Functional Brain Abnormalities Are Related to Clinical Recovery and Time to Return to Play in Athletes

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Functional Magnetic Resonance Imaging in Sports-Related Concussion:
Cerebral Blood Flow Abnormalities Predict Time to Return to Play

ABSTRACT:

OBJECTIVE: The relationship between athlete report of symptoms, neurophysiological activation and neuropsychological functioning is investigated in a sample of high school athletes.

METHODS: All athletes were evaluated using functional Magnetic Resonance Imaging (fMRI), a computer-based battery of neurocognitive tests and a subjective symptom scale. Athletes were evaluated within approximately one week of injury and again following clinical recovery using all assessment modalities.

RESULTS: This study found that abnormal fMRI results during the first week of recovery predicted clinical recovery. As a group, athletes who demonstrated hyperactivation on fMRI scans at the time of their first fMRI scan demonstrated a more prolonged clinical recovery than did athletes who did not demonstrate hyperactivation at the time of their first fMRI scan.

CONCLUSIONS: These results demonstrate the relationship between neurophysiological, neuropsychological and subjective symptom data in a relatively large sample composed primarily of concussed high school athletes. fMRI represents an important evolving technology for the understanding of brain recovery following concussion and may help shape return to play guidelines in the future.

KEY WORDS: Concussion, ImPACT, Functional Magnetic Resonance Imaging, Neuropsychological testing, Sport injury, Traumatic Brain Injury
Approximately three hundred thousand of the 1.5 million head injuries reported each year in the United States are sports-related, and approximately 9% of these require hospitalization. By far, the majority of these injuries occur in high school age or younger athletes. Over the past decade, strategies for the medical management of concussion have undergone significant transformation as scientific knowledge has accumulated to suggest that mismanagement of the injury can lead to serious consequences, particularly in the younger athlete.

Currently, return to play decisions following concussion are based on clinical recovery determined by player report of symptoms and cognitive status. Recent international concussion management guidelines have emphasized evaluation of player symptoms and neuropsychological test results as “cornerstones” of the evaluation process. The use of structural brain imaging procedures such as CT and MRI scanning, although extremely valuable in detecting more severe brain injury, has not been regarded as providing useful information regarding recovery from concussion.

While our understanding of the clinical recovery process following concussion has improved dramatically over the past decade, relatively few studies have sought to investigate neurophysiological recovery following concussion. Very recently, functional Magnetic Resonance Imaging (fMRI) paradigms have allowed researchers to evaluate changes in brain physiology in human subjects in vivo. However, to date, only a handful of studies have examined neurophysiological functioning as a result of head trauma and the studies that have been published have utilized very small sample sizes (typically fewer than ten subjects). The dearth of studies in this area is no doubt due to the fact that studies of this nature are very expensive and the equipment necessary to undertake this research is not readily available outside of a handful of academic medical centers.

This study was designed to evaluate the relationships between a neurophysiological measure of CNS functioning, clinical symptoms of concussion, neuropsychological performance and recovery in a relatively large sample of high school and collegiate athletes. Using data derived from an fMRI study acquired within one week of concussion, we demonstrate that the functioning of a network of brain regions is significantly associated with both the severity of concussion and the time to recovery.

Definitions of Concussion
A concussion has most recently been defined as a “complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces” (pg. 7), which is most often transient with symptoms frequently including amnesia, confusion, headache, dizziness and fatigue; there are typically no “hard” signs of neurological abnormality (e.g., motor or sensory loss). Structural brain imaging studies such as computer assisted tomography and magnetic resonance imaging (MRI) scans are almost always clinically negative, limiting the utility of these procedures in diagnosing injury and in understanding the underlying pathophysiology. Alterations in local brain function occur over a matter of minutes and hours following concussion-like injuries in animal models. However, there are relatively little data regarding the resolution of functional brain changes in humans, although clinical symptoms usually resolve within several weeks of injury.

In an initial study designed to evaluate functional brain abnormalities in a group of
traumatically brain injured non-athletes, McAllister et al.\textsuperscript{25} found a pattern of hyperactivation in frontal brain areas when the patients were exposed to a working memory task (N-back). Increases in brain activation were linked to increasing memory load. In other words, brain activation occurred with increasing difficulty on the memory task. In a study that evaluated concussed athletes, Jantzen et al.\textsuperscript{16} examined fMRI data in four collegiate football players within one week of injury. These athlete’s fMRI results were then compared to baseline fMRI studies and to a group of four subjects who composed a control group. When compared to control subjects, concussed players showed marked increases in amplitude and extent of BOLD (blood oxygen level dependent) activity during a finger sequencing task. In the only other published study that employed athletes, Johnston and colleagues\textsuperscript{5} found changes in brain metabolism that were also linked to performance on a series of memory tasks. Importantly, this study found a significant correlation between brain activity, as measured by fMRI and athlete report of symptoms. Although these initial studies have yielded exciting initial data, none have involved the use of acutely concussed subjects nor did they evaluate subjects throughout the recovery period. Furthermore, no studies to date have utilized younger, high school aged athletes.

\section*{METHODS}

\section*{Subjects}

This study was approved by the Institutional Review Board of the University of Pittsburgh prior to the recruitment of subjects. Subjects were 28 concussed patients and 13 age-matched controls. Athletes were between the ages of 13 and 24 years (Mean= 16.6, SD = 2.4), with a mean educational attainment of 10.4 years (SD = 2.2). The concussed athletes were recruited through the Center for Sports Medicine at the University of Pittsburgh Medical Center, and were referred by certified athletic trainers and team physicians who were present at the time of the injury. The diagnosis of concussion was diagnosed based on the criteria set forth by the recent deliberations of the Vienna and Prague Concussion in Sport (CIS) group\textsuperscript{2,27}. This definition is relatively broad and defines concussion as a “complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces.” Athletes were diagnosed with a concussion if 1) there were any observable changes in mental status or consciousness following injury, 2) there was a documented loss of consciousness or amnesia on the field and/or 3) any signs/symptoms emerged following a collision involving the head or body. The specific signs and symptoms of concussion are listed in Table 1.

Concussed athletes were identified and evaluated on the field or sideline by team medical staff, then underwent an initial post-injury clinical evaluation at the University of Pittsburgh Center for Sports Medicine. Injured athletes were invited to participate if they met age criteria (13 to 25 years), had sustained a concussion due to sport participation, reported symptoms of concussion, and demonstrated evidence of cognitive dysfunction\textsuperscript{24} on the ImPACT test battery following injury. Athletes who had at least one abnormal ImPACT composite score on the ImPACT test battery or who reported post-concussive symptoms were given the opportunity to participate in the study. Abnormal ImPACT performance was determined by below baseline test performance if the athlete had previously completed a pre-injury neuropsychological baseline. If the athlete had not previously completed baseline testing, ImPACT scores were compared to
normative values for the athlete’s age and gender reference group. In accordance to recent international guidelines, athletes were considered to be symptomatic if they reported symptoms such as headache, dizziness, excessive fatigue or sleepiness; either at rest or following physical or cognitive exertion (see Table 1 for a complete listing of symptoms). Athletes were excluded from the study based on the following factors: 1) a current psychiatric illness; 2) the existence of attention deficit disorder (ADD) or a diagnosed learning disability; 3) a history of seizures, meningitis or other neurological disorder; 4) left-handedness; 5) the current use of psychoactive medications such as anti-depressants, stimulants or anxiolytics 6) braces or other dental appliances that might distort the fMRI imaging; and 7) the existence of any non-removable ferromagnetic material in their bodies. Control subjects were student-athletes who were recruited through advertisement and informational sessions throughout area high schools and colleges, and had to meet age requirements and pass exclusionary criteria described above. All participants were carefully screened by fMRI research center medical staff to ensure safe participation in the study.

Protocol and Outcome Measures

Many but not all athletes participating in this study had completed pre-injury (baseline) testing on ImPACT as part of their high school’s concussion management program. When available, athletes’ baselines were used to provide information about pre-injury cognitive functioning to assist in determination of recovery. Regardless, of whether baseline testing had been completed, all concussed athletes evaluated in the UPMC clinic completed the ImPACT test battery which consists of a fully computerized, self-administered assessment of reaction time, visuomotor processing, visual memory, and verbal memory. The ImPACT test battery has previously been validated and has been utilized extensively in both amateur and professional athlete groups. Past psychometric studies of ImPACT have also found it to be stable across two assessment periods in non-injured athletes. In addition to the neurocognitive indices, ImPACT also contains the Post-Concussion Symptom Scale (PCS), which provides an index of self-reported symptoms. Performance on ImPACT has been shown to be significantly poorer among individuals with concussion relative to non-concussed controls, and changes in ImPACT are highly correlated with cognitive and non-cognitive symptom recovery.

Concussed athletes were reevaluated on approximately a weekly basis using ImPACT until all symptoms had resolved following vigorous physical exertion, and cognitive functions were within normative limits and/or equivalent to the athlete’s own baseline. Our goal in utilizing this protocol was to perform fMRI evaluations as well as neuropsychological and symptom evaluations under two conditions: 1) when the athlete was recently concussed and had clinical indicators of injury and; 2) again when the athlete was “normal” with regard to both self-reported symptoms and neuropsychological test performance as measured by ImPACT. If the athlete developed more a more chronic post-concussive disorder and did not return to normal symptom and/or neuropsychological levels within six weeks, they underwent the second fMRI scan and ImPACT evaluation and their involvement in the research project was terminated. However, we did continue to provide clinical care for these athletes. Non-concussed control subjects were retested on a schedule such that their second evaluation occurred at approximately the mean
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interval for the concussed patients, and not earlier than one week following their initial evaluation.

MRI Scanning and fMRI Analysis

All subjects were scanned in a GE 3.0T system. Following the acquisition of a 3-D volumetric spoiled gradient echo MRI scan (TR = 25, TE = 5, slices = 1.5 mm thick, 0 mm gap, 40° angle, FOV = 24x18) and a T1-weighted in plane image (used for alignment of fMRI to AC-PC line) (TR = 350, TE = 20, slices = 3.2 mm, np gap, FOV = 20), subjects completed the fMRI working memory paradigm.

The fMRI protocol used the N-back task (see Owen, et al, for review). N-back is a standard measure of short-term or working memory involving visual-verbal encoding and recognition. The subjects were shown a series of upper- and lower-case letters on a screen while lying supine on a bench inside the bore of the magnet. Following the presentation of each letter, they were required to indicate whether each letter was a target or non-target letter by pressing a button. Specifically, their task was simply to respond to a target letter by pressing the “Yes” button with their right index finger when the letter “X” was presented (either in upper or lower case) and the “No” button with their right middle finger for all other letters. For the 1-back condition, subjects pressed a button indicating the presence of a target letter any time the letter on the screen was exactly the same as the one that had presented on the immediately preceding trial (regardless of case) and “No” for any other condition. For the 2-back condition, a “Yes” response required that the letter on the screen be the same as the one that had been presented two trials previously. There were four repetitions of each of the three conditions in twelve 63-second scanning blocks. Reverse spiral sequences (TR=1500, TE = 26, flip angle = 60, slices = 3.2 mm, no gap, 64x64, FOV = 20) were used to measure the BOLD response.

fMRI Data Analysis

First, fMRI data were transferred off-line for processing. 3-D head motion was estimated and corrected using FIASCO. A t-score voxel-level map of the difference in each subject’s BOLD response between the 2-back and the 0-back conditions was constructed for each subject at both sessions (acute injury and recovery/follow-up for concussed athletes; Time 1 and Time 2 for controls). These t-maps were co-registered to the T1-weighted in plane images using FIASCO and then transformed into standard stereotaxic space using AFNI. Stouffer’s method was then used to combine the individuals in each group for each session. These combined maps were used to select points of interest for further analysis.

Twenty-eight athletes who had sustained sports related concussion were studied twice - once shortly after concussion, and again after clinical recovery (33.3 ± 33.8 days). Thirteen control subjects were tested twice at time intervals similar to those for the group of concussed subjects as a whole. Data was not selected for analysis and study inclusion if structural or functional images were unusable due to uncorrectable head motion or scanner malfunction.

RESULTS

Table 2 presents the neuropsychological test data for the concussed and control subjects across the two time points (post-injury and recovery for concussed athletes; Time1 and Time 2 for controls). Concussed athletes demonstrated significantly poorer performance on ImPACT relative
to non-concussed control subjects at the time 1 assessment. Concussed athletes demonstrated statistically significant changes in ImPACT composite test scores from the time of their initial post-injury assessment to the time of the recovery assessment. Cognitive functioning as measured by the ImPACT battery improved significantly over time, and was not significantly different from controls and time 2, suggesting that they had recovered from a neuropsychological perspective. These changes were evident on all ImPACT composite measures as well as on the self-report symptom inventory and appear to reflect injury-related changes.

To assess changes in brain physiology with increasing difficulty of memory task, brain regional activation during the 2-back verbal memory task with that seen in the 0-back visuomotor control condition (See Figure 1). The areas of significant activation were typical of those observed in other studies using this activation paradigm \(^{29}\). In order to identify the patterns of regional activation reflecting different networks of functional association, the z-scores from the peak voxels within each region were entered into a Principal Components Analysis (PCA) with Varimax rotation. This analysis identified three components, or networks of inter-connected brains regions. Network 1 included the middle and inferior frontal cortex (colored green in Figure 1); Network 2 included the medial frontal and superior temporal gyri (colored red), and Network 3, the posterior parietal cortex, bilaterally (colored blue).

In order to determine the relative contributions of these three networks to the symptoms of concussion, and to the recovery from the injury, composite scores were created for each of the three networks reflecting the overall change in activation from the baseline condition to the 2-back condition. The associations between these variables and other clinical indicators were then analyzed using bivariate and multivariate regression models. Figure 2a shows that the circuit involving the posterior parietal cortex was significantly correlated with both cognitive (e.g., reports of drowsiness, fatigue, difficulty concentrating, memory problems) \((r = -.49, p < .05)\) and somatic (e.g., blurred vision, headache, photophobia) \((r = -.46, p < .05)\) symptomatology following concussion; with higher symptom severity, the activation of this circuit was lower. Activity in the posterior parietal circuit was also associated with a delayed memory index (calculated from the ImPACT computerized neuropsychological screening tool and consisting of delayed recall of verbal and visual material after a twenty minute period of time) among concussed athletes \((r = .35, p < .05)\) but not controls \((r = .28, p < .05)\) (See Figure 2b). Thus, this circuit is apparently associated with both neuropsychological and non-cognitive consequences of sports-related concussion. Furthermore, the extent of hyperactivation in this region was significantly associated with the decrease in symptomatology between baseline and recovery for the cognitive \((r = .58, p < .005)\) and somatic \((r = .47, p < .04)\) symptoms.

Correlational analysis revealed that the activity in Network 1, and specifically in midline BA6, was associated with time to return to play. To investigate this relationship, we divided the group of concussed athletes into three, based on level of activation in BA6. Those athletes with the highest level of activation, took significantly longer to return to play than did the athletes in the lower two tertiles of activation (Beta=.486, p=.018). Next, a Survival Analysis was conducted to evaluate the time between entry into a study and return of the athlete to normal status \(^{12}\). This analysis (see Figure 3) revealed that the athletes with the highest degree of activation took, on average, 25.4 days longer to return to play than did the other athletes \((t= 2.50, p=.024)\). Therefore, athletes with the higher degree of activation took approximately twice as long to recover compared to the group who did not demonstrate this initial hyperactivation.
DISCUSSION

Progress in understanding the brain mechanisms that underlie cerebral concussion has been relatively slow. The limitation is no doubt due, in part, to the lack of readily available non-invasive technology that allows for the direct measurement of changes in brain function following injury. Past studies of recovery from concussion have been limited to the measurement of subjective symptoms or neuropsychological test results.

This study was designed to identify the underlying substrata of concussion and to evaluate brain regions that might be selectively vulnerable to the effects of sports-related concussion. This was accomplished by studying differences in patterns of regional brain activation between concussed subjects and age and education appropriate controls. The results of this study suggest residual post-concussive complaints are associated with regional changes in brain activation and that initial changes in brain physiology are linked to changes in neuropsychological test results, self-reported symptoms and ultimately to clinical recovery.

Traditionally, return to play decisions have been made based on concussion “guidelines”, which have based primarily on the opinion of panels of experts rather than on empirical research. More recently, these guidelines have been replaced by a more individualized approach to management based on the athlete’s recovery as measured by symptom status and neuropsychological test results. However, at the current time, the relationship of symptoms and neuropsychological test results to underlying changes in brain physiology is rudimentary at best.

The findings of this study have several implications for understanding the recovery process following sports-related concussion. First, we have confirmed previous observations that there are neurophysiological abnormalities following even mild sports-related concussion that can be measured. We have further identified three networks of brain regions in which there was alteration in activity during the performance of a short-term memory task during the acute post-concussion recovery period. Specifically, changes in activity in the network involving the dorsal attentional system were associated with both cognitive functions and somatic symptomatology. Furthermore, the activity in this region was also associated with the degree of symptomatology after recovery.

Although the results of this study must be considered as preliminary, continued projects designed to evaluate multiple parameters of recovery (e.g. neurophysiological, neuropsychological, athlete report of symptoms) may eventually help to structure return to play guidelines that are based on physiological recovery as well as on clinical recovery. Recent research has suggested that recovery as measured by neuropsychological testing and recovery as measured by self-report of symptoms may not always coincide. In other words, the athletes may report being symptom free but demonstrate decrements on neuropsychological testing. Conversely, some athletes may perform normally on neuropsychological testing but continue to complain of symptoms such as headache, dizziness and fatigue. For instance, Echemendia et al. found that a sample of collegiate athletes continued to exhibit neuropsychological deficits after they were asymptomatic with regard to non-cognitive symptoms. More recently, van Kampen et al. found that a significant number of high school and collegiate athletes who reported no symptoms following injury performed abnormally on a computer-based neurocognitive test.
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The utilization of neurocognitive testing in this group in addition to player report of symptoms resulted in a 28% increase in the identification of concussed athletes. The specific reason or reasons for this clinical dissociation between self-reported symptoms and neurocognitive test results is likely to be complicated and multi-faceted. In our opinion, the utilization of functional brain imaging techniques such as fMRI may provide the basis for understanding the clinical recovery process and how to best measure recovery.

We believe that one of the most important findings of this study is the documentation of the linkage in changes in brain activation to clinical recovery, as measured by resolution of symptoms and by improvement of neuropsychological testing results. Neuropsychological testing has become an increasingly useful tool in the management of sports related concussion over the past decade, but has not been without its critics. It is our view that studies that establish a direct link between brain physiology and neuropsychological test results go a long way towards demonstrating the utility of neuropsychological testing as a proxy for direct measurement of brain processes following concussion. An added benefit of fMRI research is the potential use of this technology to develop neuropsychological test instruments in vivo that are sensitive to dysfunction in specific brain regions and specific cognitive systems. Using fMRI technology, test developers are able to evaluate the sensitivity of individual tests to measure specific aspects of brain function and to assess changes in activation that may occur with brain injury.

Currently, fMRI remains primarily a research tool and it is unlikely that it will be widely utilized in the near future to make clinical decisions. However, we do believe that this non-invasive physiological measure will be increasingly helpful in structuring future return to play guidelines.

This study is not without limitations. First, this study is limited to a relatively small group of young (primarily high school aged) athletes. In addition, no professional athletes were included. Therefore, our results cannot be generalized beyond adolescents and athletes within their early 20’s. There are known differences with regard to neurological development between children and adults, and past neuropsychological studies have also demonstrated differences between clinical recovery in younger and older athlete groups. Most recently, significant differences have been reported in neurocognitive recovery in groups of high school and National Football League (NFL) athletes with the younger athletes recovering more slowly. Consequently, it would be useful in future studies to structure fMRI studies with subject groups across the age span. In addition, this study employed a largely male subject population, all of whom were right handed (as per design of the study). Therefore, it will be important in future studies to study brain metabolic changes in female and left handed athletes.

As preliminary research, this study has sought to increase the general understanding of the neurological underpinnings of recovery following concussion. However, a number of important questions remain unanswered and will be the focus of future research endeavors. For example, past concussion research has suggested that certain post-injury markers of injury (e.g. loss of consciousness or amnesia) may be predictive of recovery. We care currently evaluating the relationship of fMRI changes to these markers. In addition, in this current study, initial abnormality (hyperactivation) on fMRI within a week of injury were related to time to clinical recovery. However, the relationship of these fMRI results to long-term neurological morbidity is unknown. We are currently evaluating the relationship of fMRI results to clinical markers of recovery in athletes who have developed more chronic difficulties both with and without a history.
of multiple concussions.

Given the association of brain activation changes and different symptom constellations, our future research will focus on attempting to define symptom clusters that might be linked to specific areas of activation in the brain. It has long been suggested that there may be different “subtypes” of concussion, although data to support this hypothesis as to date been anecdotal. Research studies that directly evaluate regional changes in brain function as a result of different biomechanical factors (e.g. velocity of collision, blow to a specific area of the head) are likely to help unravel this mystery.
REFERENCES


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35. Thurman DJ, Branche CM, Sniezek JE: The epidemiology of sports-related traumatic
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TABLE 1. Sideline Signs and Symptoms Utilized to Diagnose Concussion on the Field

<table>
<thead>
<tr>
<th>Signs observed by staff</th>
<th>Symptoms reported by athlete</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dazed appearance</td>
<td>Headache</td>
</tr>
<tr>
<td>Confusion regarding assignment</td>
<td>Dizziness or balance problems</td>
</tr>
<tr>
<td>Forgetfulness on the field</td>
<td>Sensitivity of light</td>
</tr>
<tr>
<td>Disorientation regarding score or opponent</td>
<td>Sensitivity to noise</td>
</tr>
<tr>
<td>Slowed response to questions</td>
<td>Feeling foggy or groggy</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>Feeling slowed down</td>
</tr>
<tr>
<td>Personality change</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Retrograde amnesia (loss of memory prior to play)</td>
<td>Perceived difficulty with memory</td>
</tr>
<tr>
<td>Post-traumatic amnesia (loss of memory following injury)</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2. Sample characteristics and neuropsychological test results of concussed athletes (total n=41)

<table>
<thead>
<tr>
<th></th>
<th>Concussed</th>
<th></th>
<th>Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time 1</td>
<td>Time 2</td>
<td>Time 1</td>
<td>Time 2</td>
</tr>
<tr>
<td></td>
<td>(n=28)</td>
<td>(recovered)</td>
<td>(n=13)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>16.56 (1.4)</td>
<td>18.25 (3.49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>10.89 (1.4)</td>
<td>12.23 (3.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior History Concussions</td>
<td>0.86 (1.04)</td>
<td></td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Current Concussion LOC</td>
<td>21.4%</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Current Concussion RGA</td>
<td>25.0%</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Current Concussion AGA</td>
<td>57.1%</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Verbal Memory Composite</td>
<td>79.29 (16.17)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>89.11 (7.37)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90.54 (8.16)</td>
<td>94.42 (5.20)</td>
</tr>
<tr>
<td>Visual Memory Composite</td>
<td>66.79 (17.99)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>81.0 (9.94)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>82.46 (8.33)</td>
<td>86.92 (8.55)</td>
</tr>
<tr>
<td>Visual Motor Speed Composite</td>
<td>35.67 (8.62)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>42.31 (6.05)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>41.34 (6.89)</td>
<td>43.10 (6.87)</td>
</tr>
<tr>
<td>Reaction Time Composite</td>
<td>.635 (.165)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>.501 (.058)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>.53 (.06)</td>
<td>.50 (.06)</td>
</tr>
<tr>
<td>Total Symptom Score</td>
<td>27.25 (25.96)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.11 (7.51)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.46 (6.01)</td>
<td>3.42 (5.32)</td>
</tr>
</tbody>
</table>

Note. Superscripted letter pairs indicate significant differences were observed between ImPACT composites at post-injury versus recovery assessments. $p < 0.01$ for all comparisons.
Figure 1. Areas of significant increases in regional brain activity in all study subjects (Controls and Concussed) in a verbal memory condition (2-back) relative to the visual-motor control condition (0-back).
Figure 2a. Scatterplot between activation in the posterior parietal cortex and the cognitive \( (r = -0.49) \) and somatic \( (r = -0.46) \) symptoms of concussion assessed with the PCSS.

Figure 2b. Scatterplot of the activation in the posterior parietal circuit and the delayed memory index calculated from ImPACT among concussed athletes \( (r = 0.35) \) but not controls \( (r = 0.28) \).
Figure 3. Kaplan-Meier plot of the survival functions of time to return-to-play in the concussed athletes. The three lines represent the three tertiles of activation of the brain regional network involving the middle and inferior frontal cortex. Those athletes with the greatest functional activation in this network had the longest time to recovery of function. The group with the lowest activation recovered in an average 22.6 days, the Middle group in 21.8 days and the highest group in 45.8 days.