

# Neural Substrates of Symptoms of Depression Following Concussion in Male Athletes With Persisting Postconcussion Symptoms

Jen-Kai Chen, BA; Karen M. Johnston, MD, PhD; Michael Petrides, PhD; Alain Ptito, PhD

**Context:** Depressed mood is frequently reported by individuals who have sustained cerebral concussion but little is known about the nature of this alteration in mood state.

**Objective:** To investigate whether the symptoms of depression reflect an ongoing pathophysiological change following concussion.

**Design:** Cohort study with male athletes using functional and structural neuroimaging.

**Setting:** Hospital laboratory and imaging facility.

**Participants:** Fifty-six male athletes with and without concussion were divided into (1) a no depression symptom, concussed group, (2) a mild depression symptom, concussed group, (3) a moderate depression symptom, concussed group, and (4) a healthy control group.

**Interventions:** All athletes filled out a postconcussive symptoms checklist and the Beck Depression Inventory II and underwent a magnetic resonance imaging session, which included T1, T2, and fluid-attenuated inversion recovery sequences, as well as functional magnetic resonance imaging (fMRI), during which they performed a working memory task.

**Main Outcome Measures:** (1) Behavioral: response speed and accuracy on the working memory task performed during the fMRI session; (2) functional imaging: brain activation patterns associated with the working memory task obtained using blood oxygen level-dependent fMRI; and (3) structural imaging: voxel-based morphometry examining gray matter concentration.

**Results:** (1) Behavioral: there was no performance difference between the groups; and (2) imaging: athletes with concussion with depression symptoms showed reduced activation in the dorsolateral prefrontal cortex and striatum and attenuated deactivation in medial frontal and temporal regions. The severity of symptoms of depression correlated with neural responses in brain areas that are implicated in major depression. Voxel-based morphometry confirmed gray matter loss in these areas.

**Conclusions:** The results suggest that depressed mood following a concussion may reflect an underlying pathophysiology consistent with a limbic-frontal model of depression. Given that depression is associated with considerable functional disability, this finding has important clinical implications for the management of individuals with a cerebral concussion.

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**Author Affiliations:** Montreal Neurological Institute (Mr Chen and Drs Petrides and Ptito) and Department of Psychology (Dr Petrides), McGill University, Montreal, Quebec, and Concussion Clinic NeuroRehabilitation Program, Toronto Rehabilitation Division of Neurosurgery, University of Toronto, Toronto, Ontario (Dr Johnston), Canada.

**M**ILD TRAUMATIC BRAIN injury and concussion account for as many as 90% of all cases of head injury.<sup>1</sup> After a cerebral concussion, individuals often report a cluster of symptoms referred to as postconcussive symptoms (PCS). In addition to somatic symptoms, such as headaches and fatigue, these include cognitive deficits (eg, problems with memory, concentration, planning, and organization) as well as psychiatric complications, such as anxiety, irritability, and depression.

Most studies on concussion have focused on the somatic and cognitive aspects, with the psychiatric dimension of PCS remain-

ing largely unexplored. The psychiatric issue is particularly relevant in sport concussion<sup>2</sup> because symptoms of depression in athletes with concussion have often been attributed to the loss of position on the team, lack of teammate support, poorly defined timeline to recovery, and the fact that this injury, being "invisible," raises issues of treatment compliance or malingering. An acknowledgment of the importance of affective symptoms associated with concussion injury and recovery was raised at the most recent International Conference on Concussion in Sport.<sup>3</sup> In addition, the anecdotal success of treatment with antidepressants in isolated sport concussion cases raises awareness of the im-

**Table 1. Demographic and Clinical Characteristics of Athletes With Concussion**

Characteristic	Mean (SD)			
	Control (n = 16)	Concussion, No Depression <sup>a</sup> (n = 16)	Concussion, Mild Depression <sup>a</sup> (n = 16)	Concussion, Moderate Depression <sup>a</sup> (n = 8)
Age, y	20 (1.2)	26 (5.6)	29 (6.7)	30 (7.4)
PCS score	6 (3.5)	13 (13.9)	27 (18.6)	58 (19.8)
BDI-II <sup>9</sup> score	1 (3.7)	5 (2.7)	14 (3.7)	26 (6.7)
No. of concussions	0.6 (0.5)	3.4 (1.8)	3.9 (1.5)	3.7 (1.5)
Time since injury, mo	NA	7.3 (9.6)	5.9 (6.3)	4.9 (4.7)

Abbreviations: BDI-II, Beck Depression Inventory II; NA, not applicable; PCS, postconcussion symptoms.

<sup>a</sup>No depression group, BDI-II score less than 10; minimal/mild depression group, BDI-II score, 10 to 19; and moderate depression group, BDI-II score, 20 to 29.

portance of the evaluation of symptoms of depression following concussion.

Previous functional imaging studies have suggested an association between prefrontal dysfunction and major depression.<sup>4-7</sup> Because the prefrontal cortex is often implicated following head injury, the question arises as to whether the symptoms of depression are reflecting a pathophysiological change due to the concussion. The present study was designed to examine neural responses associated with a working memory task in athletes with concussion who complained of symptoms of depression, athletes with concussion who did not report symptoms of depression, and noninjured control athletes. The primary objective was to understand the underlying neural mechanisms of depression symptoms expressed by athletes following a cerebral concussion.

## METHODS

### PARTICIPANTS

Fifty-six right-handed male athletes were studied: 40 with concussion and 16 healthy controls. The concussion group consisted of athletes involved in contact sports at recreational, amateur, and professional levels. They were referred to the McGill Sports Medicine Clinic for consultation related to their concussive injury from sports. Their concussions were, in general, observed and verified by the team medical personnel present during the game; the athletes then agreed to report to the research team.

Subjects in the control group were recruited from McGill varsity hockey and football teams. They were screened before the study to ensure that they had no neurological or psychiatric disorders and that they did not have a concussion in at least the 12 months preceding the study. A detailed description of the sample is provided in **Table 1**.

The severity of the PCS in each participant at the time of the study was assessed using a 21-item checklist adapted from the Postconcussive Symptom Scale–Revised.<sup>8</sup> The presence of symptoms of depression was evaluated using the Beck Depression Inventory II (BDI-II).<sup>9</sup> Athletes with concussion were subdivided according to Spreen and Strauss<sup>10</sup> into 3 groups based on their BDI-II score: (1) no depression symptom group, consisting of athletes with a BDI-II score ranging from 0 to 9, (2) mild depression symptom group, consisting of athletes with a BDI-II score ranging from 10 to 19, and (3) moderate depression symptom group, consisting of athletes with a BDI-II score ranging from 20 to 29.

None of the athletes had a history of mood disorder, required a referral to a psychiatrist, or were taking psychotropic medication at the time of the study. All subjects gave informed, written consent for their participation in the study, which was approved by the Research Ethics Board of the Montreal Neurological Institute and Hospital, McGill University.

### WORKING MEMORY TASK

An externally ordered working memory task using pseudo-words as stimuli (ie, experimental condition) and a control task (ie, baseline condition) were used for the functional magnetic resonance imaging (fMRI) studies. Briefly, the format of stimulus presentation, mode of response, and the timing of events were identical in both conditions, except that they differed in terms of working memory requirements. The working memory task was adapted from the Petrides externally ordered task,<sup>11,12</sup> which requires the subjects to keep track of the serial presentation of 4 items selected randomly from a set of 5 items and to make a decision as to whether the test item, presented after a short delay, was among the 4 previously presented items or whether it was the item not presented. The subjects made their response by pressing the appropriate mouse key. In the baseline control task condition, 1 item was presented 4 times successively followed by a short delay, after which 1 of 2 items associated with either a left or a right mouse button press was presented and the subjects had to make the appropriate response. The subjects learned prior to scanning which one of these 2 items was associated with a left mouse button press and which one, with a right button press. The baseline task was introduced to obtain baseline activation and to “subtract out” any activation related to the motor and perceptual components of the working memory task.

### IMAGING PROCEDURES

Scanning was carried out using a 1.5-T Siemens Sonata scanner (Siemens AG, Erlangen, Germany).

#### Functional

Each scanning session started with the acquisition of high-resolution (1-mm<sup>3</sup>), T1-weighted, 3-dimensional structural images for anatomical localization of the functional data. Changes in neural activity were then measured using blood oxygenation level–dependent (BOLD) fMRI, by means of a T2\*-weighted, gradient-echo echo planar imaging sequence (repetition time [TR], 3000 milliseconds; echo time [TE], 51 milliseconds; flip angle [FA], 90). A total of 120 acquisitions

were collected in each functional scan. Twenty oblique, contiguous slices covering the entire brain (7-mm thickness,  $-35^\circ$  relative to the anterior commissure–posterior commissure line, interleaved signal order) were taken during each acquisition. Each functional scan consisted of 6 alternating blocks (60 seconds each) of working memory and baseline conditions. All stimuli were presented via an LCD projector to a screen placed in front of the scanner, then to the subject via a mirror mounted on the head coil. The subjects' responses were recorded by a magnetic resonance imaging (MRI)–compatible mouse.

### Structural

All subjects underwent routine MRI examination, including axial T2-weighted turbo spin echo (TR, 3910 milliseconds; TE, 81 milliseconds; FA, 150) and axial fluid-attenuated inversion recovery (TR, 9000 milliseconds; TE, 66 milliseconds; FA, 180) sequences. These MRIs, as well as the T1-weighted, 3-dimensional gradient echo images acquired as part of the functional scans, were evaluated by an expert clinical neuroradiologist for obvious signs of axonal injury and/or abnormal signal intensity, size, and location in the brain.

### fMRI DATA PROCESSING AND ANALYSIS

Before statistical analyses, all frames in each functional scan were first realigned to the third frame in that run to correct transient head movements due to breathing and swallowing during data acquisition. The images were then spatially smoothed with a 6-mm full-width-at-half-maximum gaussian filter to increase the signal-to-noise ratio of the data and the tolerance of the subsequent analysis steps to residual motion in the scans and to minimize resampling artifacts. The motion-corrected data were analyzed statistically using *fmrstat*<sup>13</sup> (available at <http://www.math.mcgill.ca/keith/fmrstat>). The BOLD data were first converted to a percentage of the whole volume. Significant BOLD change percentages were determined at each voxel, based on a linear model with correlated errors. The mean parametric *t* maps were constructed for each individual by averaging functional data across scans using linear regression analyses. To obtain the average group *t* maps, all individual data were first normalized to the Montreal Neurological Institute template (MNI305) constructed from the average stereotaxic MRI of 305 normal subjects, then combined using a mixed-effects linear model.<sup>14</sup> The resulting *t* statistic images were thresholded using the minimum given by a Bonferroni correction and random field theory to correct for multiple comparisons. Each set of fMRI data was then coregistered to the corresponding anatomical MRI, which was corrected for intensity nonuniformity, and normalized to MNI305 standard space.

### VOXEL-BASED MORPHOMETRY ANALYSIS

Voxel-based morphometry was carried out using the T1-weighted images of each subject. The analysis steps included (1) nonuniformity correction<sup>15</sup> to remove variations in signal intensity related to radio-frequency inhomogeneity; (2) linear transformation of images into the standardized Montreal Neurological Institute 305 average template (MNI305) to normalize the images for between-subject differences in brain size and shape; (3) classification of brain tissue into white matter, gray matter, and cerebrospinal fluid using an automatic tissue-classification algorithm<sup>16</sup>; (4) blurring of the binary gray matter map extracted from the classified image using a gaussian smoothing kernel of 10 mm full width at half maximum. This step converts binary data into continuous data, which is necessary for statistical analysis. It also weighs the signal at each voxel according to the signal in neighboring voxels, thus re-

flecting the amount of gray matter within the smoothing kernel, and it reduces the effect of between-subject differences in the exact spatial location of gyri and sulci; and (5) voxelwise comparisons of group differences in gray matter concentration were performed using the *t* statistic. The significance of *t* statistics was determined by controlling the false-discovery rate using the entire gray matter as the search region (ie, exploratory approach). This yielded a *t* threshold = 3.5 at  $P < .05$ . The relationship between gray matter concentration and BDI-II scores in the concussed groups was examined using multiple regression analyses with age and PCS as confounding factors.

### STATISTICAL ANALYSIS

Analysis of variance was carried out on the demographic data. Analysis of covariance was used to compare performance on the working memory and control tasks, using age and PCS scores as covariates. Bonferroni correction was used for post hoc analysis. Finally, multiple regression analyses with BDI-II scores as the main predictor and age and PCS scores as confounding factors were carried out to examine the relationship between severity of symptoms of depression and fMRI BOLD signal change in each voxel of interest.

## RESULTS

Analysis of variance indicated significant group differences in PCS ( $F_{3,55} = 27.19$ ;  $P < .01$ ) and age ( $F_{3,55} = 6.18$ ;  $P < .01$ ). Post hoc tests showed that the control group had significantly fewer PCS than the mild ( $P < .01$ ) and moderate ( $P < .01$ ) depression symptom groups. There was no difference in PCS between the control and no depression symptom groups ( $P > .05$ ). Post hoc tests also indicated that subjects in the control group were significantly younger than those in the mild ( $P < .01$ ) and moderate ( $P < .01$ ) depression symptom groups but not significantly different from the no depression symptom group ( $P > .05$ ). Furthermore, no significant age difference was found between the concussed groups, and the concussed groups did not differ in terms of number of previous concussions ( $F_{2,39} = 2.70$ ;  $P > .05$ ) and time since injury ( $F_{2,39} = 0.15$ ;  $P > .05$ ). Because of the possible confounding effects of age and PCS, these factors were included in subsequent statistical analyses as covariates.

### BEHAVIORAL

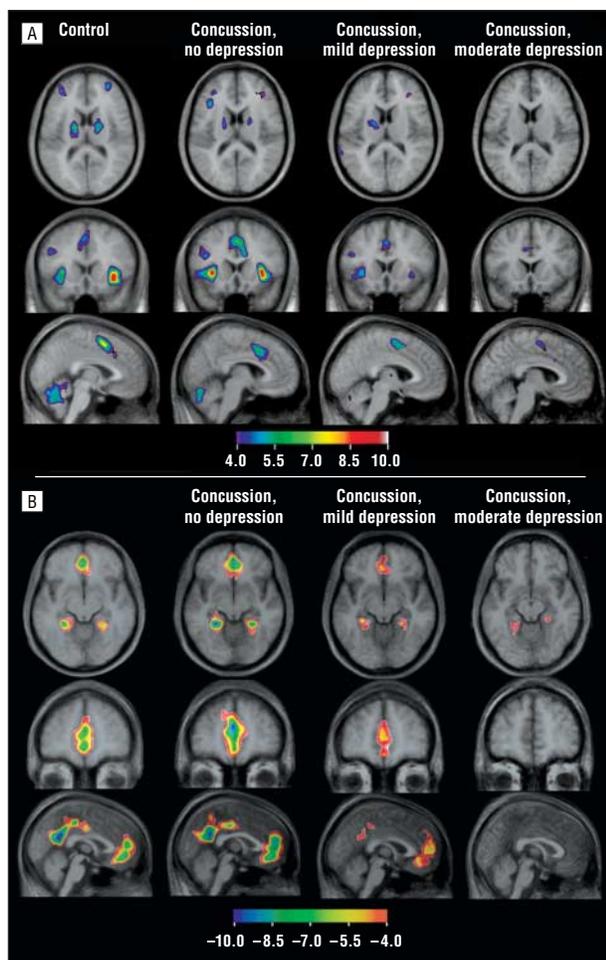
Analyses of covariance with age and PCS as covariates were performed on the accuracy (percentage correct) and speed (response speed in milliseconds) data from the working memory and control tasks collected during the fMRI session. There were no significant group differences in response accuracy (working memory,  $F_{3,55} = 1.08$ ;  $P > .05$ ; control task,  $F_{3,55} = 0.19$ ;  $P > .05$ ) and speed (working memory,  $F_{3,55} = 0.80$ ;  $P > .05$ ; control task,  $F_{3,55} = 0.37$ ;  $P > .05$ ) (**Table 2**). But as shown in Table 2, there was a trend for less accurate and slower performance in those athletes with concussion with symptoms of depression.

### FUNCTIONAL MRI

Whole-brain analysis was carried out to generate overall activation patterns for each group and the results are

**Table 2. Performance on the Working Memory and Control Tasks**

Task	Mean (SD)			
	Control (n = 16)	Concussion, No Depression (n = 16)	Concussion, Mild Depression (n = 16)	Concussion, Moderate Depression (n = 8)
Response accuracy, % correct				
Working memory	73 (10)	75 (13)	74 (13)	67 (8)
Control task	93 (8)	93 (9)	88 (10)	83 (12)
Response speed, ms				
Working memory	1161 (131)	1160 (115)	1139 (182)	1213 (197)
Control task	881 (111)	905 (127)	926 (253)	963 (213)



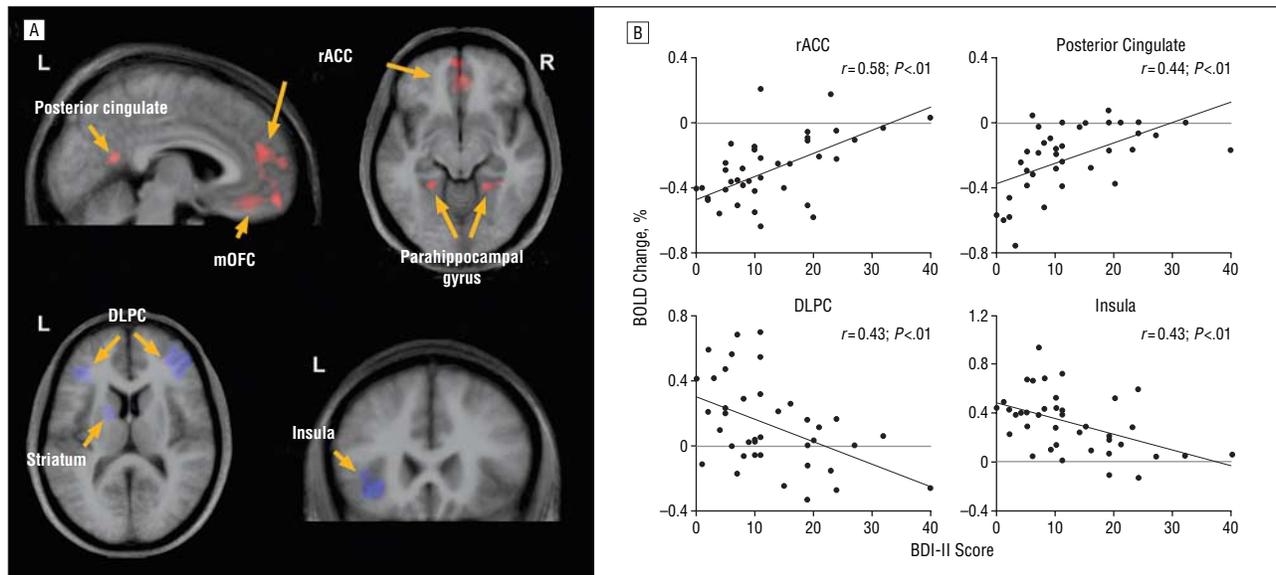
**Figure 1.** Results from functional magnetic resonance imaging study. Group average activation (A) and deactivation (B) t maps associated with the externally ordered task, superimposed on each group's average magnetic resonance image.

presented in **Figure 1**. The noninjured control group as well as the athletes with concussion who did not report symptoms of depression (BDI-II score < 10) exhibited the expected bilateral increase in fMRI signal in the dorsolateral prefrontal cortex (DLPFC), dorsal anterior cingulate cortex (dACC), insular cortex, striatum, and thalamus, consistent with our previous findings.<sup>11</sup> Athletes with concussion with mild depression symptoms showed attenuated task-related activity in these regions, with sig-

nificant BOLD changes detected only in the insular cortex (bilaterally), dACC, and left striatum. The moderate depression symptom group showed even more decreased activity in those regions, the only significant activation peak being in the dACC. In addition, examination of the negative peaks from whole-brain analysis (Figure 1B) revealed that the control and no depression symptom concussed groups showed similar deactivation patterns in the rostral anterior cingulate cortex (rACC), posterior cingulate cortex, medial orbitofrontal cortex (mOFC), and parahippocampal gyrus (bilateral). In contrast, the mild depression symptom group showed less deactivation in these areas, and this attenuation was even more pronounced in those athletes with moderate depression symptoms.

To examine further the relationship between brain activations and the severity of depression symptoms, voxel-wise regression analyses were performed on the entire fMRI time series using scores on the BDI-II as a predictor, with age and PCS as covariates. This allowed identification of the cerebral regions where changes in BOLD signals were modulated by the scores on the BDI-II. After removing the effect of age and PCS, the magnitude of fMRI BOLD signals in the rACC, mOFC, posterior cingulate, and left and right parahippocampal gyri was found to be positively correlated with BDI-II scores. Furthermore, both the right and left DLPFC, left insula, and left striatum were found to be negatively correlated with the severity of depression symptoms as assessed with the BDI-II (**Figure 2**).

As expected, athletes with a higher rating on the PCS Scale usually scored higher on the BDI-II (**Figure 3A**). This, however, was not always the case; a subgroup of athletes with concussion (n=6) had significant PCS complaints but normal scores on the BDI-II. As shown in Figure 3B, C, and D, this group of athletes showed reduced task-related cerebral activations in the right DLPFC compared with the controls, as seen in those with symptoms of depression. However, there was a crucial difference in the rACC and the mOFC between the 2 groups with high PCS scores with and without depression symptoms. In these cerebral areas, athletes with high PCS but normal BDI-II scores showed similar negative BOLD signal changes as the control group. In contrast, these negative BOLD responses were significantly attenuated in those athletes with high PCS scores and symptoms of depression. This difference can be illustrated further by contrasting the BOLD responses of this group with those reporting mild depression



**Figure 2.** Relationship between Beck Depression Inventory II<sup>9</sup> (BDI-II) scores and blood oxygenation level–dependent (BOLD) signal changes. A and B, The higher the scores, the lower the percentage of BOLD signal changes in the right (R) and left (L) dorsolateral prefrontal cortex (DLPC), left striatum, and left insula (shown in blue). In addition, the higher the BDI-II scores, the less the negative percentage of BOLD signal changes in the rostral anterior (rACC) and posterior cingulate, medial orbitofrontal cortex (mOFC), and left and right parahippocampal gyri (in red).

symptoms. Both groups had similar PCS scores (25 vs 27) and showed reduced activations in the right DLPC when compared with the control subjects. However, only those with symptoms of depression had significantly fewer task-related BOLD decreases in the rACC and the mOFC, and they showed greater signal reduction in the right DLPC compared with the no depression symptom but high PCS score group.

#### STRUCTURAL MRI AND VOXEL-BASED MORPHOMETRY

The MRIs were evaluated by a clinical neuroradiologist and were all found to be normal.

Group comparisons of gray matter concentration are shown in **Figure 4**. Differences in gray matter concentration were noted between the control and mild depression symptom group in the rACC, left DLPC, left insula, and left parahippocampal gyrus. The moderate depression symptom group also showed less gray matter density in these areas in addition to reduced gray matter concentration in the right DLPC and right insula. Finally, differences in gray matter density were found between the control and no depression symptom athletes with concussion in the left and right insula.

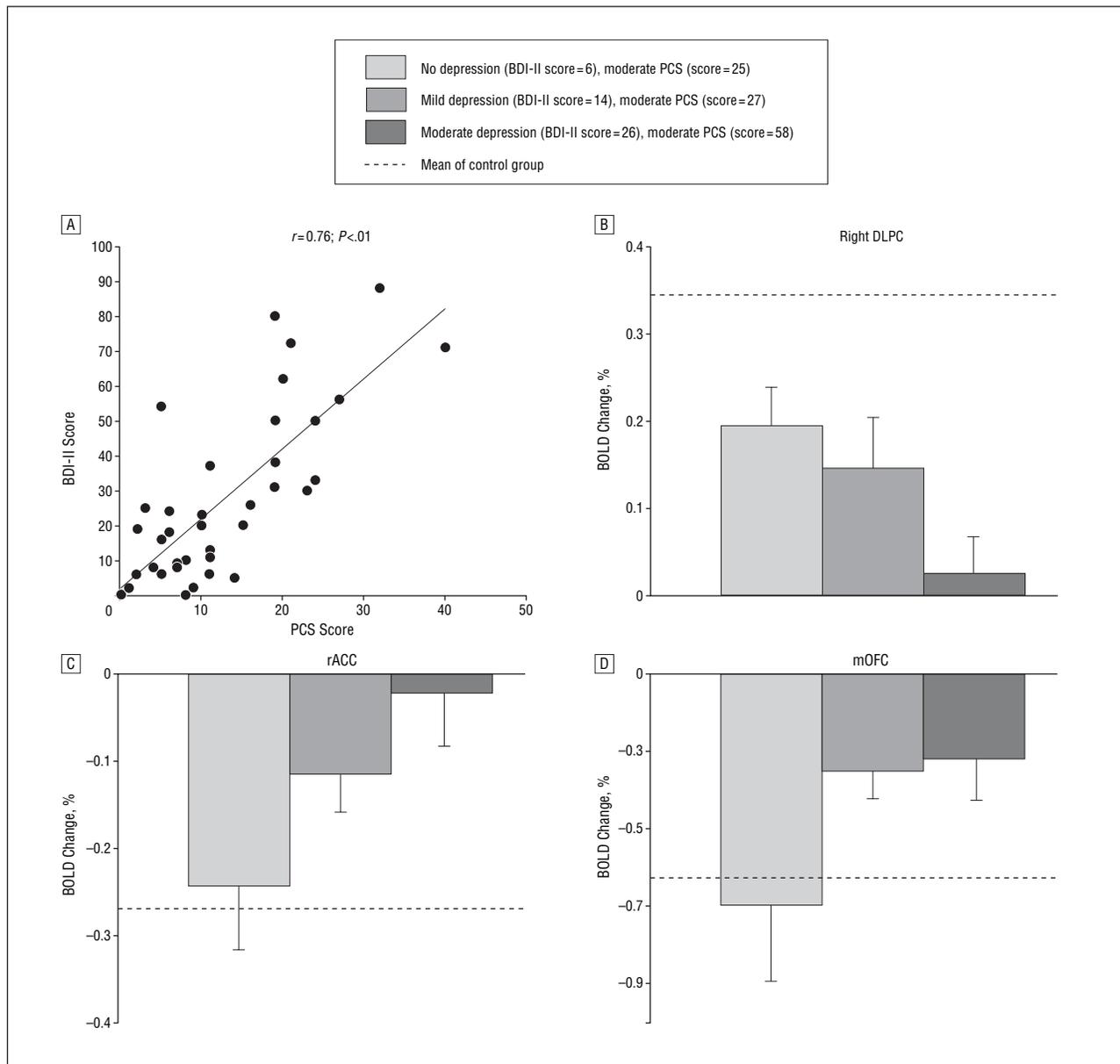
Multiple regression analysis controlling for age and PCS revealed a significant effect of BDI-II scores on gray matter density in the rACC (**Figure 5**). Specifically, an increase in the severity of depression symptoms was associated with further reduction of gray matter in this area.

#### COMMENT

Depressed mood is frequently reported by individuals who have sustained a cerebral concussion,<sup>17,18</sup> but little is known about the neural substrate of this alteration in mood state. Herein, we report differences in neural activity in athletes

with concussion and symptoms of depression, athletes with concussion without symptoms of depression, and normal control subjects. Functional MRI results showed that those athletes with concussion and mild symptoms of depression had fewer task-related BOLD signal increases in the prefrontal region and striatum, and this reduced activation was even more pronounced in those with moderate symptoms of depression. Similar findings have been reported by McAllister and colleagues<sup>19-21</sup> in a series of fMRI studies using n-back tasks. In these studies, patients with mild head injury showed less task-related brain activity than the control group when comparing 1-back vs 0-back conditions. Interestingly, patients with head injury showed a greater increase in brain activation when working memory demand increased (ie, 2-back vs 1-back) relative to the control subjects. In the present study, working memory tasks that required active monitoring and manipulation of information activated the DLPC, striatum, and thalamus in healthy subjects. These areas are known to be involved in the performance of such tasks. Dopaminergic input into the striatum and frontal cortex plays a major regulatory role in neural activity in these areas and there is considerable evidence pointing to the role of the dopaminergic system in depression. These include reports of reduction of the dopamine level in patients with depression<sup>22,23</sup> and the antidepressant effects of selective dopaminergic agents such as amineptine<sup>24,25</sup> and pramipexole dihydrochloride.<sup>26,27</sup> Thus, our finding may indicate an abnormal dopaminergic function within this cortico-striato-thalamic system in athletes with concussion with symptoms of depression. This possibility is supported by studies that demonstrate antidepressant effects of repetitive transcranial magnetic stimulation in the DLPC,<sup>28</sup> presumably by inducing dopamine release in the striatum.<sup>29</sup>

We also found that athletes with concussion with symptoms of depression had different neural responses in the parahippocampal gyrus, mOFC, rACC, and pos-

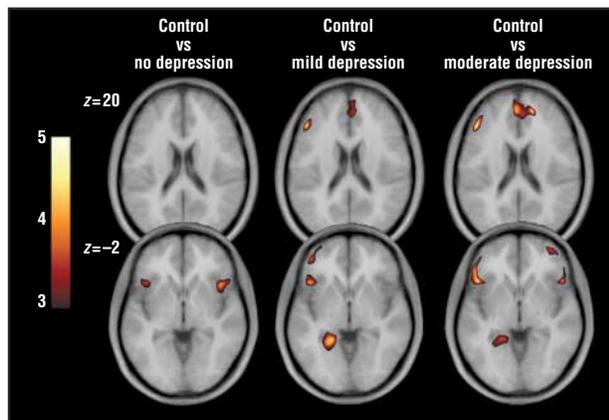


**Figure 3.** Relationship between postconcussive symptoms (PCS) and depression. A, Scores on the PCS Scale correlated significantly with the Beck Depression Inventory II<sup>9</sup> (BDI-II) scores. B, Blood oxygenation level–dependent (BOLD) signal attenuation in the right dorsolateral prefrontal cortex (DLPC) occurred in athletes with concussion both with and without depression. Athletes with PCS and depression showed more signal reduction than athletes with PCS alone. C and D, Athletes with depression showed smaller negative BOLD signals in the rostral anterior cingulate cortex (rACC) (C) and medial orbitofrontal cortex (mOFC) (D). This pattern was not seen in athletes with concussion and PCS without depression.

terior cingulate cortex. In these regions, athletes with depression symptoms showed less reduction in activity relative to the control group. This attenuation was positively correlated with the severity of symptoms of depression expressed by these athletes. Functional imaging studies with healthy subjects have frequently shown a decrease in activities in these brain regions when performing working memory and other cognitive tasks that require attention.<sup>30-32</sup> Furthermore, reduction of neural activity in these areas appears to be inversely correlated with activity in the DLPC,<sup>33,34</sup> with the degree of reduction increasing with the demands of the task.<sup>31,35</sup> Thus, it is necessary to consider the role of task difficulty in the activity reported herein. Paus et al<sup>36</sup> reviewed 107 blood-flow activation

studies and concluded that increased activity in the anterior cingulate is likely to occur in the more difficult tasks. It can therefore be argued that the increased BOLD signal in athletes with depression symptoms may simply reflect greater cognitive demand. This is unlikely, however, because the athletes with symptoms of depression did not show a statistically significant difference in performance. Thus, task difficulty may be excluded as a factor responsible for the level of activity in the anterior cingulate region. A more plausible explanation why athletes with symptoms of depression showed less reduction in activity relative to the control group during the performance of the working memory task (ie, the normal response in healthy subjects) is that in these athletes ac-

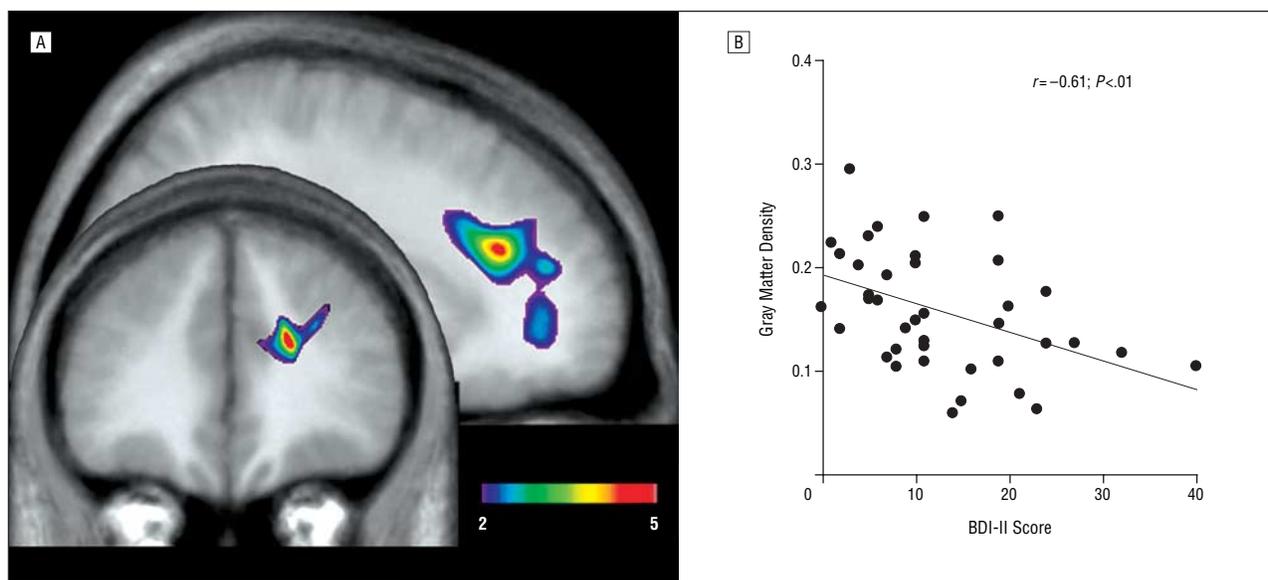
tivity in the rACC and mOFC may have been increased relative to the normal subjects. Elevated neural activities in these regions have been associated with experimentally induced anxiety and sadness in normal subjects and in patients with major depressive disorder (MDD).<sup>37-39</sup> Positron emission tomographic studies on major depression have also reported increased metabolism in the rACC,<sup>40,41</sup> reversible with antidepressant medication.<sup>40</sup> In a study using fMRI, Rose et al<sup>42</sup> reported that patients with MDD had relatively higher fMRI signals in the mOFC and rACC when performing an n-back working memory task than normal control subjects. Although none of the athletes with symptoms of depression reported herein were clinically diagnosed with MDD, our results are strikingly similar to existing functional neuroimaging findings in major depression and are consistent with a limbic-frontal model of depression.<sup>43,44</sup> They suggest that symptoms of depression following head trauma may share the same underlying neural mechanism as MDD.



**Figure 4.** Voxel-based morphometry results for regions showing less gray matter density in concussed groups vs normal controls. All concussed groups showed reduced gray matter concentration in the insula cortex. Those athletes with depression showed additional gray matter loss in the left dorsolateral prefrontal cortex, anterior cingulate, and left parahippocampal gyrus.

The presence of abnormal neural activity in athletes with concussion with symptoms of depression demonstrated by our fMRI data is in keeping with the results of our voxel-based morphometric study. We found that athletes with concussion with depression symptoms showed reduced gray matter density in brain regions necessary to carry out the working memory task. The concussed groups in the present study consisted of athletes who sustained a cerebral concussion on average 5 to 7 months previously and who continued to experience a variable degree of PCS. Other voxel-based morphometric studies have shown both gray and white matter losses in head trauma populations,<sup>45,46</sup> and our findings lend further support to the existence of an organic basis to persistent PCS.<sup>47</sup> As shown in Figure 4 and Figure 5, gray matter loss was also noted in the no depression symptom, concussed group in the insular cortex bilaterally. However, only those athletes with concussion with symptoms of depression displayed further gray matter reduction in the medial frontal and temporal regions, and the reduced gray matter volume in the rACC was negatively correlated with the severity of depression symptoms. These findings are consistent with the roles of these cerebral areas in affective disorders; they are also in accordance with findings of hypometabolism in the left DLPC in patients with depression<sup>48,49</sup> and with the antidepressant effects of repetitive transcranial magnetic stimulation applied to this cortical region.<sup>50-52</sup>

Studies that examined outcomes following traumatic brain injury have reported a prevalence of depression a few years after the injury.<sup>53-55</sup> The question arises as to whether the symptoms of depression represent an emotional reaction to the trauma and to the ongoing PCS or whether there is an underlying pathological nature. Levin et al<sup>56</sup> found that patients with mild brain injury with documented lesions on computed tomographic scan were at greater risk for major depressive episodes 3 months postinjury. Recently, Jorge et al<sup>17</sup> reported that depression following head trauma was equally frequent among



**Figure 5.** Voxelwise regression analysis showed an inverse relationship between the severity of depression measured by the Beck Depression Inventory II<sup>9</sup> (BDI-II) and gray matter density in the anterior cingulate.

mild, moderate, and severe cases 1 year postinjury. In addition to poorer functional outcome, patients with head injury with depression also showed, as we did, significantly reduced gray matter volumes in the left prefrontal cortex. The athletes with concussion in the present study were young individuals without a medical history of mood disorder. It is therefore not likely that our concussed sample had a preexisting reduction in gray matter density that led to their vulnerability to develop depressive disorder following concussion. In addition, we also found reduced gray matter concentration in the concussed but no depression symptom group. Thus, the structural changes reported herein were likely due to concussion, and the symptoms of depression were probably the result of a pathological state in the medial prefrontal region caused by the trauma. These results, together with findings from previous studies, point to an underlying pathological nature to the symptoms of depression following brain trauma. Our data also indicate that the presence of PCS with depression symptoms is associated with a greater reduction in cerebral activity in the DLPC than with PCS alone and are consistent with reports of greater disability and poorer outcome in patients with head trauma with depression.<sup>57</sup>

Some potential limitations of the present study merit consideration. First, our study focused primarily on complex concussions (ie, with persistent PCS) in young male athletes. This sampling limits the generalizability of our findings to the athlete with concussion and head injury populations at large. For instance, studies have repeatedly found sex differences in depression; hence, our finding may not apply to a female population. Furthermore, the athletes with concussion in our study represent the “complex” concussion subtype defined by the new concussion classification introduced by the International Conference on Concussion in Sports.<sup>3</sup> Thus, our finding may not be applicable to the “simple” concussion subtype in which symptoms disappear within days and symptoms of depression experienced during this limited period are likely to be related to exogenous factors (eg, reaction to trauma, missing play) rather than endogenous factors (eg, brain lesion, altered physiology). Also, our results may not be representative of more severe forms of head injury in which lesions are usually visible by conventional morphological imaging such as computed tomography and MRI, and the pathological changes following such injury may differ from those described herein. Finally, we did not test a control group with symptoms of depression and no concussion. Because we found that athletes with concussion with symptoms of depression showed BOLD response patterns consistent with functional neuroimaging findings in clinical depression, we suggest that they may share the same underlying pathological nature in the medial prefrontal region. This conclusion would be strengthened if we can demonstrate the same activation pattern between athletes with concussion with depression symptoms and athletes without concussion with depression.

Investigations on the long-term consequences of head injury have pointed to a link between a history of brain injury and an increase in the likelihood of developing major depression later in life.<sup>58,59</sup> Given that depression is asso-

ciated with significant functional deficits, early identification of the nature of depression symptoms following head trauma (psychological vs pathological) has important implications for early intervention and successful outcome.

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**Correspondence:** Alain Ptito, PhD, Neuropsychology/Cognitive Neuroscience Unit, Montreal Neurological Institute, 3801 University St, Montreal, QC H3A 2B4, Canada (alain.ptito@mcgill.ca).

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