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Acute and Subacute Changes in Neural Activation during the Recovery from Sport-Related Concussion

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Abstract

To study the natural recovery from sports concussion, 12 concussed high school football athletes and 12 matched uninjured teammates were evaluated with symptom rating scales, tests of postural balance and cognition, and an event-related fMRI study during performance of a load-dependent working memory task at 13 h and 7 weeks following injury. Injured athletes showed the expected postconcussive symptoms and cognitive decline with decreased reaction time (RT) and increased RT variability on a working memory task during the acute period and an apparent full recovery 7 weeks later. Brain activation patterns showed decreased activation of right hemisphere attentional networks in injured athletes relative to controls during the acute period with a reversed pattern of activation (injured > controls) in the same networks at 7 weeks following injury. These changes coincided with a decrease in self-reported postconcussive symptoms and improved cognitive test performance in the injured athletes. Results from this exploratory study suggest that decreased activation of right hemisphere attentional networks mediate the cognitive changes and postconcussion symptoms observed during the acute period following concussion. Conversely, improvement in cognitive functioning and postconcussive symptoms during the subacute period may be mediated by compensatory increases in activation of this same attentional network. (*JINS*, 2013, *19*, 863–872)

Keywords: fMRI, Brain activation, Mild TBI, Cognitive compensation, Brain injury, Attention networks

INTRODUCTION

Judicious decisions regarding safe return-to-play after sport-related concussion require an understanding of physiological and functional recovery mechanisms and sensitive measures of their critical components. To date, our understanding of the mechanisms is incomplete. Whereas prospective studies have shown that most athletes show good recovery of subjective symptoms and cognitive abilities within approximately 1 week of injury (Belanger & Vanderploeg, 2005; Broglio & Puetz, 2008; Collins et al., 1999; Guskiewicz et al., 2003; Macciocchi, Barth, Alves, Rimel, & Jane, 1996; McCrea et al., 2003), functional imaging studies after concussion often show brain activation abnormalities (Chen, Kareken, Fastenau, Trexler, & Hutchins, 2003; Chen et al., 2004; Chen, Johnston, Petrides, & Pito, 2008a, b; Slobounov et al., 2010) or altered regional connectivity (Johnson et al., 2012) that persist for longer intervals.

In a positron emission tomography (PET) study, Chen et al. (2003) examined resting glucose metabolism of concussed athletes imaged 1–2 weeks after injury and found no differences from healthy controls. In contrast, functional imaging studies using a cognitive challenge often show differences in activation patterns in concussed athletes compared with healthy controls (Chen et al., 2003; Jantzen, Anderson, Steinberg, & Kelso, 2004; Lovell et al., 2007; Pardini et al., 2010; Slobounov et al., 2010). Using PET, Chen and colleagues (2003) observed that concussed players demonstrated decreased activation in the right prefrontal region when

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performing a spatial working memory task. In contrast, Jantzen and colleagues (2004) conducted a functional MRI (fMRI) study of four athletes at preseason and 1 week post concussion and found increased activation in the parietal, lateral frontal, and cerebellar regions on a finger sequencing task. Lovell and colleagues (2007), using a verbal working memory task (N-Back), found a positive correlation between activation in midline Brodmann area (BA) 6 and time to return to play; additionally, activation in left dorsolateral prefrontal and biparietal regions was inversely related to the severity of postconcussive symptoms. In a follow-up fMRI study, Pardini et al. (2010) found that postconcussive symptom severity was associated with regionally specific hyperactivation, suggesting that concussed athletes were recruiting additional cognitive resources to compensate for functional difficulties. In an fMRI study using a spatial memory and navigation task, Slobounov and colleagues (2010) imaged asymptomatic concussed athletes a month post injury; compared to healthy controls, injured athletes showed a larger spatial extent of activation in the parietal, right dorsolateral prefrontal cortex, and right hippocampus during the encoding phase of the task without a difference in percent signal change.

Results from these task activation functional imaging studies comparing concussed and healthy athletes may be described as inconsistent. This is likely due to several factors, including the choice of activation task, between group task performance differences, the extent of symptoms reported by the concussed athlete at the time of study (Chen et al., 2008b; Pardini et al., 2010), and the use of non-athlete controls (e.g., Chen et al., 2004).

An important methodological factor related to fMRI studies involves the use of blocked trial or event-related trial designs. Blocked designs summate brain activation across a series of trials. As such, it is not possible to study component mental operations that unfold over the course of a single trial, as in working memory tasks that involves maintenance intervals extending over several seconds. Furthermore, it is not possible to eliminate incorrect trial performance from brain maps generated from a blocked design format; inclusion of error trial data can yield misleading activation results (Sadek & Hammeke, 2002). Event-related trial designs can successfully address these issues.

Time from concussion to imaging can be a critical factor in the interpretation of functional imaging studies. Studies can range from a few days (e.g., Lovell et al., 2007) to several months following injury (Chen et al., 2008b). While it is assumed that brain abnormalities occur immediately following concussion, none of the extant functional imaging studies have examined concussed athletes within hours of injury.

The current fMRI study used an event-related trial design to examine brain activation patterns arising from three phases (encode, maintenance, and response) of a working memory task administered to athletes with sports-related concussion and athletic control subjects imaged 13 h and 7 weeks post injury. This longitudinal design allows an examination of the evolution of changes in brain activation from the acute to subacute state. Both the concussed athletes and non-concussed controls, selected from a pool of athletic teammates, were administered a battery of cognitive tasks at preseason. This allowed for individual matching of controls to concussed athletes on demographic variables, preseason baseline cognitive test performance, and symptom ratings.

METHODS

Subjects

Participants for this study were selected from a larger prospective study (McCrea, Hammeke, Olsen, Leo, & Gasparovic, 2004) of high school varsity football players in the Milwaukee, Wisconsin, area that aimed to study cognitive and symptomatic recovery following concussion. Over 3600 players from 2000 through 2005 completed preseason baseline studies involving completion of a demographic survey of head injury history, existence of base rate postconcussion symptoms (Graded Symptom Checklist – GSC; Lovell & Collins, 1998) and a cognitive screening (Standardized Assessment of Concussion, SAC; McCrea, 2001). During the study, 103 players sustained concussions during the season following their baseline and were intensely studied beginning on the sideline immediately following injury and at several time points extending through 7 weeks after injury. The research protocol was approved by the IRB of Children's Hospital of Wisconsin and the Medical College of Wisconsin. Signed informed consent was obtained from all participants and their parents.

From the larger pool of concussed players, 21 players, who sustained either an American Academy of Neurology Grade 3 ($n = 7$) or Grade 2 ($n = 14$) concussion (Practice Parameter, 1997), consented to complete imaging studies. Grade 3 requires a loss of consciousness (LOC), whereas Grade 2 involves no LOC but postconcussion symptoms persisting for more than 15 min. Athletes with Grade 1 concussions were excluded because of the low incidence of symptomatic complaints and behavioral deficit at 13 h post injury. Of the 21 Grade 3 and 2 players, six subjects (five Grade 2 and one Grade 3) were excluded from further analysis for the following reasons: claustrophobic reaction in the scanner (one), technical issues with behavioral response recording device that yielded incomplete data (two), poor Sternberg task performance defined by response accuracy $<70\%$ on one or more trial categories (two), and excessive head movement not adequately corrected by post-processing methods (one). This left 9 Grade 2 and 6 Grade 3 participants.

The six Grade 3 subjects were then individually matched with six Grade 2 subjects based on education, age, and preseason GSC and SAC scores. We equated the size of the two injured subgroups to avoid over-representing the injured group with subjects having the milder, Grade 2 concussions. Our goal was to identify a concussion sample that stratified the severity spectrum over the Grade 2 to 3 range. In addition, we were able to reduce extraneous sources of group differences by individually matching the two groups on preseason variables. Overall, the selected Grade 2 and Grade 3 injured athletes did

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not differ from excluded injured athletes in age, education, GPA, weight, height, preseason GSC, preseason SAC, or 13 h SAC or cognitive measures; thus, the current sample of injured athletes is thought representative of Grade 2 and Grade 3 concussions in our sample.

The duration of LOC in the Grade 3 concussions ranged from 2 to 5 s, consistent with the brief LOC found in other studies of sports-related concussion (McCrea et al., 2003). Eleven injured players had intervals of posttraumatic amnesia ranging from less than 1 min to 7 h (mean = 21 min; *SD* = 92 min). Injured players had postconcussive symptoms ranging from 30 min to 13 days (mean = 3 days; *SD* = 5 days).

For each of the 12 injured players, an uninjured teammate, matched in education, age, and preseason GSC and SAC scores, was selected to complete all study procedures designed for the injured players. In most cases, these control subjects were identified, recruited for study, and initiated study procedures on the day of injury of their matched injured teammate.

Procedures

Before the football season, the certified athletic trainers (ATC) for each participating high school were trained on the study protocol, operational definition of concussion, and the inclusion/exclusion criteria. *Concussion* was defined according to AAN guidelines (Practice Parameter, 1997). The athletic trainers examined a concussed athlete immediately after the injury and following the completion of the game or practice session. The athletic trainer would then contact one of the study investigators (M.M. or T.H.). If the investigator confirmed that the injured athlete met study criteria, a scanning session was scheduled. Players with AAN Grade 3 (any LOC) and Grade 2 (no LOC, symptoms persist $>$ 15 min) concussions underwent fMRI studies at the Medical College of Wisconsin on the day following the day of injury (median time of fMRI following injury = 13 h; range = 12–48 h; *SD* = 3.7 h) and again 7 weeks later (median = 49 days; range = 35–63 days; *SD* = 6.8). Control subjects underwent imaging studies at comparable intervals. In addition to fMRI studies following injury, the players underwent a symptom assessment and brief cognitive screening with the SAC at several time points after injury, along with a brief neuropsychological test battery (McCrea et al., 2003) measuring attention, memory, working memory, and information processing speed, postural steadiness and postconcussive symptom ratings. The individual tests for these domains are provided in Table 1. To correct for multiple comparisons, a false discovery rate method was applied.

Functional MRI Activation Task

The Sternberg task (1966) was used in an event-related fMRI paradigm to assess memory-scanning speed under conditions of varying memory load. Sternberg task activation maps derived from healthy subjects indicate that the anterior cingulate, dorsolateral prefrontal, and parietal regions form a network that is positively correlated with task difficulty (Narayanan et al., 2005). This task has also been shown to be sensitive to the effects of MTBI (Kumar, Rao, Chandramouli, & Pillai, 2009; Malojcic, Mubrin, Coric, Susnic, & Spilich, 2008; Newsome et al., 2008)

For the present study, the task consisted of three phases: *Encode, Maintenance* and *Response*. On each trial, the subject was presented visually with 2, 4, or 6 single digits for 2 s (*Encode phase*). The stimulus was then removed and the subject was instructed to hold the digits in memory for 2.5, 5.0, or 7.5 s (*Maintenance phase).* At the end of the maintenance delay period, the subject was presented with a single probe digit and instructed to make a keypress with the right index finger if the probe digit matched one of the numbers held in memory or a right middle finger keypress if the digit did not match (*Response phase);* matches occurred on 50% of trials. The three trial conditions—number of digits presented ("set size"), maintenance delay interval, and probe digit match—were pseudorandomly ordered across trials. Reaction time (RT) on the Sternberg task typically demonstrates a positive linear relationship with set size, with the slope interpreted as an index of memory scanning speed and the intercept an index of simple motor response time.

Imaging Acquisition and Processing

Whole brain functional imaging was conducted on a 1.5 Tesla General Electric Signa scanner with repetition time (TR) = 2500 ms and data gathered from 22 contiguous sagittal 6-mm-thick slices (voxel size: 3.75 × 3.75 × 6 mm). The Sternberg task had four imaging runs each consisting of 152 consecutive images (6.34 min). Each run had 24 trials for a total of 96 trials. Before functional imaging, high-resolution, three-dimensional spoiled gradient-recalled at steady-state (GRASS) anatomic images were collected for anatomic localization and co-registration.

Functional images were generated using Analysis of Functional NeuroImages (AFNI: http://afni.nimh.nih.gov/afni). Individual subject imaging data were first spatially registered to reduce the effects of head motion using an iterative linear least squares method. Individual subject's images were then transformed to Talairach space and the resulting image time series were shifted to the onset of the first image within a TR to compensate for timing offsets introduced by the acquisition. Voxel-wise data were blurred 6 mm FWHM for purposes of smoothing. A deconvolution analysis was used to generate hemodynamic response functions (HRFs) from the fMRI signal on a voxel-wise basis. This analysis produced an HRF estimate for each of 18 conditions [Set Size (2, 4, and 6 digits) × Maintenance delay (2.5, 5.0, and 7.5 s) × Group (Injured *vs*. Controls)] without making a priori assumptions regarding the shape, delay, or magnitude of the HRF. To equate for performance across subjects, only trials in which the subjects had a correct response were included. Because participants were excluded if response accuracy was less than 70%, a minimum of 23 correct trials were available in all conditions to support estimation of the HRF.

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Table 1. Demographic, behavioral, and neuropsychological data for injured and control athletes

	Injured		Controls			
	Mean	*SD*	Mean	*SD*	*p*	*d*
Preseason baseline						
Age	16.5	0.52	16.5	0.52	1.00	0.00
GPA	3.2	0.5	3.3	0.4	.48	0.22
GSC	7.7	6.4	6.9	13.3	.88	0.08
SAC	26.6	1.4	26.7	1.4	.89	0.06
13-hr assessment						
SAC	25.2	4.3	27.4	2.5	.13	0.64*
GSC	20.0	15.3	2.0	3.5	*.001*	1.63**
BESS	15.9	3.2	11.7	4.2	*.01*	1.12**
HVLT Total	24.5	5.6	26.6	4.3	.34	0.42
HVLT Delayed Recall	7.5	3.9	10.1	1.6	*.05*	0.87**
HVLT Recognition	21.8	1.7	22.9	1.0	.09	0.79*
Trails A	27.3	10.5	26.5	7.6	.84	0.09
Trails B	58.8	26.8	61.5	19.0	.78	0.12
Symbol Digit	52.7	12.0	55.3	8.3	.56	0.25
Symbol Digit Recall	10.6	3.7	12.3	2.8	.24	0.52*
Stroop Word	92.1	18.4	96.4	19.1	.59	0.23
Stroop Color	66.4	13.0	71.6	11.8	.33	0.42
Stroop Color-Word	42.1	12.4	42.4	8.2	.95	0.03
Letter-Number Sequencing	12.9	3.2	11.4	2.3	.20	0.54*
Controlled Oral Word Ass.	31.0	14.4	31.6	6.7	.91	0.05
7-week assessment						
SAC	27.0	2.3	27.3	1.8	.77	0.12
GSC	2.2	3.0	0.3	0.7	*.05*	0.83**
BESS	12.8	4.4	11.9	5.1	.67	0.18
HVLT Total	24.8	4.9	26.8	5.2	.34	0.40
HVLT Delayed Recall	8.5	2.3	9.4	3.0	.41	0.34
HVLT Recognition	22.5	1.5	22.8	1.7	.61	0.21
Trails A	20.8	6.2	22.1	5.1	.59	0.22
Trails B	48.7	18.6	53.6	16.4	.50	0.28
Symbol Digit	55.7	13.0	59.9	13.6	.44	0.32
Symbol Digit Recall	10.3	4.5	11.7	4.1	.43	0.33
Stroop Word	98.4	19.3	102.0	16.0	.63	0.20
Stroop Color	76.8	12.8	76.3	13.5	.93	0.04
Stroop Color-Word	49.0	12.6	47.8	9.4	.79	0.11
Letter-Number Sequencing	13.3	2.6	11.9	2.3	.20	0.54*
Controlled Oral Word Ass.	37.3	13.2	33.1	8.2	.35	0.39

GPA = Grade Point Average; SAC = Standardized Assessment of Concussion; GSC = Graded Symptom Checklist; BESS = Balance Error Scoring System; HVLT = Hopkins Verbal Learning Test; *d* = Cohen's *d*; italics = $p \leq 0.5$; *medium effect ($d = 0.50 – 0.79$); **large effect ($d \geq 0.80$).

The third image of the trial sequence (acquired 5 s after trial onset to account for the delay in the hemodynamic response) was used to define the Encode phase. The Maintenance phase was defined by image 4 for the 2.5-s delay interval trials, the average of images 4 and 5 for the 5.0-s delay, and images 4, 5, and 6 for the 7.5-s delay. The Response phase was defined as the image immediately following the last image of the Maintenance phase. To gain additional statistical power to detect group differences, we increased the number of trials per imaging session by collapsing across set size. The effects of set size on brain activation have been reported previously by others (Kumar et al., 2009; Malojcic et al., 2008; Narayanan et al., 2005). Whole-brain voxel-wise, 2 Group (Injured *vs.* Controls) × 2 Session (13-h *vs.* 7-week) repeated measures analyses of variance (ANOVAs) were conducted separately for the Encode, Maintenance, and Response phases. A Monte Carlo analysis with 10,000 simulations would require an individual voxel probability threshold of $p < .005$ in combination with a cluster volume threshold of 809 microliters to achieve a family-wise probability threshold of $p < .05$. Because of the relatively small sample size of concussed and control athletes ($n = 12$ each), we reduced the minimum cluster volume threshold to 500 microliters (see Discussion regarding study limitations based on sample size).

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RESULTS

Preseason Baseline

Injured players were well matched to Controls in age, academic performance in the form of grade point average and preseason (baseline) assessment of symptoms and mental status (see Table 1).

Post Injury Symptoms and Neuropsychological Measures (Table 1)

Injured players reported significantly more concussion-related symptoms on the GCS than Controls ($p = .001$). Although not surviving the false discovery rate (FDR) correction for multiple comparisons, injured players also had lower postural steadiness scores (BESS, $p = .01$) and recalled fewer words from a word list than did controls [Hopkins Verbal Learning Test (HVLT) Delayed Recall, $p = .05$] compared to Control players at 13 h after injury; group comparisons on both measures yielded large effect sizes (Cohen's *d*), indicating that the relatively small sample size prevented these group differences from being statistically significant. Moderate effect sizes were also observed for the SAC, HVLT Recognition, and Letter-Number Sequencing. At 7 weeks post injury, no significant differences were observed between the Injured and Control players, although a large effect size was observed with the GSC (Injured > Controls). The large effect size for the GSC at 7 weeks is of little clinical significance, since neither Injured nor Control subjects reported substantive postconcussive symptoms; the large effect size was a byproduct of a floor effect, and resulting reduced variance, observed in the Control group.

Sternberg Behavioral Data (Table 2, Figure 1)

A three-way [Group (2) × Set Size (3) × Session (2)] repeated measures ANOVA of Sternberg task accuracy showed significant effects of Set Size ($p = .002$), Session ($p = .014$), and Group × Session ($p = .024$). At 13 h post injury, Injured athletes, collapsed over the three set sizes, were less accurate than Controls (mean 93.4% *vs*. 97.5% correct, respectively; $p < .05$); at 7 weeks post injury, the groups were not significantly different (98% *vs*. 97% correct, respectively; $p > .05$). When results were examined by set size, group accuracy differences were observed for set size 6 ($p < .05$) at the 13-h assessment. Moderate to strong effect sizes for group differences were observed at 13 h for all three set sizes. In contrast, at the 7-week session, no differences in accuracy were seen for any of the set sizes.

A three-way repeated measures ANOVA was performed on Sternberg reaction time (RT) data; significant main effects were observed for Set Size ($p < .001$), Session ($p = .002$), and Group × Session ($p = .05$). Neither the Group × Set Size nor the Group × Set Size × Session effects were significant indicating that RT was not disrupted disproportionately as a function of working memory load in the Injured group.

Table 2. Results of Sternberg task

	Injured			Controls				
	Mean	*SD*	Range	Mean	*SD*	Range	*p*	*d*
13-hr assessment								
Percent accuracy								
Set Size 2	95.8	4.7	84–100	98.2	2.5	94–100	.14	0.63*
Set Size 4	95.3	6.0	84–100	98.2	3.1	91–100	.16	0.61*
Set Size 6	89.1	11.2	72–100	96.1	3.8	88–100	*.05*	0.84**
Total accuracy	93.4	6.3	83–100	97.5	2.2	93–100	*.05*	0.87*
Reaction time (ms)								
Set Size 2	874	264	541–1355	723	158	450–991	.10	0.69*
Set Size 4	1048	389	639–1781	850	160	583–1110	.12	0.67*
Set Size 6	1117	374	675–1862	903	160	615–1115	.08	0.74*
Overall mean RT	1013	339	642–1666	825	153	549–1056	.09	0.72*
7-week assessment								
Percent accuracy								
Set Size 2	97.7	4.2	88–100	99.0	1.5	97–100	.33	0.41
Set Size 4	97.9	2.4	94–100	98.2	2.1	94–100	.78	0.13
Set Size 6	95.3	6.0	81–100	95.8	4.1	88–100	.81	0.10
Total accuracy	97.0	3.5	89–100	97.7	1.6	95–100	.54	0.26
Reaction time (ms)								
Set Size 2	730	158	533–1121	678	141	501–928	.41	0.35
Set Size 4	837	216	595–1318	785	146	623–1120	.50	0.28
Set Size 6	934	239	649–1406	874	212	616–1263	.52	0.27
Overall mean RT	834	201	607–1282	779	161	590–1074	.47	0.30

d = Cohen's *d*; italics = $p \leq 0.5$; *medium effect ($d = 0.50 - 0.79$); **large effect ($d \geq 0.80$).

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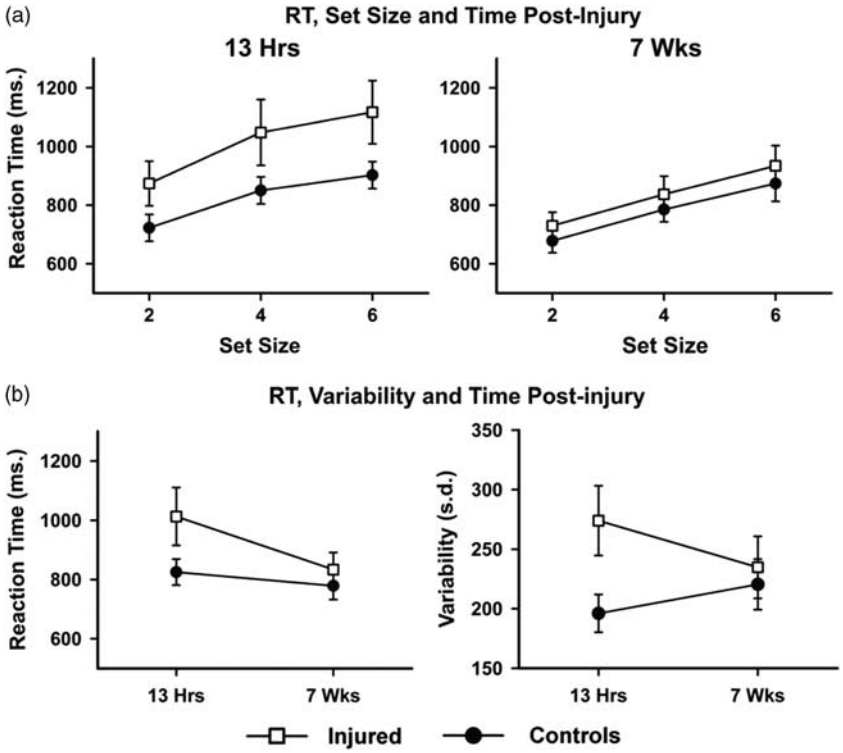

Fig. 1. Behavioral results of Sternberg task for Injured and Control subjects. Panel A shows the mean RTs for set size 2, 4, and 6 from the day following injury and 7 weeks later. Panel B shows the average reaction time (RT) for all set sizes (Group × Time interaction, $p = .05$) and the intertrial variability in RT on the day following injury and 7 weeks later (Group × Time interaction, $p = 02$).

Group differences for each set size and the overall mean RT were characterized by approximately equivalent moderate effect sizes at the 13-h session, indicating slower RTs for the Injured group (Table 2; Figure 1A). At the 7-week session, group differences were characterized by considerably smaller effect sizes. The Group × Session interaction indicated that the Injured players experienced significant improvement in RT between the 13-h and 7-week sessions (left panel of Figure 1B), whereas no change in RT occurred for Control players. As shown in the right panel of Figure 1B, Injured players demonstrated significantly more inter-trial RT variability (as indicated by standard deviation) than Controls at 13 h post injury (group × Session interaction, $p < .03$); this increased variability in the Injured subjects diminished to the level of the Controls by 7 weeks post injury.

Functional Imaging Results (Table 3, Figures 2 and 3)

To improve signal-to-noise in the fMRI analysis, we averaged the BOLD response over the three set sizes; this decision was justified by the absence of Group × Set Size interactions in the task performance data. No significant Group or Session main effects were identified for any of the three task phases. In contrast, we observed significant Group × Session interaction effects in 10 brain regions (Table 3; Figure 2) distributed over each of the task phases: Encode (3), Maintenance (3), and Response (4). Of these 10 regions, all but one was located in the right hemisphere. The BOLD activations giving rise to the interaction effects are plotted in Figure 3. In a majority of the regions (7 of 10), Injured subjects demonstrated less task activation at 13 h post injury relative to Controls; at 7 weeks post injury, the pattern reverses with Injured subjects showing greater activation than Controls (upper panel of Figure 3). The right inferior frontal gyrus (IFG) demonstrated this pattern during all three task phases (Encode, Maintenance, and Response). Similar interaction patterns were observed in the right inferior occipital gyrus (IOG) during Encode and in the right superior frontal gyrus (SFG) and right angular gyrus (AG) during Response. The opposite pattern (lower panel of Figure 3), Injured subjects having greater activation at 13 h and lower activation at 7 weeks relative to Controls, occurred in the right insula (Maintenance and Response) and left paracentral lobule (Maintenance).

In the injured players, we conducted exploratory correlations between activation in the ROIs and behavioral measures including the GSC, SAC, delayed memory, Sternberg accuracy, RT, and RT variance. After application of a FDR threshold, no significant correlations between activation levels in the ROIs and behavioral indices were identified.

DISCUSSION

This fMRI study is the first to document an anomalous pattern of brain activation within 24 h of a sport-related

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Table 3. Brain regions showing Group (Injured *vs*. Control) × Session (13-hr *vs*. 7-week) interaction in BOLD activation during each phase (Encode, Maintenance and Response) of Sternberg task

#	Region	Side	BA	Center of mass			Volume
				x	y	z	μL
	Encode						
1	Inferior occipital gyrus	R	18	28	−79	−10	773
2	Inferior frontal gyrus	R	6,9	32	2	32	737
3	SMA	R	6	7	5	53	537
	Maintenance						
4	Insula	R	13,38	40	7	−7	868
5	Inferior frontal gyrus	R	6,9	33	5	33	537
6	Paracentral lobule	L	5	−4	−34	51	508
	Response						
7	Superior frontal gyrus	R	9	14	46	30	776
8	Angular gyrus	R	39	47	−54	31	676
9	Insula	R	13,38	41	8	−7	651
10	Inferior frontal gyrus	R	6,9	34	6	29	541

# Denotes the region of interest shown in Fig. 2; Side represents the hemisphere of activation; CM = Center of Mass depicted in x, y and z Talairach coordinates; Volume represents microliters of tissue activated above threshold (see text).

concussion. During this acute phase, the injured athletes demonstrated *underactivation* of right hemisphere attentional networks relative to control athletes in most ROIs. In contrast, when we repeated the imaging examination during the subacute phase (7 weeks), the pattern reversed: injured athletes demonstrated greater activation than control athletes. These findings suggest that underactivation of attentional brain circuits may underlie the poor cognitive performance and subjective complaints of concussed players during the acute period. Conversely, the improvement in complaints and cognitive performance of concussed players during the subacute period are associated with increased activation of these same brain regions relative to controls. As noted by prior studies conducted during the subacute period (Jantzen et al., 2004; Lovell et al., 2007; Pardini et al., 2010), hyperactivation may represent a compensatory brain response that mediates recovery. Our study is the first to demonstrate the reversal in activation patterns that occurs in the transition from the acute to subacute recovery phases from concussion.

The underactivation in concussed athletes relative to controls during the acute period is seen primarily in right hemisphere regions commonly associated with attention. We (Arrington, Carr, Mayer, & Rao, 2000) and others (see Corbetta & Shulman, 2011, for review) have shown in fMRI studies of healthy subjects that activation of right hemisphere attentional networks occurs in the same right parietal and right inferior frontal regions where lesions produce hemispatial neglect (Heilman, Watson & Valenstein, 2012; Mesulam, 2000). It is noteworthy that

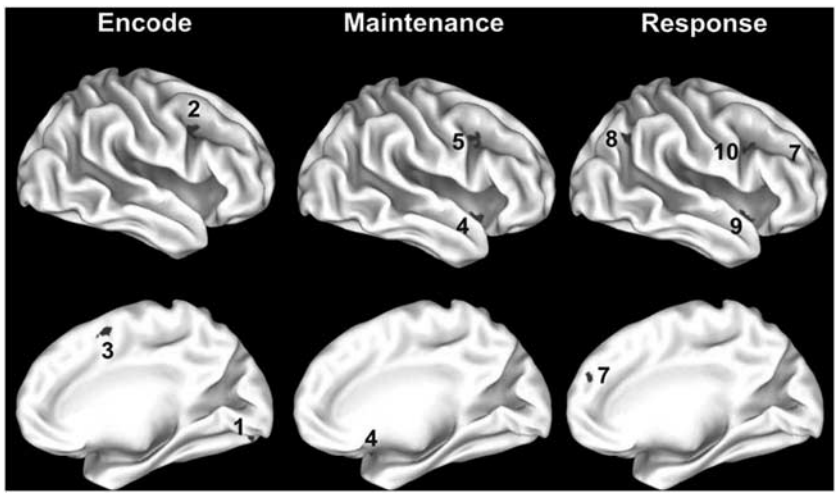

Fig. 2. Regions showing differences (Group × Session) in brain activation between Injured and Control players. Numbers correspond to brain regions identified in Table 3.

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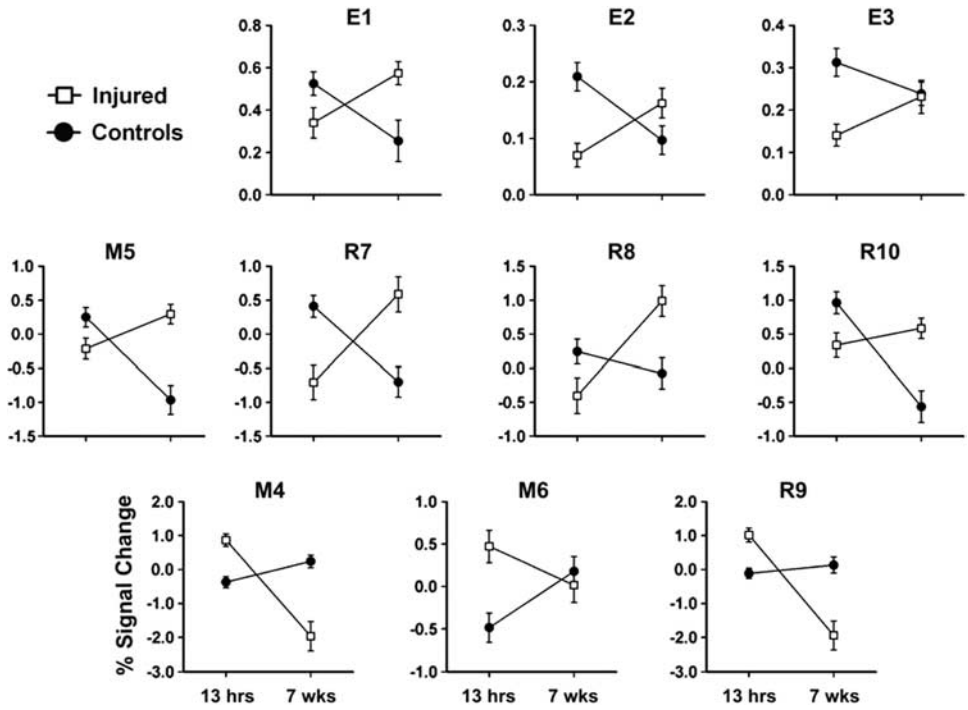

Fig. 3. Activation plots for each of 10 regions of interest (ROIs) identified in Table 2 and Figure 2. Plots in upper two rows show underactivation in ROI for Injured athletes relative to Controls at 13 h and hyperactivation in ROI for Injured athletes relative to Controls at 7 weeks post injury. Plots in the bottom row show hyperactivation in ROI for Injured athletes relative to Controls at 13 h and underactivation in ROI for Injured athletes relative to Controls at 7 weeks post injury.

the right hemisphere regions showing underactivation during the acute period in our concussed subjects overlap with attentional regions identified in these prior lesion and fMRI studies. Mayer and colleagues (2009) imaged concussed individuals of unspecified etiology at a mean interval of 11 days post injury and found decreased activation in a "bottom-up" attentional circuit. It should be noted that Mayer et al. study examined more severe injuries (e.g., mostly Grade 3 concussions) on average than the current study. Based on the Mayer et al. study and our own findings, it would appear that the acute phase of recovery is characterized primarily by an underactivation of attentional circuits.

Our imaging findings obtained during the acute period, when combined with imaging findings from other studies of sport-related concussion during the subacute and more remote periods of recovery (Chen et al., 2008b; Jantzen et al., 2004; Lovell et al., 2007; Pardini et al., 2010), suggest that multiple stages of recovery exist after concussion. In the *acute* stage when the effects of trauma are most severe, the individual shows both signs of abnormal neurophysiological function, postconcussion symptoms, and neurocognitive impairment. A *subacute* stage emerges when the neurophysiological substrates that support neurocognitive functions have recovered sufficiently to permit the individual to achieve normal performance levels on most standardized tests through compensatory cognitive operations. These compensatory cognitive operations likely involve the recruitment of additional attentional resources to perform tasks. Such compensatory operations are manifested by increased activation of core attentional circuitry needed to perform the task (e.g., Jantzen et al., 2004; Lovell et al., 2007; Pardini et al., 2010; Slobounov et al., 2010). Increased activation of these circuits further suggests that, despite appearing clinically recovered on neurocognitive testing, the injured individual during this stage of recovery will show signs of diminished mental stamina and fatigue prematurely when the cognitive demands are sufficiently prolonged. Signs of performance difficulties may also appear in this stage if the task is sufficiently challenging. Since brain functions have not yet fully normalized, it is possible that the athlete is neurophysiologically vulnerable to the effects of recurrent injury during this intermediate stage. The *chronic* stage of recovery occurs when both neurocognitive functioning is normal and the neurophysiological substrate has returned to its normal profile of operation, as evidenced by resolution of abnormalities on functional neuroimaging further out from injury (Chen et al., 2008b).

Injured athletes reported more postconcussive symptoms than Controls 13 h post injury. Additionally, while no significant cognitive and behavioral deficits survived the FDR correction for multiple comparisons, moderate to large effect sizes were seen at the 13-h assessment on multiple performance indices suggesting that the small sample size prevented the group comparisons from being statistically significant. The moderate to large effect sizes occurred on the SAC, BESS, delayed recall and recognition of a wordlist, and a working memory task (Letter-Number Sequencing), arguably among the most sensitive measures in our concussion battery. Nonetheless, on the whole, the cognitive deficits seen

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in the concussed players during the acute stage were generally mild with performances on many neuropsychological tests on the day following injury being comparable to control subjects. This relative lack of discrepancy in cognitive performance between injured and control subjects suggests a rapid recovery of general cognitive capacities in this mildly injured sample. Also, the close matching of injured and control subjects on preseason baseline variables and concurrent assessments conducted on paired athletes likely minimized incidental methodological differences (e.g., rigid adherence to timeline for study protocol in injured players and a more relaxed timeline for controls).

The lack of a group difference in slope in RT across the set sizes between injured and control was unexpected. Instead, newly concussed players had slower RT at all set size levels with a moderate effect size. This pattern of generalized slowing in choice RT is consistent with the findings of other researchers (Malojcic et al., 2008) and was accompanied by greater reaction time variability in the injured athletes during the acute period. Overall, performance on the Sternberg task suggests a generalized reduction in performance speed that is not specific to working memory load and is consistent with other investigations demonstrating a slowing of attentional shifts and decision-making in mild TBI victims (Mayer et al., 2009; Halterman et al., 2006). Such a generalized effect may be especially salient during the acute period after concussion, before the injured player has a chance to develop efficient compensatory strategies.

Altered brain activation patterns in injured athletes were seen in all phases of the Sternberg task (i.e., *Encode*, *Maintenance,* and *Response* phases), but the involved regions and direction of activation change across the task phases was not uniform. One exception to this was the right inferior frontal gyrus that showed decreased activation in acutely injured athletes relative to controls in all phases of the task. It is noteworthy that this region has shown *increased* activation in injured athletes during the subacute period in response to working memory measures (Lovell et al., 2007; Pardini et al., 2010; Slobounov et al., 2010).

A limitation of this study is the relatively small number of concussed and healthy participants. This is evidenced by the absence of significant group differences on behavioral testing despite medium to large effect sizes at the 13-h session. Because of the small sample sizes, we relaxed the minimal cluster size threshold that defines a significant brain activation effect from 809 to 500 microliters. Given the absence of functional imaging studies conducted during the acute period following sport-related concussion, we believed we were justified in using a more liberal criteria. The results of our study should be viewed as exploratory and require replication with a larger sample. Although we studied equal numbers of athletes with Grade 2 and Grade 3 concussions, we were unable to examine possible brain activation differences based on severity of injury given the small sample sizes in each subgroup ($n = 6$). Another limitation of this study is the inclusion of imaging sessions that capture only the acute and subacute recovery periods. Ideally, a third session conducted during the chronic period would more fully characterize the entire recovery period.

In summary, in this study of closely matched concussed and control athletes, we have demonstrated underactivation in right hemisphere attentional networks within 24 h of injury, followed by hyperactivation at 7 weeks post injury. This pattern of change in brain activation in the concussed athletes coincided with reduced postconcussive symptoms and improvements in neurocognitive performance. These findings suggest that fMRI may be an accurate imaging biomarker for documenting the brain changes that occur during the transition from acute to subacute stages of recovery. Furthermore, fMRI may prove to be a useful measure for assessing the efficacy of interventions designed to speed recovery at varying stages of recovery from concussion.

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