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Postconcussive Symptoms Are Associated With Compensatory Cortical Recruitment During a Working Memory Task

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Abstract

BACKGROUND—The severity of sports-related concussion is often characterized by the number and severity of postconcussive symptoms (eg, headache, dizziness, difficulty concentrating). Although the level of postconcussive symptoms after injury is believed to index the severity of the neurological insult sustained, studies examining the relationship between symptom severity and neural functioning in concussed athletes remain rare.

OBJECTIVE—This exploratory study examined the association between self-reported symptom severity and functional activation on a working memory task in a group of 16 recently concussed student athletes.

METHODS—Functional magnetic resonance imaging was used to examine the relationship of symptom severity to brain activation during a working memory task in 16 concussed subjects.

RESULTS—Findings indicated that symptom severity was associated with regionally specific hyperactivation during a working memory task, even though symptom severity was not significantly related to task accuracy.

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CONCLUSION—The results add to a growing body of literature that demonstrates that functional neuroimaging may have the potential to serve as a sensitive biomarker of the severity of concussion and mild traumatic brain injury.

Keywords

Brain function; Concussion; Functional magnetic resonance imaging; Symptoms; Working memory

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Concussion is “a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces [that] typically results in the rapid onset of short lived impairment of neurological function.”[1] Changes in mental status can include loss of consciousness, retrograde and anterograde amnesia, and confusion, all of which can serve as immediate indicators of concussion.1 In addition to these acute mental status changes, concussion generally results in a range of somatic symptoms including, but not limited to, headache, fatigue, nausea, drowsiness, dizziness, sleep disturbances, visual changes, and personality changes.1,2

Recreation- and sports-related concussion occurs in 1.6 to 3.8 million people per year.[3] Younger athletes (ie, high school age) demonstrate protracted recovery compared with college-level and professional athletes and are also at greater risk of second impact syndrome.[4-6] The time to recover from concussion among high school athletes ranges, on average, from 7 to 14 days, although functional impairment from sports-related or other mild traumatic brain injury may persist well beyond that time period.5,7-10

Athletes are not considered recovered from a concussion until they are asymptomatic at rest and asymptomatic with gradually increasing levels of noncontact physical exertion.[2,11] It is critical to monitor both the presence and severity of postconcussive symptoms as well as to track recovery of function to make return-to-play decisions. Using athlete symptom reports in addition to neurocognitive testing most accurately discriminates between concussed and nonconcussed athletes.12,13 Postural control evaluation has also been shown to be a useful tool in concussion assessment and management.14,15 An approach to concussion management that includes multiple assessment domains (eg, neurocognitive testing, postural control, symptom report) has been found to be most sensitive.[13,14] However, symptom report has historically been most relied on for determination of recovery, and some researchers continue to assert that neurocognitive testing is not indicated until an athlete is symptom free.11

With some injuries, athletes report being symptom free, but continue to demonstrate neurocognitive dysfunction (eg, difficulties with memory, reaction time). Other injured athletes demonstrate cognitive recovery first, and still others may demonstrate recovery of symptoms and cognitive functioning simultaneously.[16-20] Athletes who are concussed yet report being symptom free may continue to demonstrate neurocognitive impairment, functional abnormalities, and/or electrophysiological impairment compared with noninjured controls.19,21,22

Electrophysiological studies have demonstrated an inverse relationship between symptom severity and P300 amplitude in concussed athletes.[21] We recently reported in a functional magnetic resonance imaging (fMRI) study that hypoactivation in the posterior parietal cortex during performance of a working memory task was associated with cognitive and somatic symptoms of concussion.[23] Chen et al24 reported differences in functional activation when comparing concussed athletes with and without depression symptoms, even though their behavioral task performance was not different. Also, the severity of depression

symptoms was correlated with functional activation in brain areas that have been found to be linked to major depression. There is increased activation during a working memory task in nonathlete patients sustaining mild TBI within a month of evaluation compared with controls.22 More specifically, a moderate working memory load was associated with greater activation changes in concussed patients, whereas high memory load was associated with less increased activation in concussed patients. Asymptomatic concussed athletes' pattern of functional activation closely resembled the pattern of control subjects' activation and not that of symptomatic concussed athletes.25

Somatic symptom report has been consistently related to decrements in neuropsychological functioning after concussion.[19,26] Individual symptoms and symptom clusters such as headache, posttraumatic migraine, and mental "fogginess" have also been linked with decreased performance on cognitive testing after concussion.[27-29]

Smits et al[30] examined the relationship between severity of postconcussive symptoms and brain function using a sample of 21 patients assessed 18 to 40 days after mild head injury and 12 nonconcussed healthy controls. Lower response accuracy was found in patients with higher postconcussive symptoms vs those with moderate symptoms and controls during the moderate- and high-level working memory load tasks (1-back and 2-back, respectively). On imaging, participants with higher post-concussive symptoms demonstrated increased activation on the high working memory load task and also showed activation outside the normal working memory network, indicating that highly symptomatic individuals recruited a more widespread cortical network.

The purpose of this exploratory study was to describe and evaluate the relationship between concussion symptom severity (as measured using the Post-Concussion Symptom Scale [PCSS]) and functional brain activation on a working memory task among a group of concussed athletes. We hypothesized that the severity of concussion symptoms would be significantly associated with the extent of functional brain activation in the posterior parietal cortex.

SUBJECTS AND METHODS

Subjects

The subjects of this study were a subgroup of concussion patients from the much larger fMRI and Sports-Related Concussion study.[23] This study was approved by the Institutional Review Board of the University of Pittsburgh before the recruitment of subjects. Concussed athletes were recruited through the Center for Sports Medicine at the University of Pittsburgh Medical Center. Concussion was diagnosed based on the criteria set forth by the Concussion in Sport group.[1,11,15]

The selected subgroup consists of those participants scanned on a 3-T MAGNETOM Allegra scanner (Siemens Medical Solutions USA, Malvern, Pennsylvania). This selection yielded 16 patients, 10 male and 6 female. This group is 94% Caucasian (6% African American). Patient of ages ranging from 14 to 23 years (median 16.3 years) and equivalent education ranging from 7 to 17 years (median 10.0 years) at the time of concussion.

The subjects were scanned approximately 1 week post-concussion (median, 6.5 days; range, 3-12 days). The 22-item PCSS was administered to each subject several times over the course of recovery.31,32 We analyzed MRI data from those scans with respect to the total concussion symptom score measured most recently before the scan. These measurements occurred from 2 to 9 days post-concussion (median 5.0 days), and 0 to 4 days before imaging (median 1.0 day). At the time of the scan, the research assistant asked each

participant whether he or she was still experiencing postconcussive symptoms, and all participants indicated that they were. In addition, the clinical practitioners charged with regularly monitoring the participants' recovery reported that, at the time of the scan, none of the participants had fully recovered from their concussions. For this sample, the mean time to recovery was 57.93 days (range, 16-211 days). Consequently, although patients may have been at different stages of recovery at the time of the scan, none of the participants were fully recovered.

Measures

The PCSS is a 7-point Likert-type instrument that is widely used in the assessment of symptoms in concussed athletes, both acutely and throughout the recovery process.[32] Athletes rate their current experience of each of 22 commonly reported symptoms of concussion on a scale of 0 (none) to 6 (severe). The sum of all symptom ratings, the total symptom score, is used as a general measure of symptom severity after concussion.

Magnetic Resonance Imaging

Each imaging session included a 3-dimensional sagittal MPRAGE (1 × 1 × 1-mm resolution) for anatomic reference, T1-weighted high-resolution volumes acquired to match the slice locations of the functional images, and 3 functional acquisitions of an N-BACK protocol, which were acquired as echo-planar images at 64 × 64-resolution, done with nearly isotropic 3.2-mm. voxels (TR/TE = 2000 ms/ 30 ms, flip angle = 60 degrees, gap = 0). Each acquisition of the N-BACK protocol collected 143 volumes of 26 slices oriented parallel to the anterior commissure-posterior commissure line, yielding a total of 429 volumes over the 3 intervals of 4.8 minutes each. The T1-weighted in-plane anatomic images were taken in the same slice planes with the same between-plane resolution, but with an in-plane resolution of 0.78 mm. This high-resolution T1-weighted volume of images is used in the process of coregistering the functional volume to the MPRAGE structural images and takes roughly 1 minute to acquire.

Experimental Design

During the N-BACK acquisitions, the subject watched a series of mixed-case letters presented 1 at a time on a screen in the bore of the scanner. Their task was to determine whether the presented letter was a target letter and to respond by pressing 1 of 2 buttons. If the letter was in fact a target, the yes button was pressed with the right index finger; if not, the no button was pressed with the right middle finger.

The 2 task types used in this analysis were the 0-back and 2-back working memory tasks. In the 0-back condition, the letter X (in upper or lower case) was a target, and all other letters were not. In the 2-back condition, a letter was a target if it matched the letter presented 2 trials previously, regardless of case. Response accuracy and reaction times were recorded. There were 6 blocks of each of the 2 trial types, with each block containing 15 trials in each condition. The order in which the conditions were presented in each acquisition was chosen to minimize possible biases based on early or late occurrence within an acquisition or within the scanning session and was the same for all subjects. The trial conditions were balanced within each acquisition so that acquisitions could be dropped from the analysis without unbalancing the experimental design. The trial duration was 2.1 seconds, deliberately chosen to be slightly longer than the TR of 2.0 seconds. Because the order of acquisition of each slice within each volume was known, it was straightforward to associate each slice with its position in the stimulus acquisition sequence.

The protocol included fixation intervals and written directions with each block. The fixation intervals require only that the subject look at a cross on the screen. Written instructions are presented on the projection screen at the ends of the fixation intervals.

fMRI Data Processing

Magnetic resonance images were processed and analyzed offline on a cluster of Linux workstations using the software packages AFNI[33,34] and FIASCO/FIAT.[35,36] Motion correction was done in 3 dimensions using Fourier interpolation.[35,37,38] No subjects were dropped because of magnitude of motion, but individual volumes associated with rapid motion were dropped from the analysis. The time-averaged displacement before motion correction for voxels within the brain in images retained for analysis ranged from 0.6 to 2.4 mm; the maximum excursion distance for any brain was 3.2 mm.

After motion correction, median and interquartile range values were calculated for each voxel in each acquisition, outlier voxels were set to a boundary value, and slices containing high numbers of outliers were dropped from the analysis. Gaussian smoothing was applied in the slice planes with a full width at half maximum of 2 voxels to improve the signal-to-noise ratio. The time series for every voxel was high-pass filtered, removing variations slower than the trial frequency to detrend the voxel time series in each acquisition.

Functional images were coregistered to each subject's whole-head structural images using rigid body transformations implemented by Fourier interpolation, matching the in-plane structural images as an intermediate stage. Transformations into Talairach space were based on anatomic landmarks applied to the structural and functional data using AFNI software.[39] All-group analysis was performed in Talairach coordinates at 1-mm isotropic resolution.

The subjects' task performance was checked to verify attention to the task; examination of the task performance from a much larger group of subjects from the fMRI and Sports-Related Concussion study indicates that an accuracy of 70% or greater can be expected from attentive subjects. Based on this requirement, 1 acquisition from 1 subject was dropped from the current analysis, the subject having apparently misunderstood the task. An error in data collection caused the loss of 1 acquisition from 1 additional subject. Among concussed participants in the current study, the average accuracy was high in both N-back conditions, but 0-back (95% accuracy) was an easier task than the 2-back (81% accuracy). Symptom severity was not significantly correlated with N-back performance in either condition (0-back, r =0.21, P = .45; 2-back, r =0.31, P = .24), indicating that more symptomatic individuals did not have significantly more difficulty accurately completing the N-back task.

Statistical Analysis

Because the concussion symptom severity score was highly skewed, an appropriate normalizing transformation was applied before it was used in regression models. Examination of the scores for 96 concussed subjects from the larger fMRI and Sports-Related Concussion study led to the selection of the square root transformation. As a result, all analyses outlined in the following were based on the square root-transformed concussion symptom severity score.

The data were analyzed by 2 separate but complementary procedures. First, activation maps were generated representing the blood oxygenated level-dependent response (BOLD) for the 2-back vs 0-back contrast across all subjects. Specifically, within-individual t cores representing the 2-back vs 0-back contrast were calculated for each voxel and then transformed to Talairach space using nearest-neighbor interpolation. These within-individual t scores were then combined across subjects using Stouffer's method[40] to produce voxel level z score maps for the group. A voxel-level z score of ±2 was used as a statistical

threshold. This procedure identified brain regions where an increased or decreased BOLD response for the 2-back vs 0-back contrast across all subjects. Specifically, within-individual response was observed for the 2-back condition relative to the 0-back condition across all subjects combined.

For the second step of the analysis, a whole-brain voxel-by-voxel regression analysis was performed in which the within-individual *z* scores for the 2-back vs 0-back contrast were regressed onto the square rooted scores. These analyses were weighted using the square root of the number of valid images for that subject. These regressions produced voxelwise test statistics that were used to identify where the square root of total PCSS scores were significantly associated with the 2-back vs 0-back BOLD contrast.

Several criteria were used to identify significant regions of interest (ROIs) for these voxel-level regressions. First, significant associations at the voxel level were thresholded as a *z* score of ±2.5. Masking using the standard Collins et al[27] template was used to eliminate voxels that fell outside the boundary of the brain. In addition, voxels that were not observed across all participants at the boundaries of the brain were also excluded. Mathematical morphology[41] was applied to eliminate small regions, by eroding 5 times on 10 or fewer neighbors and then flooding surviving regions back to their original boundaries. Only those regions with volumes of 50 mm^3 or greater were retained.

After the identification of significant regions of interest from the regression analysis, an overall summary statistic (R^2) representing the strength of the linear association between the PCSS scores and the BOLD response to the 2-back vs 0-back condition was calculated for each ROI identified. Specifically, the median percentage of signal change for the 2-back vs 0-back contrast was extracted for each subject within each ROI. The subjects' median percentage of signal change for each region was then regressed onto the square root of the PCSS score. Individual subject outliers in a particular ROI were eliminated if their Cook's distance score,[42] taken as an *F* statistic, had a percentile value greater than 40%.

RESULTS

Figure 1 depicts brain regions where the BOLD response was significantly higher for the 2-back vs 0-back contrast in yellow/red, whereas regions where the BOLD response was significantly lower for the 2-back vs 0-back contrast are depicted in blue. Consistent with meta-analytic evidence,[43] the 2-back task resulted in an increased BOLD response relative to the 0-back in a large-scale frontoparietal network that included the lateral premotor cortex, dorsal cingulate, dorsolateral and ventrolateral prefrontal cortex, and medial and lateral posterior parietal cortex.

Regions where a significant linear association was found between the square-rooted PCSS scores and the BOLD response for the 2-back vs 0-back contrast are also presented in Figure 1. Regions representing a positive linear association are depicted in black and those representing a negative association are depicted in white. More specific detail on cluster size, strength of association, and localization of peak voxels for the regression analysis are presented in Table 1 for positive associations and Table 2 for negative associations.

As seen in Figure 1, PCSS symptom severity was significantly associated with an increased BOLD response for the 2-back vs 0-back contrast within several regions including the premotor cortex and posterior parietal cortex. Interestingly, the regions tended to be on the boundaries of areas that exhibited a positive BOLD response to the 2-back vs 0-back condition across all subjects. Figure 2 depicts a prototypic regression line for the association between concussion symptom severity and the medial percentage of signal change for the 2-back vs 0-back contrast in an ROI in the premotor cortex (ROI 3 in Table 1). As seen in

Figure 2, participants reporting high levels of concussion symptoms experienced a greater BOLD response during the 2-back task in this region than those with low concussion symptoms.

Conversely, Figure 1 and Table 2 show significant ROIs for which increased concussion symptom severity was associated with a lower BOLD response for the 2-back vs 0-back contrast. These regions correspond only weakly with regions where the BOLD response to the 2-back condition differed from that for the 0-back condition. Specifically, most were not directly associated with significant 2-back task-related increases or decreases in the BOLD response relative to the 0-back condition.

DISCUSSION

There are 3 major findings of this study. First, the severity of concussion symptoms is linked to differential patterns of brain activation to a working memory task. Second, more highly symptomatic concussed individuals recruit additional cognitive resources during the acute phase of recovery from concussion. Third, there are circumscribed bilateral prefrontal and parietal cortical regions where increased activation is correlated with symptom severity. These findings are supportive of the hope that functional imaging may serve as a sensitive biomarker for mild traumatic brain injury.

The results of this study suggest that increased symptom severity in concussed athletes was associated with region-specific hyper-activation during a working memory task. ROIs identified as showing a positive slope of activation with increasing task difficulty tended to lie at the boundaries of regions of activation. This could be because of recruitment of additional cognitive resources and expansion of the functional field to perform tasks accurately or because the BOLD response of the central regions of activation is saturated for all subjects so that differential metabolic activity associated with the task is in fact fairly uniformly distributed across the regions of activation. It is difficult to distinguish between these 2 possible explanations because of the block design of the study. Future studies should examine the dynamics of the BOLD response using a simple visuomotor task to determine whether changes occur in the context of concussion and recovery.[44,45]

These data suggest that during the course of recovery from the acute injury patients with increased concussion symptoms require more cognitive resources to complete tasks of similar difficulty (and with similar success). Given increased activation in more symptomatic concussed athletes and no differences in task performances between more symptomatic and less symptomatic athletes, it is reasonable to conclude that more severely concussed subjects find the task more difficult and thus recruit more cognitive resources to successfully perform the memory task. These data, therefore, may provide information relevant to understanding the neural basis of the clinical observation of decreased academic and related performances during acute recovery from brain injury.

Findings in the current study are very similar to those of the Smits et al[30] study examining fMRI and working memory performance in mild head injury patients 18 to 40 days after injury. In both studies, increased activation and cortical recruitment of additional cognitive resources were observed in patients with more severe postconcussive symptoms. Thus, this pattern seems evident at various time points post-injury.

The greatest limitation in studies of sports-related concussion and indeed most mild traumatic brain injury research is the lack of a sensitive and reliable biomarker that accurately indicates concussion severity. Such a biomarker would be helpful for the diagnosis and management of mild traumatic brain injury and for the refinement of treatment strategies and recovery of functional outcomes.

Structural imaging studies are almost always unremarkable when a concussion has occurred. The limited evidence from fMRI research, however, suggests that this may hold promise as a biomarker to indicate the presence of and recovery from central nervous system dysfunction associated with sports-related concussion. Clear abnormalities in signal have been associated with concussion in general, with cognitive changes, and with symptom severity. fMRI studies have found more diffuse activation in concussed vs control athletes.[25,46] Postconcussion changes in functional activation, despite a lack of evidence of reduced neurocognitive performance (accuracy and speed) on tasks, have been observed in comparisons with noninjured controls[22,25] and personal preinjury scans.25 Concussed participants show increased amplitude and extent of regional brain activation, chiefly in the bilateral inferosuperior parietal region, dorsolateral regions, and prefrontal cortex.25 Adult athletes who had sustained concussion 1 to 14 months before an fMRI study showed weaker activation changes in the right mid-dorsolateral prefrontal cortex compared with controls when completing verbal and visual working memory tasks.[46] fMRI abnormalities are also predictive of time to recovery; those athletes with the greatest extent of fMRI activation took almost twice as long to recover from their injury than did the less affected athletes.[23] In nonathletes, studies have found differences in functional activation during working memory tasks between concussed and nonconcussed individuals using positron emission tomography.[10,47] Thus, fMRI and other functional imaging modalities may hold the promise of increasing our sensitivity to a neurologically meaningful alteration in mental status as revealed by changes in neural response to cognitive demands.

There are several factors that need to be kept in mind while considering these results. First, we did not include a non-concussed control group in the study. We did this because our goal was to examine the correlates of concussion symptom severity among individuals who had experienced a mild traumatic brain injury. Assessing these symptoms in nonconcussed controls would be problematic because any symptoms reported would not have been caused by a recent head injury. The average scores on the PCSS for nonconcussed individuals are typically higher than those reported by individuals who have recovered from concussion,[5] suggesting that data from nonconcussed individuals might actually decrease the explanatory power of the study. Second, we did not obtain PCSS ratings on the same day as the fMRI study in all cases; the median time between PCSS and fMRI was 1 day. Future studies should include a same-day symptom report rather than gathering this information in the days leading up to the scan. Despite this limitation, a significant association between concussion symptom severity and a greater neural response to a working memory task was still observed, suggesting that symptom severity can prospectively predict hyperactive brain function during a working memory task days later in concussed athletes. A third limitation is that subjects in the study ranged in age from 14 to 23 years, and, given that the age of individuals with concussion is related to their recovery time,[5] the inclusion of this broad age spectrum does not address potential brain function differences attributed to age. The analysis of this question is beyond the scope of this small study (n = 16), but future research with larger samples will likely be able to address this important issue. Fourth, some readers might consider that by not analyzing the data from the 1-back condition we were missing important information. Unpublished analyses of N-back performance by our group show that the 1-back and 2-back activations (relative to the 0-back control) are quite similar, but that the 2-back is a more challenging task and consequently provides greater sensitivity to central nervous system abnormalities. Future studies with larger samples might be in a position to examine the extent to which the increase in regional activation as a function of task demand varies as a function of concussion severity.

Data from the current study suggest that concussion severity based on symptom report is linked to differential patterns of activation to a working memory task. There is evidence that areas of activation in more highly symptomatic concussed individuals occur near the borders

of activated areas in less symptomatic concussed individuals, indicating recruitment of additional cognitive resources during the acute concussed phase. Finally, the data demonstrate that there are circumscribed bilateral frontal and parietal cortical regions where increased activation is correlated with symptom severity. The data reported here and elsewhere demonstrate that fMRI has the potential to serve as a sensitive biomarker of the presence and severity of concussion and mild traumatic brain injury.[23] Specifically, multiple studies referenced here demonstrated that functional imaging results for acutely concussed individuals differ from those of controls and that fMRI results are predictive of time to recovery. The current study demonstrates that functional imaging results are correlated with symptom severity.

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ABBREVIATIONS

BOLD	blood oxygenated level-dependent response
fMRI	functional magnetic resonance imaging
PCSS	Post-Concussion Symptom Scale
ROI	region of interest

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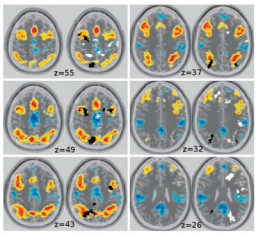

FIGURE 1.

Neural response for the 2-back vs 0-back contrast overlaid with significant associations between the neural response and symptom severity. Pictures represent different axial slices with Z coordinates representing vertical location based on the Talairach atlas. Positive levels of the blood oxygenation level dependent response (BOLD) are shown in yellow/red and negative levels are shown in blue for the 2-back vs 0-back contrast. Voxels are thresholded at a z score of ±2, with color saturation at a z score of ±7 or more. Regions where the BOLD response for the 2-back vs 0-back contrast increases with concussion severity are shown in black, and regions where the BOLD response decreases with concussion severity are shown in white. Regions of interest have been projected to the nearest slice from slabs 6 mm thick, for a maximum projection distance of 3 mm.

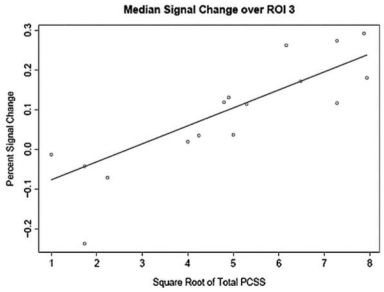

FIGURE 2.

Linear association between concussion symptom severity and median percentage of signal change in the premotor cortex for the 2-back vs 0-back contrast. Brain region 3 from Table 1 was used to generate the figure. Peak voxel for the region was located at Talairach coordinates −28, 3, 47. Linear association depicted has an adjusted $R^2 = 0.43$. PCSS, Post-Concussion Symptom Scale; ROI, region of interest.

TABLE 1

Location of Positive Associations Between Concussion Symptom Severity and the 2-Back Vs 0-Back Contrast[a]

ROI	Voxels	Outliers	R^2_{adj}	*t*	*P*	Talairach Coordinates	Structure
1	88	1	0.57	4.45	.0007	(−44, 3, 49)	Left premotor cortex
2	2107	1	0.66	5.34	.0001	(−21, −71, 41)	Left superior parietal lobe Left superior occipital gyrus
3	567	1	0.73	6.24	3.0E-5	(−28, −3, 47)	Left premotor cortex
4	147	0	0.59	4.72	.0003	(−32, −22, −4)	Left dorsal hippocampus
5	107	1	0.42	3.32	.0055	(−29, −61, 24)	Left mid. occipital gyrus
6	96	0	0.6	4.90	.0002	(−6, −42, 38)	Left posterior cingulate
7	77	1	0.55	4.26	.0009	(19, 5, 44)	Right medial frontal cortex, right anterior cingulate
8	387	1	0.79	7.27	6.3E-6	(36, 2, 43)	Right premotor cortex
9	124	1	0.38	3.12	.0081	(34, −74, 31)	Right superior parietal, right angular gyrus

[a]ROI, region of interest; adj, adjusted.

TABLE 2

Location of Negative Associations Between Concussion Symptom Severity and the 2-Back Vs 0-Back Contrast[a]

ROI	Voxels	Outliers	R^2_{adj}	*t*	*P*	Talairach Coordinates	Structure
1	268	1	0.57	−4.42	.0007	(−44, −5, 15)	Left insula, left precentral gyrus
2	150	1	0.63	−4.99	.0002	(−52, −10, 2)	Left superior temporal gyrus
3	136	1	0.43	−3.41	.0047	(−48, 29, −7)	Left inferior frontal gyrus
4	396	1	0.74	−6.35	2.5E-5	(−39, −9, 0)	Left insula
5	1171	2	0.89	−10.43	2.3E-7	(−23, −92, 6)	Left cuneus, left inferior and middle occipital gyrus
6	520	1	0.72	−6.08	3.9E-5	(−31, −73, 6)	Left middle occipital gyrus
7	72	0	0.60	−4.85	.0003	(−34, −21, 54)	Left primary motor cortex
8	121	1	0.39	−3.16	.0075	(−28, −75, −2)	Left lingual gyrus
9	191	1	0.83	−8.31	1.5E-6	(−18, −51, 54)	Left superior parietal lobule, left precuneus
10	152	1	0.78	−7.21	6.9E-6	(−20, 39, 16)	Left anterior cingulate
11	211	1	0.63	−5.03	.0002	(−20, 40, 5)	Left anterior cingulate
12	217	2	0.46	−3.45	.0048	(−13, 46, 27)	Left superior frontal gyrus
13	1029	0	0.69	−5.83	4.3E-5	(−11, −54, 8)	Left posterior cingulate, left lingual gyrus
14	65	0	0.57	−4.61	.0004	(−12, 21, 16)	Left anterior cingulate
15	229	0	0.57	−4.56	.0005	(1, −12, 49)	Right supplementary motor area
16	385	1	0.34	−2.86	.0135	(2, −81,−2)	Right precuneus; right lingual gyrus
17	79	1	0.42	−3.34	.0054	(1, 17, 8)	Right caudate
18	103	0	0.59	−4.74	.0003	(7, −43, 50)	Right precuneus
19	123	0	0.52	−4.13	.0010	(8, −41, 4)	Right posterior cingulate
20	201	2	0.59	−4.48	.0008	(13, −48, 55)	Right precuneus
21	1317	1	0.83	−8.36	1.4E-6	(21, −94, 7)	Right cuneus, right middle occipital gyrus
22	177	0	0.59	−4.79	.0003	(15, −26, 1)	Right thalamus
23	82	0	0.50	−4.01	.0013	(13, 8, 33)	Right cingulate gyrus
24	160	0	0.58	−4.66	.0004	(17, −42, 2)	Right precuneus
25	122	1	0.64	−5.04	.0002	(16, −75, 28)	Right precuneus
26	999	1	0.67	−5.37	.0001	(22, −75, 18)	Right precuneus, right middle occipital gyrus, right cuneus
27	104	0	0.63	−5.12	.0002	(28, −34, 56)	Right postcentral gyrus
28	651	1	0.67	−5.48	.0001	(45, −9, 17)	Right postcentral gyrus, right precentral gyrus, right insula

ROI	Voxels	Outliers	R^2_{adj}	*t*	*P*	Talairach Coordinates	Structure
29	440	2	0.74	−6.12	.0001	(40, −4, 2)	Right insula
30	183	1	0.69	−5.73	.0001	(36, −22, 54)	Right primary motor cortex
31	105	1	0.65	−5.24	.0002	(39, −15, 3)	Right insula
32	112	1	0.59	−4.56	.0005	(38, −9, 23)	Right insula, right postcentral gyrus
33	279	1	0.60	−4.68	.0004	(44, −30, 27)	Right inferior parietal lobule
34	151	1	0.27	−2.50	.0267	(54, −20, 51)	Right postcentral gyrus
35	95	2	0.61	−4.64	.0006	(61, −14, 32)	Right postcentral gyrus

[a]ROI, region of interest; adj, adjusted.