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

OBJECTIVE: The relationship between athlete reports 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 1 week of injury and again after 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 athletes who did not demonstrate hyperactivation at the time of their first fMRI scan.

CONCLUSION: 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 after concussion and may help shape return-to-play guidelines in the future.

KEY WORDS: Concussion, Functional magnetic resonance imaging, ImPACT, Neuropsychological testing, Sport injury, Traumatic brain injury

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Approximately 300,000 of the 1.5 million head injuries reported each year in the United States are sports-related, and approximately 9% of these require hospitalization (39). By far, the majority of these injuries occur in high school-aged 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 younger athletes (4, 12, 25, 26).

Currently, return-to-play decisions after concussion are based on clinical recovery, as determined by player reports of symptoms and cognitive status. Recent international concussion management guidelines (2, 30) 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 computed tomography and magnetic resonance imaging (MRI), although extremely valuable in detecting more severe brain injury, has not been regarded as providing useful information regarding recovery from concussion.

Although our understanding of the clinical recovery process after concussion has improved dramatically over the past decade, relatively few studies have sought to investigate neurophysiological recovery after 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 in humans as a result of head trauma, and the studies that have been published have used very small sample sizes (typically fewer than 10 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 a handful of academic medical centers.

This study was designed to evaluate the relationships between a neurophysiological measure of central nervous system 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 1 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" (2, p 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 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 after concussion-like injuries in animal models (3, 16). However, there are relatively little data regarding the resolution of functional brain changes in humans, although clinical symptoms usually resolve within 1 to 2 weeks of injury (6, 26, 29).

In an initial study designed to evaluate functional brain abnormalities in a group of traumatically brain injured nonathletes, McAllister et al. (28) 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. (19) examined fMRI data in four collegiate football players within 1 week of injury. These athletes' fMRI results were then compared with baseline fMRI studies and with a group of four subjects who composed a control group. When compared with control subjects, concussed players showed marked increases in amplitude and extent of blood oxygen level dependent (BOLD) activity during a finger sequencing task. In the only other published study that used athletes, Chen et al. (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 reports 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. The current study is exploratory in nature and is designed to investigate the relationship between cognitive, neurophysiological, and self-report components of acute concussion and recovery. It was our hypothesis that brain activation would be associated with traditional clinical determinants of recovery (neuropsychological testing and symptoms self-report).

PATIENTS AND METHODS

Patients

This study was approved by the Institutional Review Board of the University of Pittsburgh before the recruitment of patients. There were 28 concussed patients and 13 age-matched controls. The athletes were between the ages of 13 and 24 years (mean, 16.6 yr; standard deviation, 2.4 yr) with a mean educational attainment of 10.4 years (standard deviation, 2.2 yr). 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 group (2, 30). 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 or symptoms emerged after a collision involving the head or body. The specific signs and symptoms of concussion are listed in *Table 1*. Concussed athletes represent the broad spectrum of concussion severity ranging from individuals who did and did not experience a loss of consciousness or amnesia.

Concussed athletes were identified and evaluated on the field or sideline by team medical staff (e.g., physicians and certified athletic trainers), then underwent an initial postinjury clinical evaluation at the University of Pittsburgh Center for Sports Medicine. All on-field staff received training in the identification of concussion through a series of workshops and used standardized forms to document on-field signs and symptoms. Due to the fact that concussions are often observed directly, particularly within the context of a sport such as football in which there are multiple collisions on every play, we were not able to establish region of the head or body that was struck or the exact mechanism of injury. The diagnosis of concussion was, therefore, made on the basis of clinical signs and symptoms.

Injured athletes were invited to participate if they met age criteria (13–25 yr), had sustained a concussion as a result of sport participation, reported symptoms of concussion, and demonstrated evidence of cognitive dysfunction (27) on the ImPACT test battery after 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 preinjury neuropsychological baseline. If the athlete had not previously completed baseline testing, ImPACT scores were compared with normative values for the athlete's age and sex reference group.

In accordance with recent international guidelines (2, 30), athletes were considered to be symptomatic if they reported symptoms such as headache, dizziness, excessive fatigue, or sleepiness either at rest or after 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 atten-

TABLE 1. Sideline signs and symptoms used to diagnose concussion on the field

Signs observed by staff	Symptoms reported by athlete
Dazed appearance	Headache
Confusion regarding assignment	Dizziness or balance problems
Forgetfulness on the field	Sensitivity of light
Disorientation regarding score or opponent	Sensitivity to noise
Slowed response to questions	Feeling foggy or groggy
Loss of consciousness	Feeling slowed down
Personality change	Difficulty concentrating
Retrograde amnesia (loss of memory before play)	Perceived difficulty with memory
Posttraumatic amnesia (loss of memory after injury)	Perceived difficulty with memory

tion deficit disorder 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 antidepressants, stimulants, or anxiolytics; 6) braces or other dental appliances that might distort the fMRI imaging; and 7) the existence of any nonremovable ferromagnetic material in their bodies. Control subjects were student-athletes who were recruited through advertisement and informational sessions throughout area high schools and colleges; they were required to meet age requirements and pass the 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 preinjury (baseline) testing on ImPACT as part of their high school's concussion management program. When available, the athletes' baselines were used to provide information about preinjury cognitive functioning to assist in determination of recovery. Regardless of whether or not baseline testing had been completed, all concussed athletes evaluated in the University of Pittsburgh Medical Center 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 (27). The ImPACT test battery has previously been validated and has been used extensively in both amateur (17, 18, 25, 26, 36) and professional (33) athlete groups. Past psychometric studies of ImPACT have also found it to be stable across two assessment periods in noninjured athletes (17). In addition to the neurocognitive indices, ImPACT also contains the Post-Concussion Symptom Scale, which provides an index of self-reported symptoms (22, 23). Performance on ImPACT has been shown to be significantly worse among individuals with concussion relative to non-concussed controls, and changes in ImPACT are highly correlated with cognitive and noncognitive symptom recovery (17, 25, 26).

Concussed athletes were reevaluated on approximately a weekly basis using ImPACT until all symptoms had resolved after vigorous physical exertion and cognitive functions were within normative limits and/or equivalent to the athlete's own baseline (25). Our goal in using 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) when the athlete was "normal" with regard to both self-reported symptoms and neuropsychological test performance as measured by ImPACT. If the athlete developed a more chronic postconcussive disorder and did not return to normal symptom and/or neuropsychological levels within 6 weeks, he underwent the second fMRI scan and ImPACT evaluation and his 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 interval for the concussed patients, and not earlier than 1 week after their initial evaluation.

During this study, athletes were not returned to play until they were judged to be back to normal with regard to both their symptom status and ImPACT test performance. Return-to-play decisions were made by Ph.D. level neuropsychologists (MRL, MWC, JEP) in collaboration with team medical and athletic training staff. All ImPACT composite scores were required to be at or above baseline levels or within the normal range, and the athletes were required to be asymptomatic both at rest and following graduated aerobic exertion (2). Return to normal ImPACT performance was determined by comparing those athletes who had previously undergone baseline testing with their own preinjury scores. Reliable Change Index (17) scores were used to determine whether postinjury test performance was significantly below baseline or back to normal. For athletes who had not undergone baseline testing, comparison with age-appropriate normative data was used to determine normal performance.

MRI Scanning and fMRI Analysis

All subjects were scanned in a GE 3.0T system (General Electric, Milwaukee, WI). After the acquisition of a three-dimensional volumetric spoiled gradient echo MRI scan (repetition time, 25; echo time, 5; slices, 5 mm thick; 0 mm gap; 40-degree angle; field of view, 24×18) and a T1-weighted in plane image (used for alignment of fMRI to the anterior commissure-posterior commissure line) (repetition time, 350; echo time, 20; slices, 3.2 mm thick; no gap; field of view, 20), subjects completed the fMRI working memory paradigm.

The fMRI protocol used the N-back task (32). N-back is a standard measure of short-term or working memory involving visual-verbal encoding and recognition. N-Back was chosen for this study because of its extensive utilization in fMRI research. N-back has been previously used in both normal and pathological states and the expected patterns of regional brain activation with this test are well-known (11, 32, 41). 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. After the presentation of each letter, they were required to indicate whether each letter was a target or nontarget 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

TABLE 2. Sample characteristics and neuropsychological test results of concussed and control athletes (n = 41)[a]

	Concussed (n = 28)		Controls (n = 13)	
	Time 1 (n = 28) (6.6 ± 4.7 days postinjury)	Time 2 (n = 28) (35.1 ± days postinjury)	Time 1 (n = 13)	Time 2 (n = 12)
Age (yr)	16.56 (1.4)		18.25 (3.49)	
Education (yr)	10.89 (1.4)		12.23 (3.24)	
Previous history of concussions	0.86 (1.04)		0 (0.0)	
Current concussion LOC	21.4%	NA	NA	
Current concussion RGA	25.0%	NA	NA	
Current concussion AGA	57.1%	NA	NA	
Verbal memory composite	79.29 (16.17) [b]	89.11 (7.37) [b]	90.54 (8.16)	94.42 (5.20)
Visual memory composite	66.79 (17.99) [b]	81.0 (9.94) [b]	82.46 (8.33)	86.92 (8.55)
Visual motor speed composite	35.67 (8.62) [b]	42.31 (6.05) [b]	41.34 (6.89)	43.10 (6.87)
Reaction time Composite	0.635 (0.165) [b]	0.501 (0.058) [b]	053 (0.06)	0.50 (0.06)
Total Symptom Score	27.25 (25.96) [b]	3.11 (7.51) [b]	3.46 (6.01)	3.42 (5.32)

[a] LOC, loss of consciousness; RGA, retrograde amnesia; AGA, anterograde amnesia.
[b] Superscripted letter pairs indicate significant differences were observed between ImPACT composites at post-injury versus recovery assessments. P < 0.01.

"X" was presented (either in upper or lower case) and the "no" button with their right middle finger for all other letters. For the one-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 two-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 12 63-second scanning blocks. Reverse spiral sequences (repetition time, 1500; echo time, 26; flip angle, 60; slices, 3.2 mm thick; no gap; 64 × 64; field of view, 20) were used to measure the BOLD response.

fMRI Data Analysis

First, fMRI data were transferred offline for processing. Three-dimensional head motion was estimated and corrected using Functional Image Analysis Software Computational Olio (Carnegie Mellon University, Pittsburg, PA) (10, 20, 21). A *t* score voxel-level map of the difference in each subject's BOLD response between the two-back and the zero-back conditions was constructed for each subject at both sessions (acute injury and recovery/follow-up for concussed athletes; Times 1 and 2 for controls). These *t* maps were coregistered to the T1-weighted in-plane images using Functional Image Analysis Software Computational Olio and then transformed into standard stereotaxic space (38) using analysis of functional neuroimaging (7, 8). Stouffer's method (21) 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 (6.6 ± 4.7 d) and again after clinical recovery (33.3 + 33.8 d). 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 because of 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 (postinjury and recovery for concussed athletes; Times 1 and 2 for controls). Concussed athletes demonstrated significantly worse 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 postinjury 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 seem to reflect injury-related changes.

To assess changes in brain physiology with increasing difficulty of memory task, brain regional activation during the two-back verbal memory task was compared with that seen in the zero-back visuomotor control condition (*Fig. 1*) across a group map of control and concussed subjects. The groups were collapsed with the purpose of statistically identifying regions of interest. The areas of significant activation were typical of those observed in other studies using this activation paradigm (32). In order to understand the relationships among the brain regions activated during the performance of memory tasks, we examined the functional connectivity among specific brain regions (13, 14). Whereas *t* tests and associated methods are useful for determining regional activity that occurs above a given threshold (functional specialization), it is important to conduct analyses that identify functionally associated brain

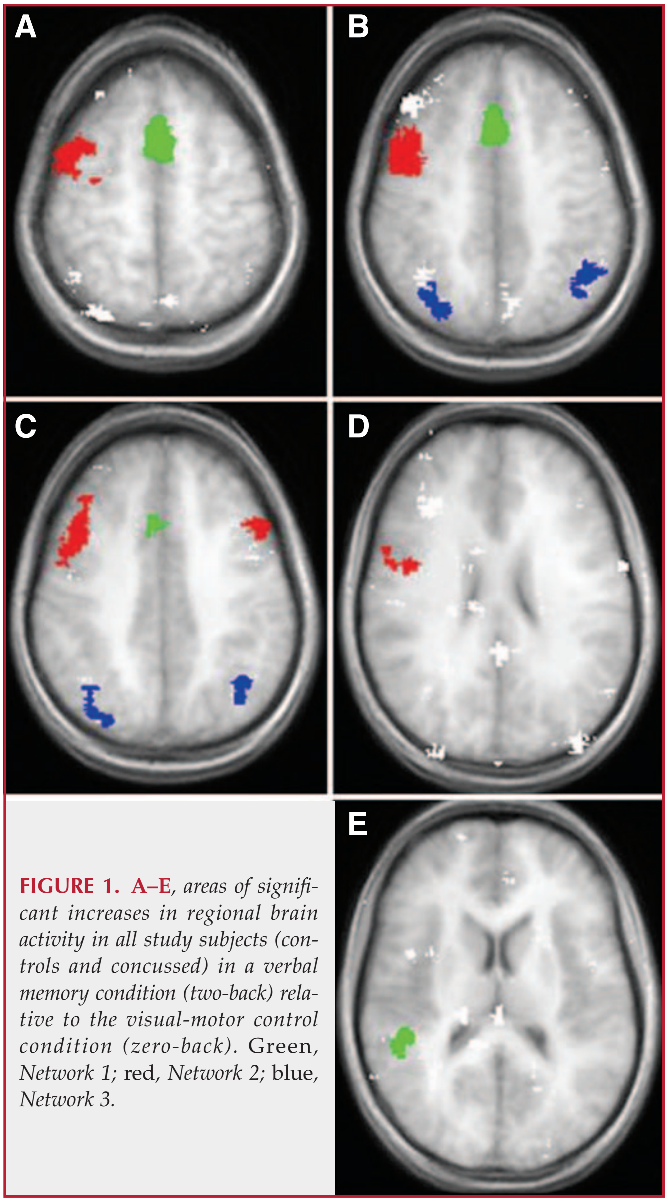

FIGURE 1. A–E, *areas of significant increases in regional brain activity in all study subjects (controls and concussed) in a verbal memory condition (two-back) relative to the visual-motor control condition (zero-back).* Green, *Network 1*; red, *Network 2*; blue, *Network 3.*

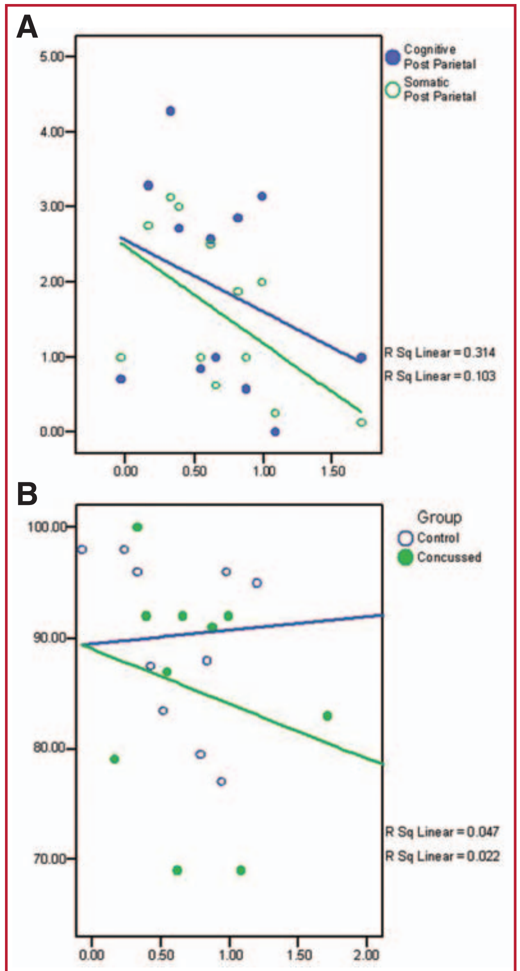

FIGURE 2. A, *scatterplot between activation in the posterior parietal cortex and the cognitive (r = −0.49) and somatic (r = −0.46) symptoms of concussion assessed with the Post-Concussion Symptom Scale. The x-axis represents the average activation of each foci within the region of interest and are expressed as standard (z) scores with a mean of 0 and a standard deviation of 1. The y-axis represents the number of symptoms as measured by the Post-Concussion Symptom Scale.* **B**, *scatterplot of the activation in the posterior parietal circuit and the delayed memory index calculated from ImPACT demonstrated a significant correlation in concussed athletes (r = 0.35) but not in controls (r = 0.28). The x-axis represents the average activation of each foci within the region of interest and are expressed as standard (z) scores with a mean of 0 and a standard deviation of 1. The y-axis represents the raw scores (percent correct) on the ImPACT Delayed Memory composite score.*

regions (13). We used principal components analysis to examine the pattern of covariation of regional cerebral blood flow and to determine the relationships between the brain regions activated by the N-back task (two-back versus zero-back). In order to identify the patterns of regional activation, the z scores from the peak voxels within each region were entered into a principal components analysis with varimax rotation. This analysis identified three components, or networks, of interconnected brain regions. Network 1 included medial, frontal, and right temporoparietal gyri (colored green in *Fig. 1*); Network 2 included the right frontal and anterior termporal regions (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

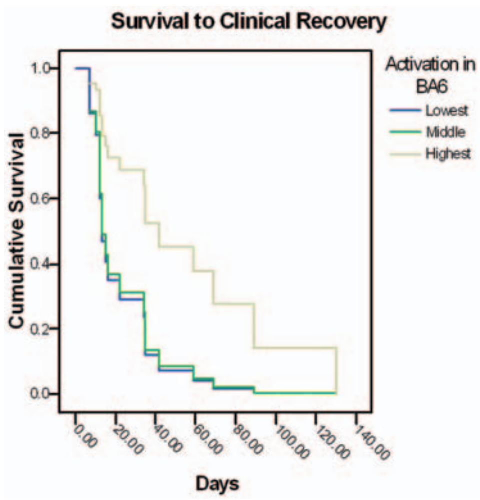

FIGURE 3. *Kaplan-Meier plot of the survival functions of time to return-to-play in the concussed athletes. The three lines represent the three tertiles of activation of the brain regional network involving the middle and inferior frontal cortex. Those athletes with the greatest functional activation in this network had the longest time to recovery of function. The group with the lowest activation recovered in an average of 22.6 days, the middle group in 21.8 days, and the highest group in 45.8 days.*

the baseline condition to the two-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) ($r = -0.49$; $P < 0.05$) and somatic (e.g., blurred vision, headache, photophobia) ($r = -0.46$; $P < 0.05$) symptomatology after 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 20-minute period of time, among concussed athletes ($r = 0.35$; $P < 0.05$) but not controls ($r = 0.28$; $P > 0.05$, not significant) (*Fig. 2B*). Thus, this circuit is apparently associated with both neuropsychological and noncognitive 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 ($r = 0.58$; $P < 0.005$) and somatic ($r = 0.47$; $P < 0.04$) symptoms.

Correlational analysis revealed that the activity in Network 1, and specifically in midline BA6 (Brodman's Area 6), was associated with time to return-to-play. To investigate this relationship, we divided the concussed athletes into three groups based on the 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 ($\beta = 0.486$; $P = 0.018$). Next, a survival analysis was conducted to evaluate the time between entry into a study and return of the athlete to normal status (15). This analysis (*Fig. 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 ($t = 2.50$; $P = 0.024$). 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 noninvasive technology that allows for the direct measurement of changes in brain function after 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 (24). 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 (2, 30). 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 after sports-related concussion. First, we have confirmed previous observations that there are neurophysiological abnormalities after even mild sports-related concussion that can be measured (5, 19). 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 (34) 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. It is important to stress that concussion is generally regarded as a nonfocal or diffuse injury that involves the disruption of physiological processes within the brain. Therefore, we do not mean to imply that our current findings are suggestive of a specific neuronal network that is characteristically affected by injury. It is possible that the utilization of other cognitive tasks in the future will identify other brain areas that demonstrate perturbation after concussion.

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. (9) found that a sample of collegiate athletes continued to exhibit neuropsychological deficits after they were asymptomatic with regard to noncognitive symptoms. More recently, Van Kampen et al. (40) found that a significant number of high school and collegiate athletes who reported no symptoms after injury performed abnormally on a computer-based neurocognitive test battery (ImPACT). 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 multifaceted. 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 (24) but has not been without its critics (35). 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 after 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. Although this study specifically utilized the N-back test, studies are now underway in our center that use different neuropsychological tasks. We are hopeful that this will eventually lead to the development of new assessment tools that can be used in both clinical practice and functional brain imaging research.

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 noninvasive 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 20s. There are known differences with regard to neurological development between children and adults (1), and past neuropsychological studies have also demonstrated differences between clinical recovery in younger and older athlete groups (12, 31). Most recently, significant differences have been reported in neurocognitive recovery in groups of high school and National Football League athletes, with the younger athletes recovering more slowly (33). Consequently, it would be useful in future studies to structure fMRI studies with subject groups across the age span. In addition, this study used 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. Finally, it is important to note that the exact interpretation of the BOLD signal in fMRI research is not without controversy (37). However, it is our belief that the correlation of this marker with neuropsychological test performance and subjective symptoms does yield useful data. We hope to continue this line of research in subsequent studies.

As preliminary research, this study has sought to increase the general understanding of the neurological underpinnings of recovery after 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 postinjury markers of injury (e.g., loss of consciousness or amnesia) may be predictive of recovery (24). We are currently evaluating the relationship of fMRI changes to these markers. In addition, in this current study, initial abnormality (hyperactivation) on fMRI within 1 week of injury was related to the 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 has to date been anecdotal (22). 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.

Disclosure

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COMMENTS

The authors have tremendous experience in evaluating athletes after head injury and in the study of predictive outcome measures. In this experiment, they attempted to find a neurophysiological correlate of injury to compare with neurocognitive testing and symptoms. They believe that functional imaging may assist athletes in understanding their injury and the timing of return-to-play, and that this may add to management based on concussion guidelines.

As they discuss, there are limitations on the use of functional magnetic resonance imaging (fMRI) in this setting, and their findings should be interpreted cautiously. Functional activation is based on the task and imaging technique used and is then subject to interpretation. Concussion is likely much more global than the localized areas of activation seen as a "red area" on a magnetic resonance imaging scan. Different tasks may show different activation volumes. Finally, how well the imaging results correlate with the patient's condition will likely be variable. This is important work that should only get better.

Douglas Kondziolka
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As I write these comments, the issues of concussion and repetitive minor brain injury in professional football players are being discussed widely in the popular press and on talk radio, even though preseason training camps will not open for some time yet. It is obvious that much more work needs to be done in this area. In this article, Lovell et al. demonstrate a relationship between clinical symptoms, neuropsychological test results, and fMRI data in a group of primarily teenage athletes with concussion. An important goal of these types of studies is the identification of indicators to permit concussed athletes at all levels to return to play as soon as possible without compromising their safety.

Alex B. Valadka
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Lovell et al. have made a valuable contribution with this investigation of neurophysiological correlates of recovery from concussion in young athletes. The authors used fMRI to study 28 patients who met a clinical definition of sports-related concussion and 13 student-athlete controls matched for age. Eligibility criteria for patients included report of symptoms of concussion and cognitive dysfunction on neuropsychological testing (previously validated in studies of recovery from concussion). Patients received an initial fMRI scan shortly after concussion and a second fMRI scan once symptoms and cognitive dysfunction had resolved, or at 6 weeks if resolution had not occurred by that time. Their finding that hyperactivation in specific brain regions on the first scan was associated with prolonged recovery advances our understanding of the mechanisms underlying concussion in young athletes.

As the authors note, current return-to-play guidelines are based on clinical parameters. In some instances, there may be a lack of adequate sensitivity to identify impairment. Functional testing such as fMRI may ultimately help to refine guidelines. Many questions remain unanswered, however, and the work by Lovell et al. should be considered preliminary. The roles of mechanism of injury, severity of the impact, age and sex of the patient, and history of previous concussion, as well as other neurological risk factors, must be elucidated. Although this study was relatively large compared with earlier ones, its size was limited, and larger trials will be needed. A single test, the N-back test, was used to assess function; evaluation of additional functional tests will be needed to demonstrate a consistent relationship between changes on fMRI and patient outcomes.

Despite these limitations, this article represents an important development in the study of concussion. The lack of structural findings in concussion has limited the use of traditional brain imaging, forcing clinicians to rely solely on symptoms, neuropsychological testing, and other ancillary assessments in the care of the concussed patient. The authors have shown that soon after a concussive event, measurable changes can be detected using advanced imaging techniques. Thus, Lovell et al. have opened a door for additional investigations and future clinical applications specifically to further refine our knowledge of concussions, its subtypes, and neuroanatomic correlates.

Todd Harshbarger
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This study is important because it demonstrates a neurophysiological correlate (fMRI activation pattern) of post-concussion neural dysfunction, defined clinically as persistent symptoms and neuropsychological impairment on standardized testing. These data support the premise that clinically significant post-concussive impairments are related to underlying neural dysfunction, even in the absence of structural brain injury. This is a critical first step to better understanding the neurobiology of concussion and is necessary for the development of proper return-to-play guidelines and for the development of potential therapies to enhance or accelerate recovery from concussion.

The specific presentation of the results still raises some questions for the non-neuroimaging clinician. By combining controls and injured patients to generate the maps of functional activation for the N-back test, the specific between-group (normals versus concussed) differences in fMRI signal are more difficult to appreciate. Nonetheless, the correlation between regional fMRI signals and symptom scores/neuropsychological function raises important questions about the neurobiological processes underlying post-concussive deficits and recovery.

It is interesting to speculate, and would be even better to demonstrate in future studies, how increased activation of medial frontal pathways is related to the longer delay to return-to-play. Is this due to persistent neuropsychological deficits and, if so, are the deficits in domains subserved by frontotemporal circuits (attention, working memory) or due to some type of hypersensitivity to somatic complaints? Alternatively, are the abnormal patterns of regional activation simply markers of recovery but perhaps less revealing of the underlying neurobiological substrate of these deficits? These questions remain to be answered by future work in the growing and important field of concussion research.

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