | 4.6 | thalamus |
| −2 | −54 | −18 | 5.5 | cerebellum |
| −36 | −60 | −22 | 5.6 | cerebellum |
| Right hemisphere | | | | |
| 36 | 38 | 30 | 5.7 | middle frontal gyrus (area 9/46) |
| 4 | 22 | 36 | 5.7 | cingulate gyrus (area 32) |
| 32 | 20 | 0 | 6.2 | rostral insula |
| 18 | −12 | 10 | 3.9[a] | thalamus |
| 8 | −44 | −22 | 4.3 | cerebellum |
| 24 | −58 | −22 | 5.1 | cerebellum |
| 2 | −68 | −24 | 5.7 | cerebellum |
| 10 | −70 | −18 | 5.2 | cerebellum |
| *Visual abstract design working memory* | | | | |
| Left hemisphere | | | | |
| −46 | 46 | 14 | 4.0[a] | middle frontal gyrus (area 46) |
| −52 | 18 | 28 | 6.4 | middle frontal gyrus |
| −42 | 56 | 12 | 4.6 | middle frontal gyrus (area 10) |
| −50 | 0 | 32 | 6.5 | precentral gyrus (area 6—premotor cortex) |
| −6 | 24 | 38 | 6.0 | cingulate gyrus (area 32) |
| −42 | −74 | −8 | 6.6 | inferior occipital gyrus (area 18) |
| −38 | −74 | −24 | 5.0 | fusiform gyrus (area 19) |
| −34 | −90 | −6 | 4.2 | fusiform gyrus (area 19) |
| −34 | 16 | 4 | 7.0 | rostral insula |
| −18 | 0 | 22 | 5.7 | caudate nucleus |
| −20 | −16 | 22 | 5.3 | caudate nucleus |
| −10 | −12 | 4 | 4.6 | thalamus |
| −40 | −64 | −24 | 7.6 | cerebellum |
| Right hemisphere | | | | |
| 36 | 38 | 32 | 5.6 | middle frontal gyrus (area 9/46) |
| 50 | 20 | 40 | 5.2 | middle frontal gyrus |
| 28 | 50 | 4 | 5.1 | middle frontal gyrus (area 10) |
| 42 | 10 | 28 | 6.2 | inferior frontal gyrus (area 44/8) |
| 4 | 22 | 36 | 8.1 | cingulate gyrus (area 32) |
| 38 | −2 | 32 | 4.1[a] | precentral gyrus (area 6/4) |
| 40 | −70 | −4 | 4.6 | fusiform gyrus (area 19) |
| 26 | −84 | −8 | 5.7 | fusiform gyrus (area 18) |
| 30 | 22 | 4 | 8.6 | rostral insula |
| 16 | −6 | 24 | 6.1 | caudate nucleus |
| 6 | −16 | 4 | 6.3 | thalamus |
| 8 | −44 | −22 | 5.1 | cerebellum |
| 0 | −56 | 20 | 7.1 | cerebellum |
| 6 | −70 | −18 | 5.8 | cerebellum |

[a] Significant using cluster analysis.

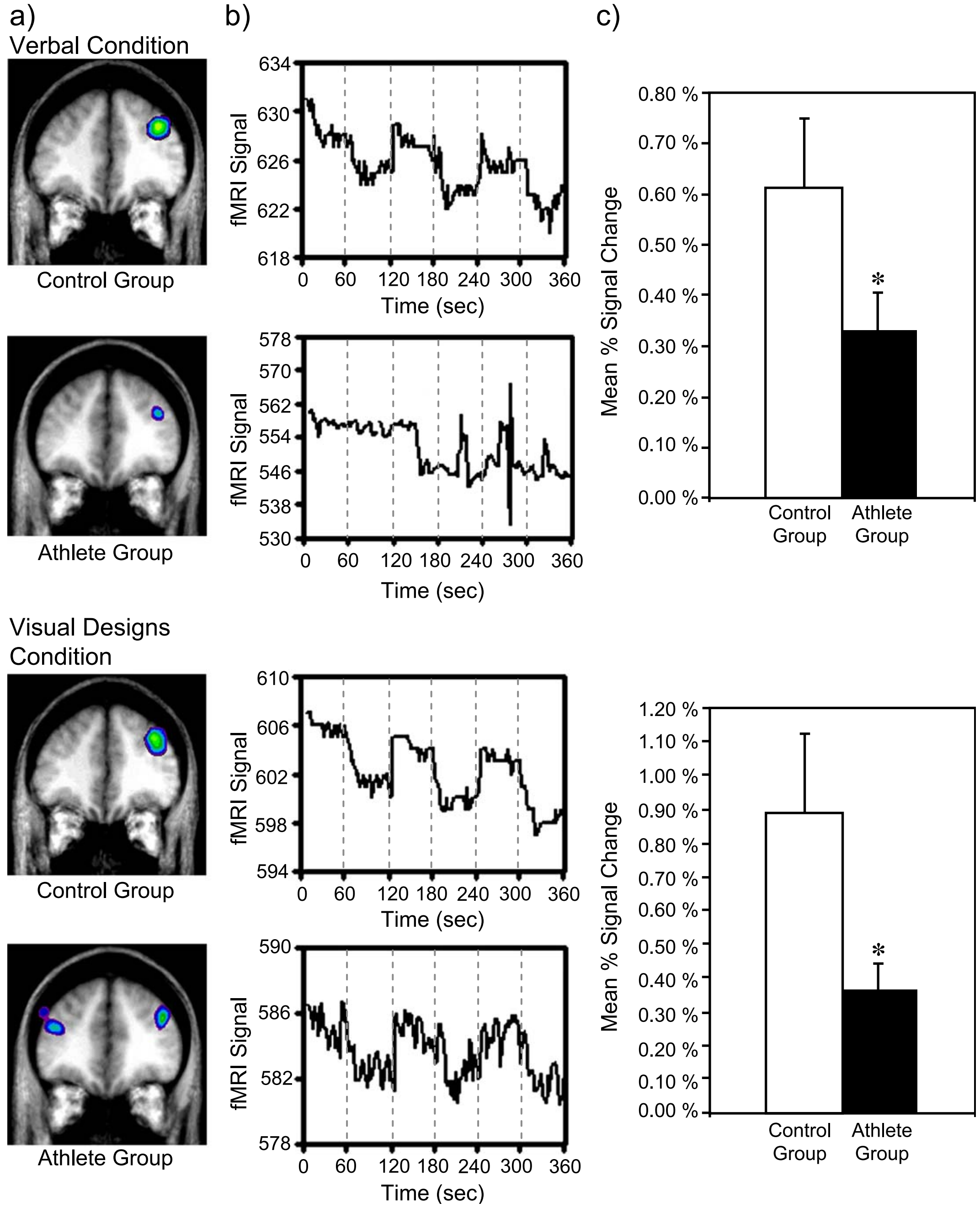

Fig. 5. (a) Average $t$ statistic maps ($y = 38$) comparing control and concussed athlete groups for both verbal and visual abstract designs conditions of the task. (b) BOLD signal across time in the right DLPC. (c) Signal change from baseline to working memory condition in right DLPC. The mean signal change and SE are shown. *, significant difference.

from the experimental design following the expected pattern of signal change illustrated in Fig. 1. For the concussed athletes, the verbal condition did not yield the expected pattern of activation, while the visual condition showed a less well-defined tendency toward the expected pattern. Independent sample $t$ tests comparing the mean percentage signal change from the baseline to the working memory conditions showed that the concussed group had significantly less signal increase compared with the control group (verbal: $t = 2.70$, $P < 0.05$; visual: $t = 2.63$, $P < 0.05$).

*Individual analysis*

Statistical t-maps ($y = 20$ and $y = 38$) for individual athletes are presented in Figs. 6 and 7 for the verbal and the visual versions of the task, respectively. As indicated by Figs. 6 and 7, great variability in the performances as well as in the activation patterns existed across the concussed athletes. While some performed poorly and did not show any task-related activation in the prefrontal regions of interest, others obtained high behavioral scores and demonstrated statistically significant activation peaks within those regions. Nevertheless, it should be noted that none of the athletes,

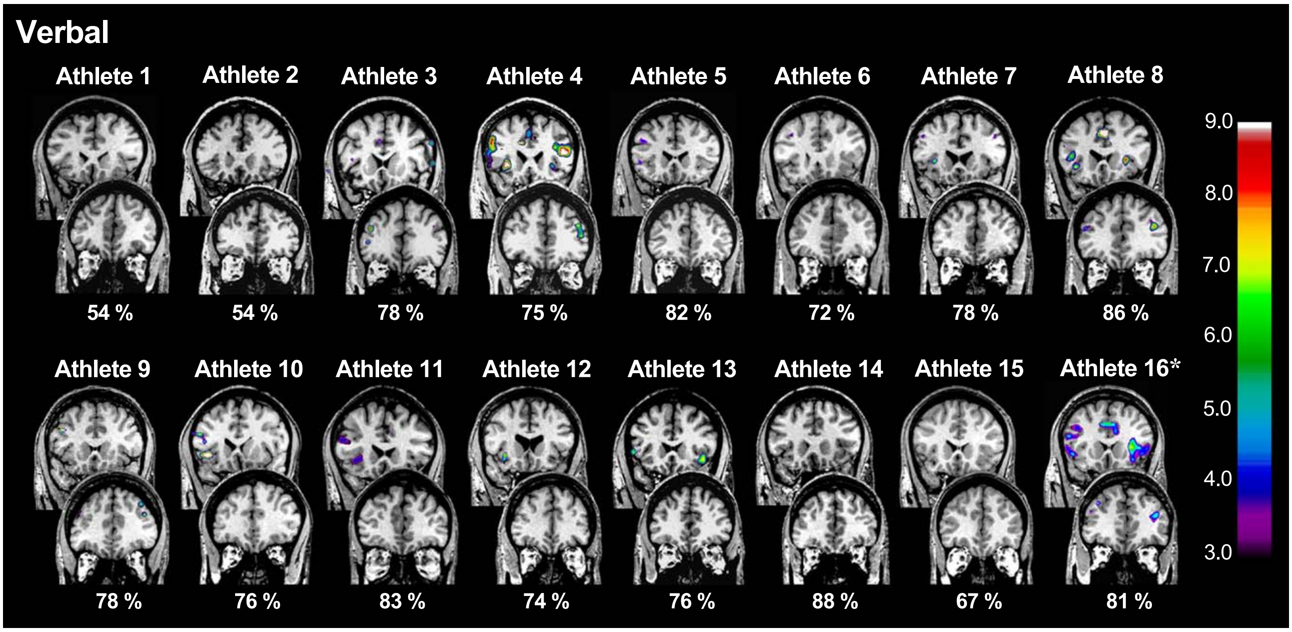

Fig. 6. Summary of each athlete's activation in the regions of interest while performing the verbal version of the working memory task. The number in percentage represents the behavioral performance on the task.*Athlete 16 was the only asymptomatic subject at the time of the study.

whether they performed well or not, showed, as did the control group, areas of activation in all the regions of interest.

To clarify further the results obtained with the athletes, two additional types of analysis were performed for each: one intended to examine the topographical pattern of the activation (i.e., the location of the peaks), and the other to examine the strength of the BOLD response against that of the control subjects. For the activation pattern analysis, the activation map of each athlete was contrasted with the mean activation map of the control group. This was accomplished by using the same in-house software to construct the t-maps. In this way, we could carry out a direct, objective comparison of the activation patterns of each concussed athlete with that of the control subjects. This was especially useful because it enabled us to identify for each athlete the presence of activation clusters outside the prefrontal regions of interest. The results of the analysis are presented in Tables 3a–d. Tables 3a and

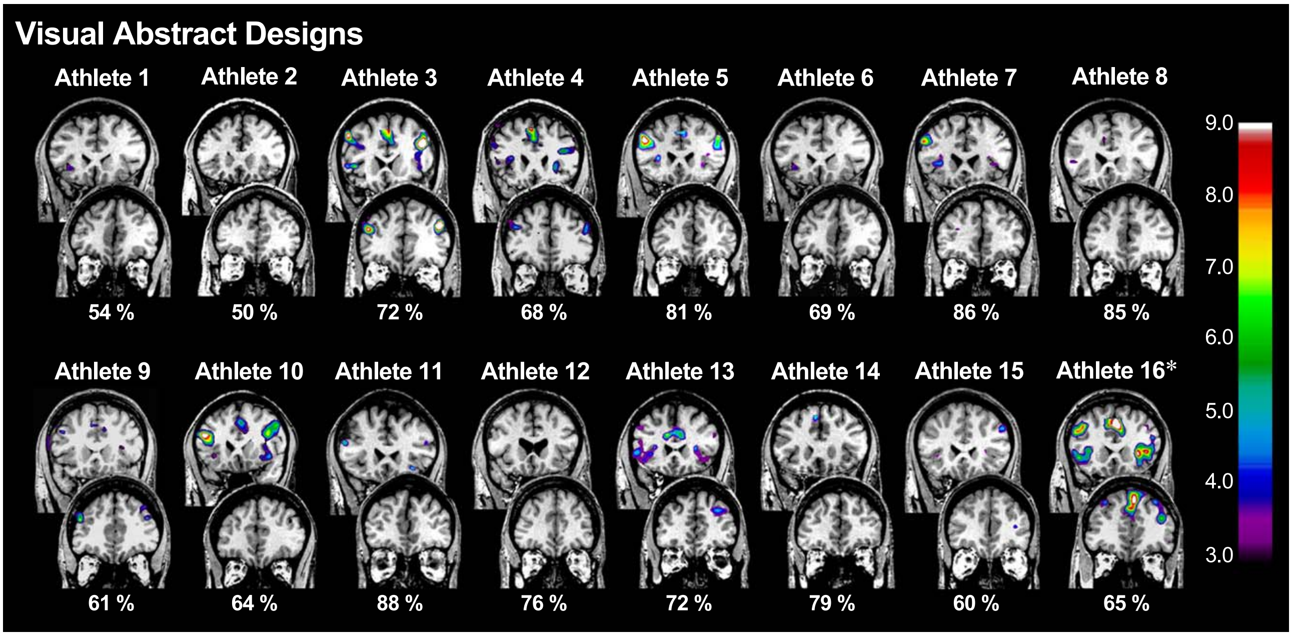

Fig. 7. Summary of each athlete's activation in the regions of interest while performing the visual abstract designs version of the working memory task. The number in percentage represents the behavioral performance on the task. *Athlete 16 was the only asymptomatic subject at the time of the study.

Table 3
For each athlete, the activation resulting from the comparison of each working memory task minus its control task was compared to that of the control group ($n = 8$)

| Subject | | DLPC | | Other Frontal | | Temporal | | Parietal | | Occipital | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *(a) Verbal (Athlete > Control)* | | | | | | | | | | | |
| Athlete 1 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 2 | Left | | | area 32 | 4.4 | | | | | | |
| | Right | | | area 10 | 4.6 | area 22 | 6.2 | area 40 | 4.6 | | |
| Athlete 3 | Left | | | area 4 | 11.0 | area 22 | 6.7 | area 7 | 7.3 | area 37 | 5.8 |
| | | | | area 6 | 8.6 | | | | | | |
| | Right | | | area 6 | 8.6 | area 22 | 8.4 | area 7/40 | 8.0 | | |
| Athlete 4 | Left | | | area 6 | 8.6 | area 22 | 6.1 | area 7/40 | 5.5 | | |
| | | | | R. Ins. | 6.2 | | | | | | |
| | Right | area 46 | 5.8 | R. Ins. | 7.1 | | | area 40 | 6.4 | | |
| Athlete 5 | Left | | | | | area 22 | 6.2 | | | area 18 | 5.6 |
| | | | | | | area 21 | 5.9 | | | | |
| | Right | | | | | area 37 | 5.1 | | | area 19 | 4.9 |
| | | | | | | area 22 | 4.6 | | | | |
| | | | | | | area 21 | 4.4 | | | | |
| Athlete 6 | Left | | | | | area 22 | 6.7 | area 40 | 5.7 | | |
| | Right | | | | | | | | | | |
| Athlete 7 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 8 | Left | | | area 6/4 | 5.3 | | | | | | |
| | Right | | | area 10 | 4.8 | | | | | | |
| Athlete 9 | Left | | | area 4 | 5.8 | area 22 | 6.0 | | | area 18 | 7.6 |
| | | | | | | area 21 | 5.4 | | | | |
| | Right | | | | | | | | | | |
| Athlete 10 | Left | | | area 4 | 6.9 | area 22 | 6.1 | area 40 | 7.5 | | |
| | Right | | | area 4 | 7.3 | area 22 | 8.5 | | | | |
| | | | | area 6 | 6.3 | | | | | | |
| Athlete 11 | Left | | | area 4 | 7.6 | area 21 | 7.4 | | | area 18 | 8.1 |
| | | | | | | area 37 | 6.2 | | | | |
| | Right | | | | | area 21 | 7.6 | | | area 18 | 7.0 |
| Athlete 12 | Left | | | | | area 21 | 4.7 | | | area 19 | 5.3 |
| | Right | | | | | area 22 | 4.5 | area 7 | 5.9 | | |
| Athlete 13 | Left | | | | | | | | | | |
| | Right | | | | | area 22 | 4.9 | | | | |
| Athlete 14 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 15 | Left | | | | | | | | | area 17 | 6.2 |
| | | | | | | | | | | area 18 | 5.5 |
| | Right | | | | | | | | | | |
| Athlete 16 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| *(b) Verbal (Athlete < Control)* | | | | | | | | | | | |
| Athlete 1 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 2 | Left | area 9/46 | −4.4 | R. Ins. | −4.4 | | | | | | |
| | Right | area 9/46 | −4.5 | area 6 | −4.0 | | | | | | |
| Athlete 3 | Left | area 9 | −6.0 | | | area 21 | −5.7 | | | | |
| | Right | | | R. Ins. | −4.8 | area 21 | −5.7 | | | | |
| Athlete 4 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 5 | Left | | | | | | | | | | |
| | Right | area 9/46 | −4.9 | R. Ins. | −4.0 | | | | | | |
| Athlete 6 | Left | | | area 8 | −4.1 | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 7 | Left | area 46 | −5.9 | | | | | | | | |
| | Right | | | R. Ins. | −4.4 | | | | | | |
| Athlete 8 | Left | area 9 | −6.3 | R. Ins. | −6.0 | area 21 | −5.9 | | | | |
| | | area 46 | −4.8 | | | | | | | | |
| | Right | | | | | | | | | | |

*(continued on next page)*

Table 3 (*continued*)

| Subject | | DLPC | | Other Frontal | | Temporal | | Parietal | | Occipital | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *(b) Verbal (Athlete < Control)* | | | | | | | | | | | |
| Athlete 9 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 10 | Left | | | | | | | area 39 | −6.5 | area 19 | −5.6 |
| | Right | | | | | | | area 39 | −7.6 | | |
| Athlete 11 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 12 | Left | area 9/46 | −5.1 | area 4/6 | −4.2 | | | area 40 | −5.1 | | |
| | Right | area 9/46 | −4.0 | | | | | area 40 | −4.6 | | |
| Athlete 13 | Left | area 9 | −4.7 | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 14 | Left | | | area 10 | −4.1 | | | | | | |
| | Right | | | R. Ins. | −4.5 | | | | | | |
| Athlete 15 | Left | | | area 6 | −4.0 | | | | | | |
| | Right | | | | | | | | | area 17 | −5.5 |
| | | | | | | | | | | area 18 | −4.6 |
| | | | | | | | | | | area 19 | −4.9 |
| Athlete 16 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| *(c) Visual abstract design (Athlete > Control)* | | | | | | | | | | | |
| Athlete 1 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 2 | Left | | | area 10 | 5.2 | area 20 | 4.3 | | | | |
| | Right | | | | | | | | | | |
| Athlete 3 | Left | area 46 | 8.0 | | | area 37 | 6.8 | | | area 18 | 8.4 |
| | | | | | | area 22 | 5.6 | | | | |
| | | | | | | area 21 | 5.4 | | | | |
| | Right | area 9/46 | 6.9 | | | | | area 40 | 5.9 | area 19 | 5.1 |
| Athlete 4 | Left | | | area 4 | 7.3 | area 37 | 7.7 | area 7/40 | 7.9 | | |
| | | | | area 6 | 6.9 | area 22 | 6.2 | | | | |
| | Right | | | | | | | area 7/40 | 6.7 | | |
| Athlete 5 | Left | area 9 | 7.1 | area 6 | 8.3 | area 22 | 4.6 | | | area 19 | 4.8 |
| | Right | | | | | area 37 | 4.6 | | | area 18 | 6.0 |
| | | | | | | | | | | area 17 | 5.7 |
| Athlete 6 | Left | | | area 4 | 5.0 | area 38 | 5.1 | | | area 18 | 6.9 |
| | Right | | | | | area 39 | 5.3 | | | | |
| Athlete 7 | Left | | | | | area 22 | 6.3 | | | | |
| | Right | | | | | | | | | | |
| Athlete 8 | Left | | | area 10 | 4.9 | | | | | | |
| | Right | | | area 10 | 5.4 | | | | | | |
| Athlete 9 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 10 | Left | area 46 | 6.6 | | | area 37 | 11.0 | area 40 | 7.1 | BA 19 | 8.2 |
| | | | | | | area 22 | 9.0 | | | | |
| | Right | | | | | area 37 | 7.9 | | | | |
| Athlete 11 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 12 | Left | | | | | | | area 40 | 8.0 | area 19 | 6.6 |
| | | | | | | | | | | area 18 | 6.5 |
| | Right | | | | | | | area 7/40 | 5.0 | area 18 | 6.6 |
| Athlete 13 | Left | | | R. Ins. | 7.4 | | | | | | |
| | | | | area 32 | 8.6 | | | | | | |
| | | | | area 4 | 7.0 | | | | | | |
| | Right | | | area 32 | 7.9 | area 21 | 5.5 | | | | |
| Athlete 14 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 15 | Left | | | | | | | | | | |
| | Right | | | | | | | | | area 18 | 8.4 |
| Athlete 16 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |

Table 3 (*continued*)

| Subject | | DLPC | | Other Frontal | | Temporal | | Parietal | | Occipital | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *(d) Visual abstract design (Athlete < Control)* | | | | | | | | | | | |
| Athlete 1 | Left | area 9 | −4.0 | | | | | | | | |
| | Right | area 9/46 | −4.0 | | | area 21 | −4.4 | area 40 | −5.8 | | |
| Athlete 2 | Left | | | | | | | | | | |
| | Right | | | R. Ins. | −5.6 | | | | | | |
| Athlete 3 | Left | | | | | | | area 40 | −4.9 | | |
| | Right | | | | | | | | | | |
| Athlete 4 | Left | | | | | | | | | | |
| | Right | | | R. Ins. | −5.1 | | | | | | |
| Athlete 5 | Left | | | | | | | | | | |
| | Right | area 9/46 | −5.1 | | | | | | | | |
| Athlete 6 | Left | area 9/46 | −4.8 | | | | | | | area 19 | −4.5 |
| | Right | | | area 6 | −5.1 | | | area 40 | −4.6 | | |
| | | | | area 10 | −4.5 | | | | | | |
| Athlete 7 | Left | | | | | | | | | area 18 | −6.6 |
| | Right | | | | | | | | | area 18 | −5.9 |
| Athlete 8 | Left | BA 9 | −5.6 | R. Ins. | −5.2 | | | | | | |
| | Right | | | | | | | | | | |
| Athlete 9 | Left | | | | | | | | | | |
| | Right | | | area 10 | −4.2 | | | | | | |
| Athlete 10 | Left | | | R. Ins. | −7.1 | | | | | | |
| | Right | area 9 | −5.4 | | | | | | | | |
| Athlete 11 | Left | | | | | | | | | | |
| | Right | area 9/46 | −4.2 | R. Ins. | −6.0 | | | | | | |
| Athlete 12 | Left | | | | | area 22 | −4.7 | | | | |
| | Right | | | | | | | | | | |
| Athlete 13 | Left | area 9 | −4.3 | | | | | | | area 18 | −5.7 |
| | Right | | | | | | | | | | |
| Athlete 14 | Left | | | R. Ins. | −4.3 | | | | | | |
| | Right | area 46 | −4.9 | R. Ins. | −5.6 | | | | | | |
| Athlete 15 | Left | area 9 | −5.4 | | | | | | | | |
| | Right | area 9/46 | −4.2 | area 10 | −5.6 | | | | | | |
| Athlete 16 | Left | | | | | | | | | | |
| | Right | | | | | | | | | | |

DLPC, dorsolateral prefrontal cortex; R. Ins., rostral insula.

Note that the numbers are the *t* value of the peak (*t* threshold 4.0). Positive *t* value indicates significantly more activation in the athlete vs. the control group, while negative *t* value indicates that the athlete has less activation than the control in that area.

3c show the brain regions where each athlete had significantly more activation than the control group for the verbal and visual working memory tasks, respectively. Note that the concussed athletes had, in general, more activation peaks outside the regions of interest, in both temporal and parietal lobes, than the control subjects. Specifically, except for three athletes, one of them asymptomatic, all had additional activations outside the regions of interest, including more posterior areas of the frontal lobe, such as the premotor (area 6) and motor (area 4) cortical regions. Significantly more activation peaks were also found in posterior cerebral regions, including parietal association cortex (areas 7 and 40), visual and auditory temporal cortex (areas 20, 21, and 22), posterior temporal association cortex (area 37), and visual cortex (areas 17, 18, and 19). Tables 3b and 3d show the areas where each athlete had significantly less activation compared with the control group for the verbal and visual design task, respectively. The results indicate that the athletes tend to have significantly less activation in the DLPC and other frontal regions compared with the control group.

We computed, for the control group, the mean percent signal change from baseline to working memory condition in each of the regions of interest. A 95% confidence interval of the percent signal change was then calculated to establish a range of ‘normal’ task-related signal variation. This range was used to determine whether the BOLD response of an individual athlete was within the range of the control group. The results are summarized in Figs. 8a and 8b for the verbal and visual design versions of the task, respectively. As indicated in the figures, except for athletes 4, 6, and 7, all had at least one ROI that had a BOLD response outside the 95% confidence range of the control group.

The above analyses demonstrated that the performance of the concussed athletes on the working memory task did not correlate well with brain activity in the regions of interest. This can be illustrated by the results obtained by athletes 9, 10, and 16, who performed well only on the verbal version of the task. Despite good performances, the corresponding activation patterns for athletes 9 and 10 were still atypical, showing additional activation peaks in the posterior cerebral regions while there was a lack of activation in at least one of the regions of interest. In contrast, athlete 16 had very similar task-related activations for both versions of the task, although he obtained a lower score on the visual design task.

### *Correlation analysis*

Two correlation analyses were carried out on the concussed athletes’ data. First, the relationship between the severity of the post-concussive symptoms and the degree of BOLD changes in the

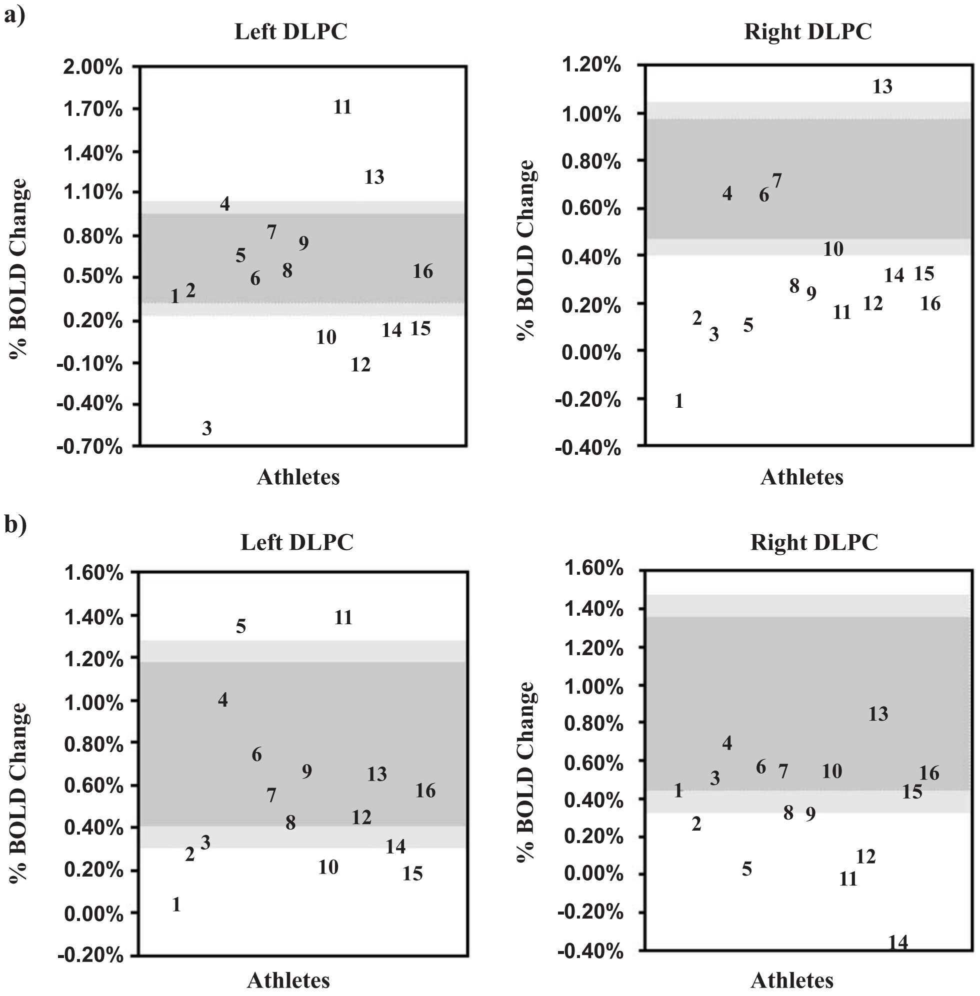

Fig. 8. Summary of the % signal change in the dorsalateral prefrontal cortex (DPLC) for each athlete while performing (a) verbal and (b) visual abstract design version of the working memory task. The dark and light shade areas represent 90% and 95% quantiles of the control group, respectively. The numbers in the four panels identify the athletes.

ROIs for each version of the task was computed using Spearman's rank correlation test. A significant negative correlation was found only for the BOLD changes in the right mid-dorsolateral prefrontal cortex for the visual design version of the task (peak coordinate: $x = 36$, $y = 38$, $z = 32$) ($p_{(16)} = -0.461$, $P < 0.05$), indicating that there was less BOLD change in the region as PCS severity increased. The relationship between the duration of PCS and BOLD signal change was also assessed. Pearson correlation tests performed on these data indicated that there was no significant correlation between the duration of PCS and the percent BOLD change in each ROI.

### *Follow up study*

We also repeated the functional imaging study in several athletes, after the resolution of their post-concussive symptoms. An example, for athlete 4, is presented in Fig. 9, which compares the performance and the fMRI results obtained 6 months following the last concussion with the result of the follow up study 3 months later. When first evaluated, the performance of this athlete on the verbal working memory task and his corresponding fMRI results were comparable to those of the control subjects. For the visual design version of the task, however, his score was in the borderline range and the fMRI results showed a weak atypical activation pattern. Consistent with an improvement in his subjective complaints and dissipation of post-concussive symptoms when he was retested 3 months later, his performance on both versions of the task improved and was within the normal range. Furthermore, an augmentation of the prefrontal activations associated with the visual design task was observed, as indicated by the subtraction analysis.

## Discussion

This study compared functional activation during the performance of a task requiring monitoring of information in working memory in a group of concussed athletes with that of normal control subjects. The control subjects showed strong activation within the mid-dorsolateral prefrontal cortex, consistent with the view that this part of the prefrontal cortex is critical for active monitoring of information in working memory (Petrides, 1991, 2000a,b). The performance of the athletes who had sustained

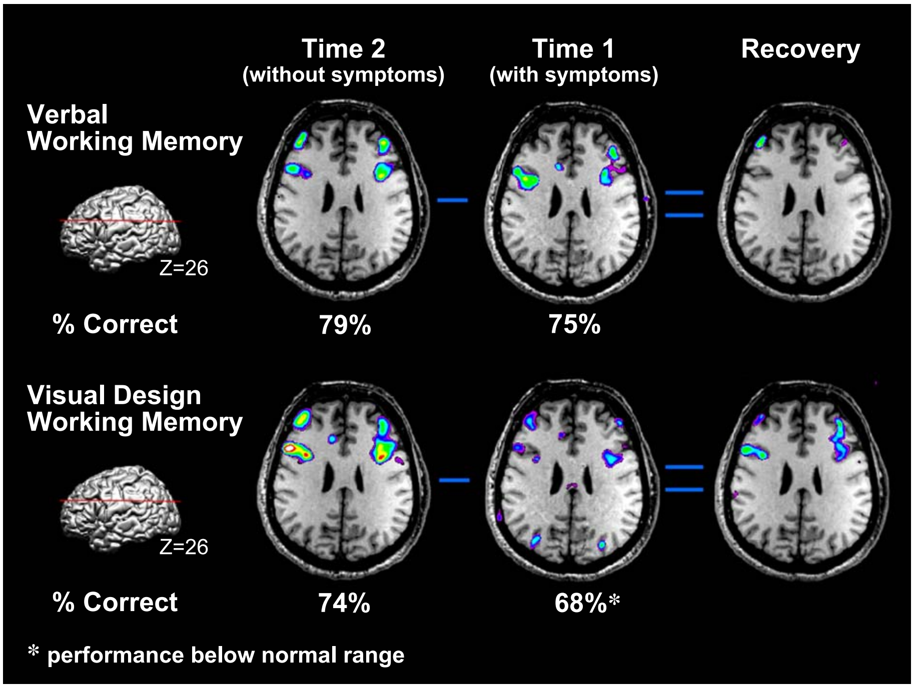

Fig. 9. Comparison of the t-maps of athlete 4 obtained 6 months after the concussion episode (Time 1), when he was still symptomatic, and 3 months later (Time 2), when the post-concussive symptoms had resolved.

concussion was not significantly different from that of the control subjects on this working memory task, although the athletes seemed to have more difficulty with the visual design version of the task. Analysis of fMRI data revealed that the athletes, as a group, had weaker BOLD changes within the right mid-dorsolateral prefrontal cortex, the crucial area for monitoring of information in working memory, and this observation was true for both the verbal and the visual design versions of the task. Abnormal patterns of activation following mild head injury have been reported in previous functional imaging studies using different versions of working memory tasks (Chen et al., 2003; McAllister et al., 1999, 2001). For example, in an fMRI study, McAllister et al. (2001) reported that mild head injury subjects showed disproportionately high increases in activation compared with a control group in response to moderate working memory processing loads. The abnormal increase in activation was lateralized to the right hemisphere, including the right dorsolateral prefrontal cortex, which was the same area that showed weaker activations in our subjects. In another study using PET and working memory (Chen et al., 2003), patients with persisting symptoms following mild head injury had smaller percent BOLD signal change in one of the ROIs within the right prefrontal cortex. Thus, our results are consistent with these previous findings.

We also performed individual analyses, comparing fMRI results of each athlete with that of the control group. Qualitative analysis examined the topographical pattern of the activation and revealed that, except for three athletes, one of them asymptomatic, all had additional activations outside the regions of interest, indicating that the concussed athletes had a more widely distributed activation pattern relative to the control group. Quantitative analysis of the fMRI data measured the BOLD signal change within the regions of interest and provided a physiological index of the functional state of those regions. Except for three athletes, all symptomatic concussed athletes had BOLD signal patterns that deviated from those of the control group in at least one region of interest. The atypical activation pattern in the concussed athletes could not be attributed simply to performance differences on the working memory task since good performance was not necessarily associated with a ‘normal’ pattern of activation. Furthermore, if the difference in activation patterns was confounded by performance, we would expect athletes 9, 10, and 16, who scored significantly below the control subjects only on the visual design version of the working memory task to show greater deviations in the activation pattern for that version of the task and not for the verbal one in which they performed well. This, however, was not the case.

In summary, our results indicate that symptomatic concussed athletes had different task-related physiological responses compared with the normal control group, regardless of their behavioral performance. One possible explanation for this difference may be individual variation in functional neuroanatomy. This is unlikely for two reasons. First, seven of eight control subjects consistently showed activations in all the regions of interest while none of the symptomatic athletes showed this pattern, even when they performed behaviorally as well as the control subjects. Second, the one athlete who was retested when his post-concussive symptoms had resolved, showed striking changes in activation pattern, from widespread distribution of cerebral activation peaks to localized frontal activation similar to that of the control subjects. In the present study, the control group was well matched with concussed athletes in terms of gender and age, but they were not athletes. This raises the question as to whether this factor might have contributed to the observed difference in activation pattern between the two groups. Although we cannot definitely rule out such a possibility, it is unlikely since the symptom-free athlete, as well as the athlete who recovered from PCS, had activation patterns that resembled those of the control group. Another more likely explanation for the difference observed in the concussed athletes is that the weaker and atypical activation patterns reflect both functional deficits in the prefrontal cortex and recruitment of other brain regions as compensatory mechanisms. This possibility is consistent with the fact that most of these athletes performed well on the tasks. Use of compensatory mechanisms through alternative cognitive resources has previously been suggested and supported by functional imaging studies with moderate and severe head injury patients (Levine et al., 2002; Ricker et al., 2001), as well as by event-related potential investigations following mild head injury (Potter et al., 2001).

Traditionally, diagnosis of the severity of head injury, as well as prognosis of injury outcome, are determined by the clinical symptom characteristics in the acute stage, such as the presence and the duration of loss of consciousness and post-traumatic amnesia; the severity of post-concussive symptoms are usually not taken into account (Alexander, 1995; Jennett, 1979). In the present study, all the athletes but one had subjective complaints of post-concussive symptoms at the time of the functional imaging study. Interestingly, the one symptom-free athlete was also the only one showing an activation pattern similar to that of the control group, while all the symptomatic athletes displayed a different activation pattern, regardless of whether they experienced loss of consciousness at the time of the injury. The duration of PCS among these athletes ranged from 1 to 14 months. Correlation analysis did not yield significant relationships between the duration of PCS and the degree of BOLD signal change in the ROIs. There was, however, a significant negative correlation between the severity of the symptoms and the BOLD changes in the right dorsolateral prefrontal cortex. This finding suggests that the presence of post-concussive symptoms can be an important, if not the most important, indicator for the diagnosis and prognosis of concussive injury. It should be noted that the severity of the post-concussion state was based on the subjective clinical observation and evaluation by the neurosurgeon. We have now incorporated a post-concussive symptoms severity scale to explore fully the clinical significance of these symptoms.

At present, the cause of the observed deviation in activation pattern among symptomatic concussed athletes remains unclear. Although diffuse axonal injury has been suggested as a possible origin of the functional alteration and persisting post-concussive symptoms following mild head injury, most of the evidence stems from severe head injury populations and may not apply to mild head injury cases. Indeed, none of our symptomatic athletes with concussion showed signs of diffuse axonal injury in their structural MRI (T1, T2, and FLAIR). Thus, the results suggest that residual functional abnormalities may be present even in the absence of apparent morphological damage. We may hypothesize that in concussion, the mechanical force is of limited magnitude and axons are not torn apart as is probably the case for severe head injury. Rather, the axons may be in a vulnerable state that affects normal signal flow. Studies that focus on the neurochemical response to head injury have noted abnormalities in neurotransmitter release following mild head trauma, including excessive release of acetylcholine (Metz, 1971; Saija et al., 1988), glutamate, and aspartate (Faden et al., 1989; Katayama et al., 1990). Alterations in brain electrical activity are also frequently observed following concussion. For example, a recent study that compared brain electrophysiological activity using event-related potential between symptomatic concussed athletes, asymptomatic concussed athletes, and controls subjects found that symptomatic athletes displayed smaller P-300 amplitudes compared with asymptomatic athletes and controls (Dupuis et al., 2000). Correlation analysis revealed that the degree of brain dysfunction measured by evoked potentials was strongly related to the severity of PCS. Although the exact consequences of these series of electrical and chemical changes are unknown, there is little doubt that abnormal neural activity and aberrant synaptic connections can be expected to occur. This could explain why these patients display functional abnormalities without detectable structural damage.

More important to the present study are the alterations in the brain vascular system following head trauma. Strebel et al. (1997) reported a complete shut down of cerebral autoregulation following MHI. Slowing of cerebral circulation (Taylor and Bell, 1966), increase in arterial blood pressure (Povlishock and Kontos, 1982), and increase in cerebral blood volume (Langfitt et al., 1982) are also associated with traumatic brain injuries. These changes are especially relevant for the functional MRI studies of head trauma that use BOLD contrast, since they are based on the assumption that an increase in neuronal activity within a brain region leads to a localized increase of blood flow in that same region. This indirect index of brain activity can be influenced by several factors, including blood flow and blood volume, and is therefore likely to detect pathological changes following mild head injury. One question raised involves the degree to which the BOLD signal reflects alterations in brain activity following head injury. Our study was focused on the brain activity associated with a working memory task sensitive to function in the frontal lobe because this region is one of those most likely to be injured following head trauma. Most concussed athletes in the present study did show weaker BOLD changes within the frontal region. Although we cannot totally rule out the possibility that there was a global metabolic decline rather than a localized deficit in frontal areas, most athletes showed decreased frontal activity but significantly more activations in the posterior cerebral regions. The increases in activation in the posterior brain areas of symptomatic athletes lend support to a localized deficit in frontal regions following concussion rather than to a global metabolic decline.

Two major concerns in the application of fMRI techniques to clinical populations are whether this imaging modality is sensitive enough to detect functional abnormalities and whether the obtained results are consistent and reliable. The present study has successfully demonstrated that fMRI is sensitive enough to detect abnormal activation patterns at the individual level and that task-related activations can be consistently and reliably produced. Thus, fMRI, in conjunction with the working memory task used here, holds great promise for evaluating clinical outcome, especially in cases where post-concussive symptoms persist and morphological imaging results are normal.

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