JOURNAL OF NEUROTRAUMA 35:267–277 (January 15, 2018)

DOI: 10.1089/neu.2017.5117

Concussion Alters the Functional Brain Processes of Visual Attention and Working Memory

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Abstract

Millions of North Americans sustain a concussion or a mild traumatic brain injury annually, and are at risk of cognitive, emotional, and physical sequelae. Although functional MRI (fMRI) studies have provided an initial framework for examining functional deficits induced by concussion, particularly working memory and attention, the temporal dynamics underlying these deficits are not well understood. We used magnetoencephalography (MEG), a modality with millisecond temporal resolution, in conjunction with a 1-back visual working memory (VWM) paradigm using scenes from everyday life to characterize spatiotemporal functional differences at specific VWM stages, in adults had had or had not had a recent concussion. MEG source-level differences between groups were determined by whole-brain analyses during encoding and recognition phases. Despite comparable behavioral performance, abnormal hypo- and hyperactivation patterns were found in brain areas involving frontoparietal, ventral occipitotemporal, temporal, and subcortical areas in concussed patients. These patterns and their timing varied as a function of VWM stagewise processing, linked to early attentional control, visuoperceptual scene processing, and VWM maintenance and retrieval processes. Parietal hypoactivation, starting at 60 ms during encoding, was correlated with symptom severity, possibly linked to impaired top-down attentional processing. Hyperactivation in the scene-selective occipitotemporal areas, the medial temporal complex, specifically the right hippocampus and orbitofrontal areas during encoding and/or recognition, lead us to posit inefficient but compensatory visuoperceptual, relational, and retrieval processing. Although injuries sustained after the concussion were considered ''mild,'' these data suggest that they can have prolonged effects on early attentional and VWM processes.

Keywords: adult brain injury; cognitive function; electrophysiology; traumatic brain injury

Introduction

Concussion, or also commonly referred to as mild traumatic brain injury (mTBI), is a global healthcare concern affecting millions in North America. The most common causes of concussion include motor vehicle accidents and falls. Whereas teens and young adults represent the highest risk group,[1] younger children (< 4 years) and older adults (≥ 65 years) are also vulnerable because of fall-related injuries, and they represent groups[2,3] whose risks are increasing. In recent years, emerging evidence has uncovered the subtle yet disabling cognitive, emotional, and physical sequelae of concussion.[1,4] Whereas in a majority of patients, full recovery is believed to occur within 3–6 months post-injury, in ~10–20% of patients, prolonged deficits have been reported years after the injury.[4–6] These deficits are predominantly related to memory and attention problems,[7–12] and are experienced as cognitive challenges in everyday life. Patients have reported poor concentration and planning abilities, increased distractibility, and slowed thinking.[10,13–16] Clinically, these self-reports are found to be associated with neuropsychological measures of depression, inattention, and information processing speed.[17]

One characteristic pattern of injury found in concussion is diffuse axonal injury (DAI). This refers to damage of the axons, primarily caused by the mechanical force that acted on the head during the course of a concussion, but also, there is secondary damage in which a cascade of pathological events follows in response to the damaged axonal cytoskeleton. It is some combination of these factors that can lead to long-range disconnections within the white matter.[18–20] The structural pathology of concussion is subtle and not easily detectable using standard imaging techniques such as a CT or an MRI. Although MRI provides improvements over CT, its resolution is not sufficient to reliably distinguish between

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microstructural injury and normal tissue.[21] Functional and electrophysiological indices such as those derived from functional MRI (fMRI)[22,23] or event-related potentials (ERP)[24,25] and magnetoencephalography (MEG) [26–28] have been valuable in this respect. They have afforded important insights into functional deficits, especially executive dysfunctions, which are associated with structural injuries after a concussion.[29,30]

Early fMRI studies in patients established an initial framework for the neural bases of working memory (WM) and attention problems in concussion.[23] These studies suggest that concussed patients exhibit an abnormal pattern of brain activations in laboratory-based verbal, auditory, and visual WM tasks, despite behavioral equivalence with healthy controls. Both hyper- and hypoactivation patterns have been reported in brain areas subserving WM, including the right parietal and prefrontal cortices,[22,31–33] and areas in the medial temporal lobe, specifically the parahippocampal gyri[11] and the right hippocampus.[34] The candidate mechanisms contributing to such neural activation differences are likely compensatory in nature, and proposals for such mechanisms range from altered allocation of WM resources,[22] reduced availability of resources,[35] to recruitment of additional resources.[36] Although fMRI-based regional changes related to WM and attention are well documented in concussion, the timing differences in the neural responses are not well characterized, and may explain whether resources are altered or additionally recruited.

From a large body of evidence, we know that visual attention and visual working memory (VWM) are intimately linked cognitive processes. Together they enable the selection of relevant visual information from the external world, and in the absence of ongoing visual input, they actively maintain this information as internal representations for temporary storage, monitoring, cognitive manipulations, and also retrieval.[37–39] The interaction among these processes occurs rapidly, within a few hundreds of milliseconds after presentation of the visual information. For example, electrophysiological studies in healthy controls suggest that attention modulates visual processing in the primary occipital (V1) and extrastriate areas, as early as 60–100 ms post-stimulus onset, and influences transmission of information through all the other stages of VWM.[40–42] In concussion, several studies have reported abnormal ERP components, emerging as differences in amplitudes or latencies compared with controls, which are found to correspond to the WM and attentional dysfunction. The P3 component, a positive-going cognitive component at latencies 300–800ms post-stimulus onset,[4] was found to be significantly attenuated in concussed patients, and its latencies were prolonged during visual and auditory oddball and visual n-back paradigms.[24,35,43–45] The P3 anomalies are thought to correspond to inefficient allocation of attentional resources largely subserving WM operations,[4,45] and have been negatively correlated with post-concussive symptom severity and behavioral outcome.[24,25,44,46] In addition to P3, abnormalities in the earlier N1/P2 complex suggest dysfunctions in visual processing and attentional selection in concussion.[35]

Together, both fMRI and ERP studies suggest atypical functional activation patterns in terms of neural sources and latencies in WM and attention circuitry in concussion. Although combining independent evidence somewhat mitigates the lack of temporal and spatial resolution associated with these techniques, we argue that the inability to study both of these aspects of VWM/attentional fast processing within the same paradigm imposes a significant barrier to our understanding of concussion-induced activation differences.[4] Therefore, in the current study, we used MEG, which allows: 1) a more direct measurement of neuronal activity than fMRI at a temporal resolution on the order of milliseconds, and 2) better spatial resolution, on the order of millimeters, than electroencephalography (EEG).[47,48] Using MEG, we characterized the spatial and temporal dynamics underlying attentional and VWM processes in concussion compared with healthy controls in a 1-back paradigm using complex scenes (photographs from everyday life).

We interrogated between-group differences in responses during 1) short-term encoding of complex scenes (visual and attentional processing, VWM maintenance) and 2) the immediate recognition (retrieval from VWM) of the repeated scenes presented after a short delay ($\sim$ 1.3 sec).[49,50] We posited that a 1-back paradigm with complex scenes would exert a high visuoperceptual and spatial-relational processing load but a relatively milder cognitive load than 2- or 3-back VWM tasks. This paradigm would reduce complexities induced by cognitive load manipulations, and would therefore provide ideal conditions in which to probe the neural mechanisms related to the stagewise processing of ecological visual events after a concussion.[51,52] Based on our prior findings in healthy controls,[50] we hypothesized involvement of prefrontal and medial temporal areas, particularly the right hippocampus and parahippocampal cortex, during active maintenance and retrieval of complex scenes at latencies of 200–400 ms, and involvement of temporo-occipital and parietal areas during early visual and perceptual processing at short latencies of 50–100 ms.

Methods

Participants

Thirty-seven male participants between the ages of 20 and 40 years, 18 with (mean age: 30 ± 7.3 years) and 19 without a recent concussion (mean age: 27 ± 5.2 years), all English-speaking, were included in this study (Table 1).

The concussion group included those with first-ever concussion diagnosed by clinicians in the emergency department at the Sunnybrook Health Sciences Centre, Toronto. Patients were recruited in a non-consecutive manner because some patients refused participation, some were not referred to the study by the attending physician, and some others had complications unrelated to the brain injury that precluded them from participation. Those requiring major orthopedic procedures were not included in the study. No patient was referred to the study after leaving the hospital.

Specific inclusion criteria were: no or <30 min loss of consciousness (LOC), no or <24 h post-traumatic amnesia (PTA), Glasgow Coma Scale (GCS) ≥13; within 24 h of injury, unremarkable CT scan and no skull fracture, and the time since injury being <3 months. Contraindications to MRI or MEG acquisition, such as presence of ferrous metal or implanted medical devices precluded participation in the study. Other exclusion criteria were the presence of neurological and/or psychiatric disorders, active substance abuse, or use of anticonvulsants, benzodiazepines, and/or GABA antagonist medications.

The controls were recruited from the community using flyers. The same exclusionary criteria as those for patients were applied for the recruitment of control participants. They had no history of a concussion, and no neurological or psychiatric disorders. Both groups were tested outside the MEG scanner using the Sports Concussion Assessment Tool 2 (SCAT2), a checklist of symptoms and their severity.[53] The total number of symptoms evaluated by SCAT2 was 22, including 9 physical (e.g., headache, blurred vision, balance problems), 6 cognitive (e.g., feeling slowed down and ''in a fog,'' difficulty concentrating and remembering), 4 emotional or behavioral (sadness or anxiety), and 3 related to sleep (e.g., drowsiness). The severity score per symptom, ranged from 0 to 6, where 0 = none and 5 or 6 = severe, with a maximum possible score of 132. To assess participants' mental and psychological health, both

Table 1. Demographics, Cognitive and Task Results

	Controls	*Concussion*	p *value*
n (all males)	19	18	
Age (years)	27 (±5.2)	30 (±7.3)	n.s.
Right-handedness	18/19	16/18	
WASI	115.9 (±7.6)	108.1 (±14.1)	0.057
Conners	6.4 (±6.8)	11.6 (±7.7)	0.035*
AUDIT	6.3 (±5.0)	8.9 (±6.5)	n.s.
GAD-7	2.7 (±4.4)	6.4 (±5.7)	0.035*
PHQ-9	2.7 (±5.0)	8.7 (±6.6)	0.004*
Time since injury (months)	—	1.2 (±0.5) range: 0.3–2.0	—
Symptom checklist[a]	2.4 (±3.9)	9.0 (±6.1)	<0.001*
Symptom severity score[a]	5.3 (±14.2)	19.8 (±18.3)	0.011*
Physical	0.7 (±1.1)	6.9 (±6.2)	—
Cognitive	0.5 (±1.2)	4.8 (±6.2)	—
Emotional/behavioral	0.4 (±1.0)	3.3 (±5.2)	—
Sleep	0.7 (±1.1)	5.1 (±4.0)	—
1-back task performance			
Accuracy (%)	96.9 (±3.4)	95.6 (±6.2)	n.s.
Reaction time (ms)	484 (±89.6)	464 (±81.0)	n.s.

[a]Sports Concussion Assessment Tool (SCAT2) for evaluation of symptom checklist and severity score; maximum possible number of symptoms 22, and symptom severity score 132.

*Statistical significance at $p < 0.05$.

WASI, Wechsler Abbreviated Scale of Intelligence; Conners 3rd ed., a test for attention-deficit/hyperactivity disorder; AUDIT, Alcohol Use Disorders Identification Test; GAD-7, Generalized Anxiety Disorder 7-item Scale; PHQ-9, Patient Health Questionnaire;

groups also completed a short assessment battery, which included the Wechsler Abbreviated Scale of Intelligence (WASI) for IQ,[54] the Alcohol Use Disorders Identification Test (AUDIT),[55] the Conners (3rd ed.™) Attention-Deficit Hyperactivity Disorder (ADHD) Test,[56] the Generalized Anxiety Disorder 7 test (GAD-7),[57] and the Patient Health Questionnaire (PHQ-9) to assess depression.[58,59]

The study was approved by the Research Ethics Boards at the Hospital for Sick Children and Sunnybrook Health Sciences Centre; all participants provided written informed consent.

VWM 1-back task

Two hundred and five scenes from everyday life were presented on a back projected screen inside the MEG scanner. The screen was at a distance of 78 cm from the participant's eyes, and images subtended a visual angle of 21 degrees horizontally and 13 degrees vertically. Forty-one scenes (20% of the total scenes presented) were randomly repeated immediately in subsequent trials. Participants were instructed to respond when they detected a repeated scene as quickly as they could using a button box. Scenes were displayed for 200 ms and then replaced by a fixation cross. The inter-stimulus interval was jittered between 1050 and 1300 ms (Fig. 1). Reaction time (RT) and accuracy were calculated based on participants' responses to the repeated stimuli. All stimuli were presented and responses captured using Presentation® software (NeuroBehavioral Systems, Inc.). The MEG trials collected during the encoding of the scenes and subsequent recognition trials (immediate recognition) were evaluated at the sensor- and source-levels, and compared between groups.

MEG acquisition and source localization

MEG data were collected using a CTF Omega 151 channel axial gradiometer system (CTF MEG, Coquitlam, Canada) at a 600 Hz sampling rate. Fiducial coils placed on the nasion, and left and right pre-auricular points provided a continuous measure of the head location in the MEG scanner. These were replaced by radio-opaque markers for structural MRI imaging. T1-weighted MRI images were acquired using a 3T MRI scanner (Magnetom Tim Trio, Siemens AG, Erlangen, Germany) using resolution three-dimensional magnetization-prepared rapid gradient echo (3D MPRAGE) sequences (repetition time [TR] = 2300 ms; echo time [TE] = 2.9 ms; flip angle [FA] = 9 degrees; field of view [FOV] = 28.8 × 19.2 cm; 256 × 256 matrix; 192 slices; 1 mm slice thickness).

The continuous MEG data were band-pass filtered at 1–50 Hz using a fifth order Butterworth filter, and were baseline corrected using SPM12 (version released October 2014; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). The data were epoched from 200 ms before the stimulus onset to 600 ms after onset (total 800 ms or 481 samples per epoch). The cardiac and eye blink artefacts were removed by independent component analysis (ICA).[60] The preprocessed MEG trials for encoding and recognition were converted from SPM to FieldTrip[61] (Donders Institute for Brain, Cognition and Behaviour; http://www.fieldtriptoolbox.org/).

Time-locked averages across trials were computed for both conditions for each participant. To inspect the sensor-level data, the global field power (GFP) across participants and channels was computed (Fig. 2). The time windows of interest for source-level analyses were informed by the GFP,[62] and were compared with baseline (–200–0 ms; 0 indicates stimulus onset): early (50–175 ms), intermediate (175–310 ms) and late (310–425 ms) time windows. These GFP-guided time windows denote the transition of evoked fields corresponding to extraction and perceptual processing of visual details immediately after stimulus onset to transformation of visual content into representations for short-term maintenance during encoding, and retrieval of this information during correct immediate recognition.[63–65]

Custom MATLAB (The MathWorks, Inc.. Natick, MA) scripts were created using high-level FieldTrip functions for sensor- and source-level visualization, forward and inverse solutions, and statistical analyses.

Co-registration was performed using the fiducials placed in MEG and in MRI. The brain surface was segmented from the realigned MRI scan. The single shell approximation method[66] was used to construct a volume conduction model on the segmented brain. Source models were constructed for each participant based on a 5 mm isotropic grid in three dimensions in Montreal

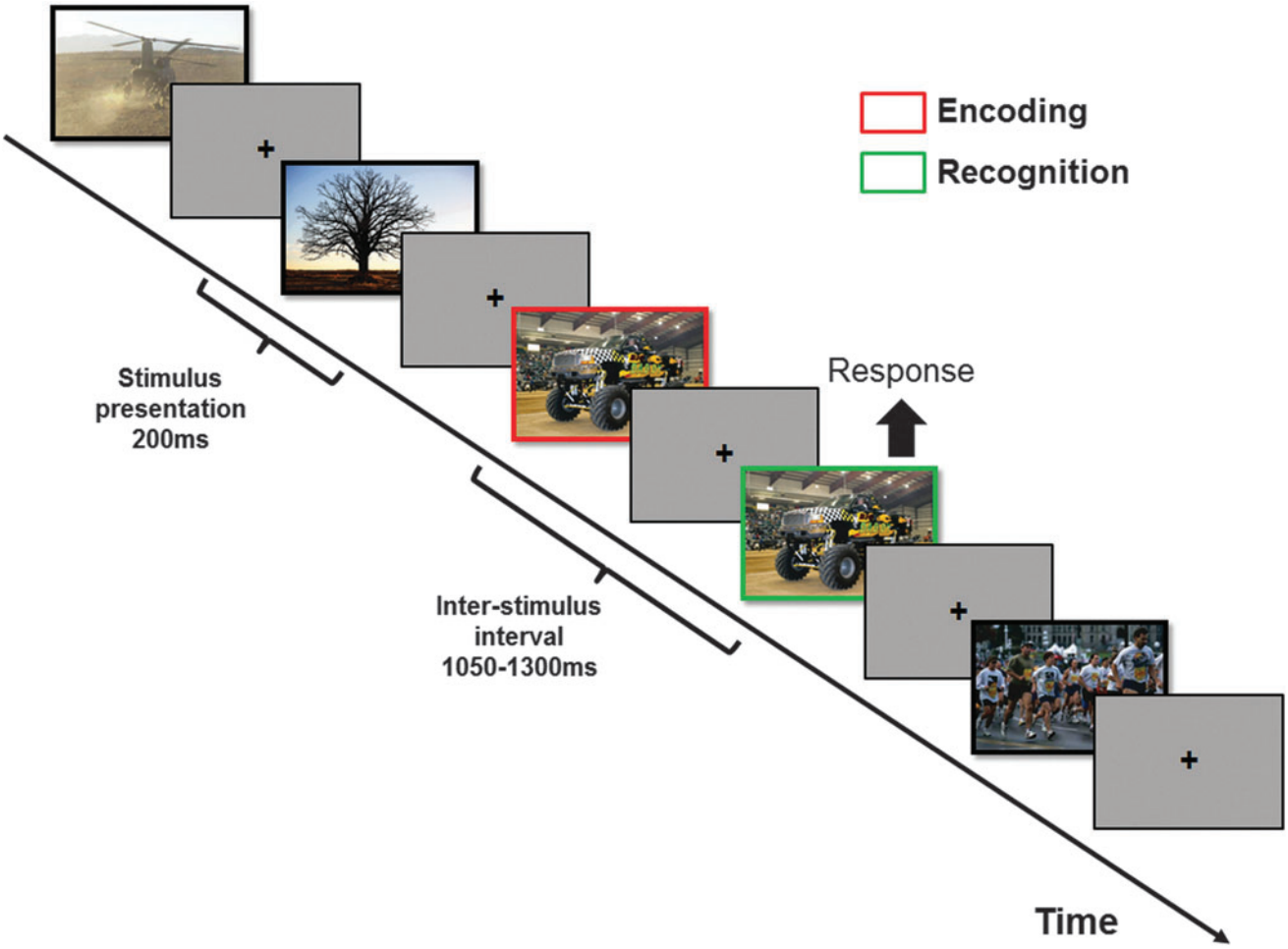

FIG. 1. Visual 1-back task with complex scenes. Color image is available online at www.liebertpub.com/neu

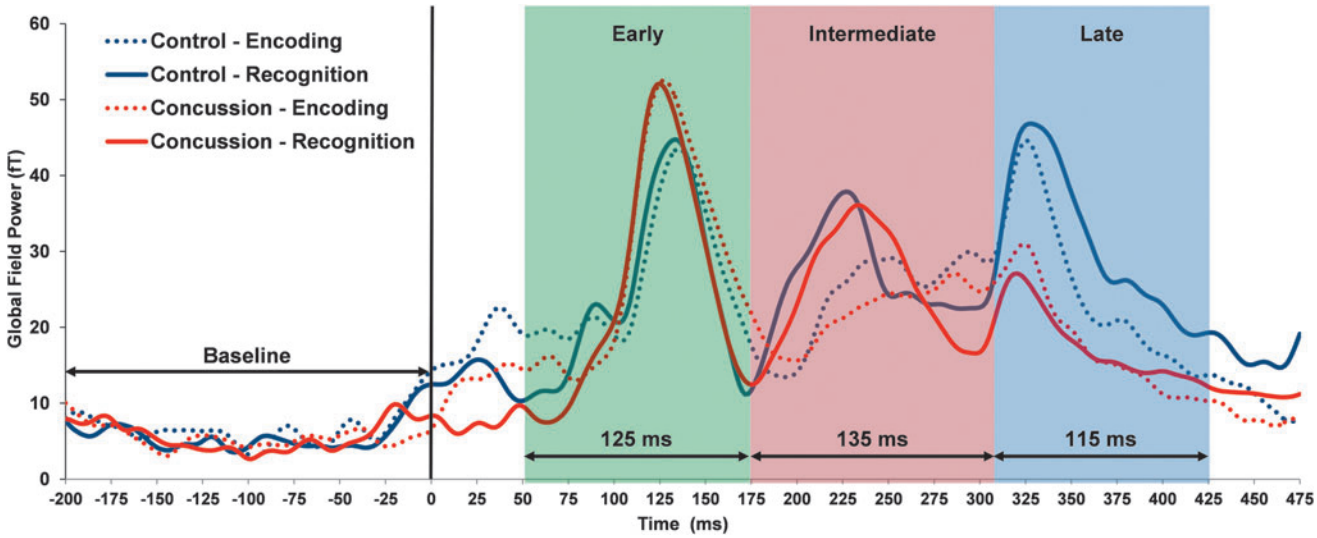

FIG. 2. Global field power on grand-averages of the sensor-level data for encoding (dotted lines) and recognition (solid lines) conditions in control (blue) and concussion (red) groups. Color image is available online at www.liebertpub.com/neu

Neurological Institute (MNI) space covering the entire template brain. The grids were warped into subject-space. The covariance matrix was computed from sensor-level data, averaged across trials, on the entire duration of the epoch from −200 to 600 ms for encoding and recognition. The linearly constrained minimum variance (LCMV)[67] beamformer was used to create a common spatial filter for each participant. Sensor MEG data were projected through the spatial filter to estimate source time series and power at each grid point for each participant and for each condition.

Power was computed for each time window of interest (baseline, early, intermediate, and late). Using this approach, source activities were also estimated at each grid point as a function of time.

Statistical analysis

The symptom checklist and severity, cognitive scores, and accuracy and reaction time (RT) on the 1-back task were compared between groups by Welch two sample *t* tests.

For the MEG data, to assess differences in activation patterns during encoding and recognition, sources of activation were localized in the early, intermediate, and late time windows, and compared between groups.[26,62] The normalized source activity and power were extracted after beamforming for baseline (−200–0 ms), and each of the active time windows (early, intermediate, and late). The normalized power at each grid point was subjected to nonparametric statistical test using Monte Carlo estimate on 1000 randomizations and T statistics. False discovery rate (FDR) correction with $\alpha = 0.05$ was used to correct for multiple comparisons. Significant activation maps were generated by thresholding the *t* values at $p_{FDR\text{-}corrected}<0.05$, and were interpolated onto the MNI template brain; MRIcron software[68] (https://www.nitrc.org/projects/mricron) was used to display the final results. Pearson's *r* was computed to measure correlations between normalized power of significant sources, transformed into a logarithmic scale, and post-concussive symptom severity in each group separately; partial correlation analysis was also computed to assess the impact of study-time intervals. The time series from the local maxima, as determined by the T statistic, were extracted for significant sources.

Finally, to assess the specific involvement of the right hippocampus, we conducted a region of interest analysis on averaged time series extracted from the left and the right hippocampus in both groups. Normalized power was compared at each time point using paired *t* tests for within-group comparisons. For sustained differences in time windows >15 ms, repeated measures ANOVA was conducted; for this analysis, if the assumption of sphericity was violated based on Mauchly's test, the degrees of freedom were corrected by a Greenhouse–Geisser method.

Results

The causes of injury in our patients included sports (33%), falls (22%), motor vehicle (22%) and other accidents (17%), and one work-related injury. Approximately half of the 18 patients (8 out of 18; 44.5%) had associated orthopedic injuries. Only four of these eight patients (22%) required surgery. The mean injury severity score (ISS) at the time of injury was 6.61 (± 6.0; median = 4.5).

Behavioral results

Table 1 summarizes the demographics, cognitive scores, and 1-back task performance results. The control and concussion groups were matched on age (t[30.5] = 1.5; $p > 0.05$). The mean time since injury in the concussion group was 1.2 (± 0.51; range: 0.3–2.0) months. The number of concussion symptoms (t[28.6] = 3.98, $p < 0.001$) and severity scores of the symptoms (t[32] = 2.69, $p = 0.011$) were higher in concussion than controls. Approximately 68% of the patients reported having trouble falling asleep, experiencing neck pain, and fatigue, and 61% had difficulty remembering, had headaches, and felt drowsy, irritable, nervous, or anxious (Fig. S1) (see online supplementary material at http://www.liebertpub.com). The scores on Conners ADHD (t[33.9] = 2.19, $p = 0.035$), GAD-7 (t[32] = 2.20, $p = 0.035$) and PHQ-9 (t[31.7] = 3.08, $p = 0.004$) were higher in the concussion group, indicating that the concussion group presented with reduced levels of attention, and increased anxiety and depression compared with the controls. The WASI scores (mean IQ in controls = 115.9 (± 7.6) and concussion = 108.1 [±14.1]) tended to be lower in the concussion group (t[27.1] = 1.98, $p = 0.057$) but they were within the average range for both groups. The AUDIT scores measuring alcohol consumption did not differ between groups (t[30] = 1.37, $p = 0.18$).

The mean accuracy on the 1-back task in the control group was 96.9% (± 3.4) and for the concussion group it was 95.6% (± 6.2), whereby the difference between groups was not significant (t[37.1] = 0.73, $p = 0.47$). The RT also did not differ between groups (mean RT controls: 484 ms [± 89.6] and concussion: 464 ms [± 81.0]; t[35] = 0.68, $p = 0.5$).

MEG results

The MEG trials collected during correct recognition trials and the preceding encoding trials (36–38 trials per condition) were subjected to source localization analyses. Three peaks in the GFP showed effects of encoding and correct recognition (Fig. 2). In both groups, the earliest peak after the stimulus onset was found in the time window ranging from 50 to 175 ms, the intermediate peak was between 175 and 310ms, and the late peak was between 310 and 425ms. These time windows (early, intermediate, and late) were used in the subsequent analyses to determine the sources of group effects during encoding and recognition trials; the results from these analyses are summarized in Table 2.

Encoding

Early. The left lingual gyrus (MNI coordinates: [−12.5, −80, 0], t = 4.1, $p = 0.001$) was more active in the concussion than the control group (98–125 ms, Fig. 3a), whereas the right superior parietal ([17.5, −50, 75], t = 3.88, $p = 0.001$), inferior parietal ([42.5, −45, 55], t = 2.99, $p < 0.001$; 60–78 ms), and left middle frontal ([−47.5, 40, 20], t = 3.04, $p = 0.001$) areas were significantly more active in the control than in the concussion group. Analyses on the virtual time courses of the right inferior parietal area confirmed significant sustained activations in controls, starting at ∼60ms ($F[1, 385] = 7.81$, $p = 0.008$) as well as a late increase from 390 to 412 ms (F[1, 455] = 5.31, $p = 0.027$) compared with concussed patients. Further, reduced activation magnitude in the right inferior parietal area was correlated with increased severity of post-concussive symptoms in the concussion group ($r = -0.60$, $p = 0.0106$), which persisted after controlling for time since injury ($p = 0.013$). The relationship was not significant in the control group ($r = -0.03$, $p = 0.89$).

Intermediate. The right hippocampus ([17.5,-30,-5], t = 3.08, $p = 0.002$) and parahippocampal cortex ([32.5,-40,-5], t = 3.0, $p = 0.002$; Fig. 3a) exhibited greater activation in the concussion group. Analyses comparing the virtual time series from the right and the left hippocampal areas demonstrated the specificity of these activations; although no differences between the left and right hippocampal activity were found in the control group, the concussion group activated the right hippocampus more than the left hippocampus. This difference was significantly greater from 248 to

Table 2. Sources of Activation Differences between Groups During Early (50–175 ms), Intermediate (175–310 ms), and Late (310–425 ms) Processing in Encoding and Recognition Trials

Time windows	*Group differences*		*Brain area*	*MNI coordinates*
Encoding				
Early	Concussion > Control	L	Lingual	[−12.5, −80, 0]
	Control > Concussion	R	Superior parietal	[17.5, −50, 75]
		R	Inferior parietal	[42.5, −45, 55]
		L	Middle frontal	[−47.5, 40, 20]
Intermediate	Concussion > Control	R	Hippocampus	[17.5,-30,-5]
Late	n.s.			
Recognition				
Early	Concussion > Control	L	Lingual	[−7.5, −80, −10]
		L	Superior temporal	[−47.5, −15, 0]
Intermediate	Control > Concussion	L	Inferior occipital	[−22.5, −100, −10]
		L	Middle occipital	[−17.5, −95, 0]
		L	Calcarine	[−17.5, −100, −5]
Late	Concussion > Control	R	Lingual, parahippocampal/ hippocampus	[12.5, −30, −10]
		R	Inferior orbitofrontal	[37.5, 30, −20]
	Control > Concussion	L	Calcarine	[−2.5, −70, 10]
		L	Supplementary motor area	[−2.5, 10, 75]
		R	Thalamus	[12.5, −15, 15]

263 ms ($\varepsilon = 0.18$, $F[1.60] = 5.60$, corrected $p = 0.01$) and from 300 to 333 ms ($\varepsilon = 0.08$, $F[1.63] = 5.23$ corrected $p = 0.012$).

Late. No activation differences were found in the late time window for encoding.

Recognition

Early. The left lingual gyrus ([−7.5, −80, −10], t = 3.2, $p = 0.001$) and the left superior temporal gyrus ([−47.5, −15, 0], t = 3.55, $p = 0.001$) were more active in the concussion than in the control group.

Intermediate. The left inferior ([−22.5, −100, −10], t = 3.68, $p = 0.001$), middle occipital ([−17.5, −95, 0], t = 3.02, $p = 0.002$) and calcarine ([−17.5, −100, −5], t = 2.94, $p = 0.002$) areas were more active in the controls than in concussed patients.

Late. The concussion group showed greater activation in the right lingual ([12.5, −30, −10], t = 3.27, $p = 0.002$) and the surrounding hippocampal/parahippocampal areas (Fig. 3b) and in the right inferior orbitofrontal region ([37.5, 30, −20], t = 3.08, $p = 0.001$), but less activation in the left calcarine ([−2.5, −70, 10], t = 2.88, $p = 0.002$), supplementary motor area ([−2.5, 10, 75], t = 2.83, $p = 0.001$), and right thalamus ([12.5, −15, 15], t = 2.69, $p = 001$) than controls. Analysis between left and right hippocampal activations confirmed that the right was more active than the left in the concussion group from 393 to 413 ms ($\varepsilon = 0.15$, $F[1.77] = 6.35$, corrected $p = 0.004$), and from 437 to 475 ms (Fig. 3c).

Discussion

Our MEG source localization and temporal findings in a scene-based 1-back paradigm demonstrate atypical neural dynamics in concussion patients within the first months post-injury. In the current study, the 1-back task is characterized by visual short-term or WM and its interaction with attention, in two different phases involving encoding and active maintenance of scenes, as well as the use of stored information for immediate recognition of repeated scenes.[69] New evidence from the whole-brain MEG analysis in concussed patients, compared with healthy controls, revealed significant patterns of hypo- and hyperactivations in brain areas typically linked with early visual selection and attentional control, visuoperceptual processing, and active retention and retrieval of complex visual scenes.

During encoding, reduced activity in the left middle frontal and right inferior parietal areas with increased activity in the left lingual areas were found in early stages after stimulus presentation in concussion, followed by increased right hippocampal activations in the intermediate processing stages. This pattern of activation in concussion suggests reduced top-down attentional control during early visual processing, and perhaps compensatory mechanisms during active VWM maintenance. During recognition, increased left lingual activation during early processing was found in concussion, followed by reduced occipital activity in the intermediate stages and finally in the late stage, and increased activity in the right hippocampal-lingual and inferior orbitofrontal areas. This suggests that inefficient visuoperceptual processing and top-down control during early stages resulted in more effortful retrieval during intermediate and later stages.

Encoding: Selective attention, scene processing and VWM maintenance differences

Emerging as early as 50–60 ms after stimulus onset, hypoactivation of the left middle frontal and right parietal areas was found in concussion patients during encoding of complex visual scenes. This reduced activity (observed in the right inferior parietal region) was exclusively associated with more severe post-concussive symptoms in these patients. Immediately following this early fronto-parietal hypoactivation, an abnormal cascade of hyperactivation in the ventral occipitotemporal-left lingual gyrus, and the medial temporal areas—the right hippocampus and parahippocampal cortex—was found. The virtual time course analyses showed that the earliest time point of differences between groups in the right inferior parietal area was at ~60–80ms, whereas in the left lingual gyrus, the activity differences peaked around ~98–127 ms.

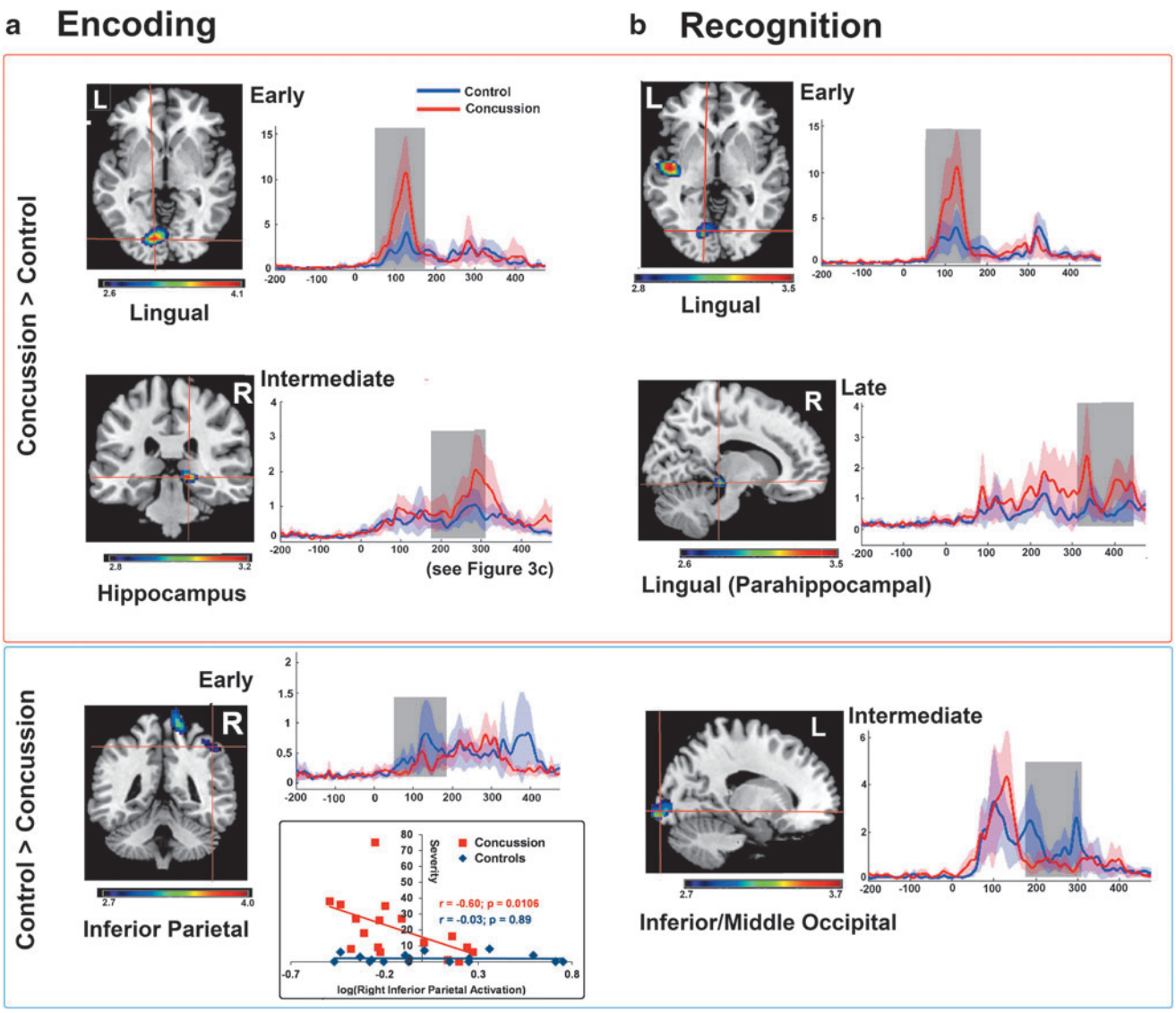

FIG. 3. Significant differences in normalized power at the source level and the corresponding source time series with standard errors in the control (blue) and the concussion (red) groups in different time windows; **(a)** encoding, **(b)** recognition, **(c)** average regional virtual time series extracted from the left (black) and right (pink) hippocampi during encoding in the concussion and the control group; pseudo-z on the y-axis represent the degree of activations in significant sources; time in milliseconds on the x-axis. Color image is available online at www.liebertpub.com/neu

This temporal profile of frontoparietal and lingual/ventral occipitotemporal activation suggests functionally relevant modulation among these areas in controls, which may be compromised in concussed patients. Typically, activation in frontoparietal areas immediately after stimulus presentation is associated with deployment of selective attention and top-down modulation of the visual areas, which in turn facilitate subsequent VWM processing.[70,71] Therefore, one would predict frontoparietal activity (as Hopf specifically predicted the parietal activity), to precede activity in the occipitotemporal-extrastriate areas in the ventral visual stream.[48] Plomp and colleagues[41] provided support for this notion. They interrogated directional interactions among attentional and visual areas at short latencies (< 100 ms) and showed that task-related attentional processes driven by frontoparietal areas were exerted immediately after stimulus onset. These processes occurred at both C1 (starting at 50 ms) and N1 latencies, and considerably influenced visual evoked responses. Importantly, they were driven through continuous parietal activity.[41] Based on these findings, we propose that the inferior parietal activity observed in our controls as early as ~60 ms had a modulatory effect on the evoked activity in the left lingual gyrus, and the lack thereof in concussed patients, observed as reduced parietal activity, may have resulted in enhanced left lingual activity.

However, the functional significance of the increased activation in concussed patients requires explanation. The left lingual activation that we found was localized to a collateral sulcus region,[72] posterior to the functionally defined parahippocampal place area (PPA) and retrosplenial complex (RSC).[73] Together, these regions have been shown to play a central role in the perception and recognition of real-world visual scenes. These areas are involved in processing higher-level visual and spatial properties of the scenes, and they form local representations in the presence of continuous visual input, which then facilitate scene recognition after a short time delay.[73] In the absence of early selective attention mechanisms in concussed patients, hyperactivation in scene-selective areas indicates

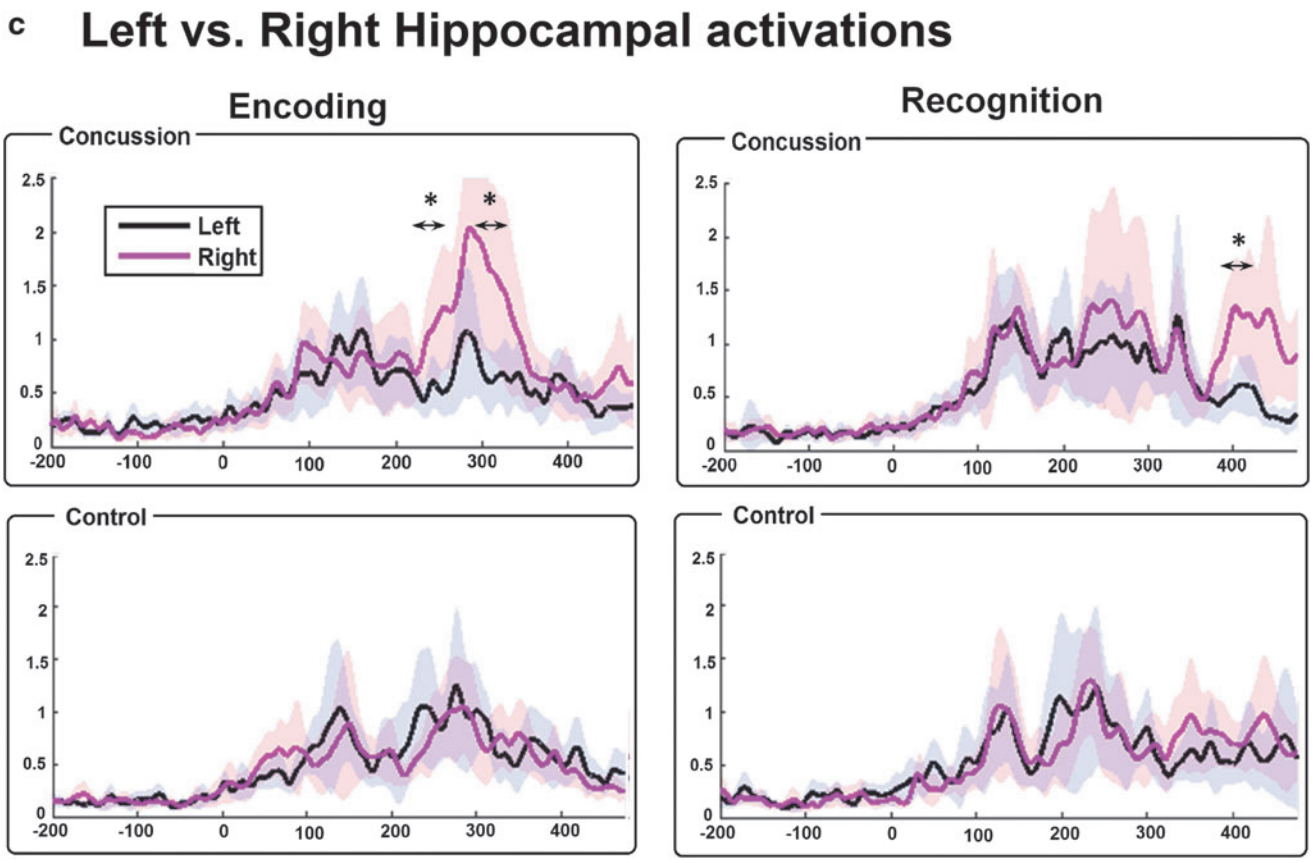

FIG. 3. (Continued)

a differential and possibly inefficient response to high visuoperceptual load in extracting salient visual details from complex scenes.

Further, we found heightened activity in the right hippocampus in concussion patients, starting at ~250–300 ms, which is 50–100 ms after the scene disappears from view. Time series analyses revealed a dissociation in activity levels between the left and right hippocampi in the concussion group; the right hippocampal activations were significantly greater than the left, which started at ~248 ms post-stimulus onset. No sustained activity differences between the hippocampi were found in controls. Recent evidence suggests that in addition to the PPA and RSC, the hippocampi are also linked to scene processing, although their precise role is considerably debated and is not currently fully understood. The hippocampi interact with scene-selective occipitotemporal areas (specifically the collateral sulcus), which are shown to be mediated by the parahippocampal gyrus and RSC.[74]

The right hippocampus is found to be preferentially engaged in the construction of complex representations when processing scenes.[74–76] It plays an important role in relational and spatial processing of constituent elements in a complex scene and in contextual binding in order to make sense of the scene.[52,77] There is evidence in the literature suggesting that increased demand for such complex stimulus processing and construction of spatial representations, and not WM demand, induces greater right hippocampal and parahippocampal activations.[69,78] Other evidence suggests a key role of these areas in actively holding or maintaining novel information.[79] This could explain why the observed differences in right hippocampal activations emerged in the time period ~50 ms after stimulus offset.

Overall in keeping with prior literature, we posit that the absence of modulatory activity between attentional and early visual processing areas may be indicative of inefficient early allocation of attentional resources,[22] or reduced availability of these resources in the *frontoparietal* areas.[35] Although these attentional inefficiencies were not sufficient to negatively impact the behavioural performance, they may be the initial trigger for the atypical cascade of *occipitotemporal* activations that followed, likely to support complex visuoperceptual and VWM processes. Specifically, the accentuated collateral sulcus (left lingual) and right hippocampal/parahippocampal activations suggest inefficient recruitment and/or more effortful perception related to complex scenes during presentation, followed by construction and relational processing and/or maintenance of complex scene representations after stimulus offset in concussed patients.[52,78–80]

VWM retrieval during immediate scene recognition

An abnormal pattern of activity was also found during immediate scene recognition in concussed patients compared with controls. Approximately 175 ms after the scene presentation, controls activated the left middle and inferior occipital and calcarine areas more than the patients, which lasted until ~350 ms. The concussion patients, on the other hand, exhibited hyperactivation of the scene-selective left lingual areas, localized to the collateral sulcus region, and the left superior temporal area (close to the rolandic operculum) at latencies ~100 ms and 140 ms, respectively. In addition, sustained hyperactivation in the right orbitofrontal areas and the right medial temporal complex were also found peaking around 450 ms. According to the model proposed by Sewards, reciprocal activations in the primary occipital, higher-order parietooccipital, and thalamic areas mediate scene recognition.[76] Pre-retrieval, a mental image of

the scene is produced based on mnemonic scene representations in the parietooccipital areas, which does not typically require active contribution from hippocampal or parahippocampal areas. Post-retrieval, the orbitofrontal and temporopolar areas contribute to the conscious awareness of scene recognition; representations of recently experienced scenes are found in the orbitofrontal area and those of familiar scenes in the temporopolar areas.

Based on this model, the increased lingual activation in the early stages suggests pre-retrieval visual processing differences, as in the encoding phase. The activation differences in the middle occipital and calcarine areas at $\sim$175–350 ms latencies suggest that the controls engaged in incidental rehearsal and mental imagery for maintaining the recently experienced scenes ''in the mind's eye.''[76] In contrast, the left lingual and superior temporal activation in patients greater than controls starting at $\sim$100 ms suggests that patients recruited different visual and recognition/retrieval mechanisms, which did not appear to rely on visual rehearsal or imagery; they perhaps favored accumulation of visual details (as in the encoding phase), verbal/semantic processing, and semantic knowledge retrieval of the encoded scenes.[39,76,81] Further, heightened activation in the late time window $\sim$450 ms in the right medial temporal complex and the sustained right orbitofrontal activation, along with the absence of later occipital/calcarine involvement, suggest that patients adopted a different strategy from the controls not only during pre-retrieval but also during post-retrieval awareness. Overall, the early and late temporofrontal hyperactivation during scene recognition appears to correspond to differential recruitment of pre- and post-retrieval resources in concussed patients. Based on spatiotemporal characteristics of activation differences, we posit that controls relied on visual mnemonic representations and visual rehearsal mechanisms, whereas patients adopted strategies of ''verbal recoding'' and/or ''reactivation'' of stored visual information.[39,69]

Conclusions and Future Research

Our findings demonstrate that although injuries sustained from a concussion may be considered ''mild,'' they can have longer-term effects on early attentional and VWM processes, even during relatively undemanding tasks. Neural responses related to the processing of ecological visual scenes were abnormal, starting as early as 60 ms and lasting up to 475 ms after presentation, and included frontoparietal, ventral occipitotemporal, medial temporal, and orbitofrontal areas. The observed temporal profile of frontoparietal and ventral occipitotemporal activations is particularly interesting, as it suggests functionally relevant modulation among these areas in controls, which may be compromised in concussed patients secondary to injury. The reduced early parietal activity was the only source of difference between groups that was associated with post-concussive symptom severity in concussed patients. This finding warrants larger-scale future investigation, as the reduced early parietal activation could serve as an objective temporal marker of post-concussive symptom prognostication.

Our choice of complex scenes as task stimuli in a 1-back paradigm resulted in a high visuoperceptual processing load, and, therefore, provided us an opportunity to investigate the patterns of neural recruitment in response to greater visual and perceptual demands than WM or cognitive demand. However, as the patients' performance was comparable with that of controls, the different functional activation patterns in patients likely represent compensatory mechanisms. Exploring these functional patterns further using measures of effective connectivity[82] and determining the triggers for these mechanisms in these patients, would be important future directions. This knowledge is of particular relevance for treatment planning for patients with mild injury but significant negative behavioral outcome. Using techniques that directly modulate brain activity such as noninvasive brain stimulation,[83] specifically excitatory stimulation centered on the frontoparietal areas, may be a future avenue to explore for these patients.

Acknowledgments

We thank Amanda Robertson and Allison Bethune who recruited the patients and conducted the testing. We are also grateful to Anne Keller and Marc Lalancette for their valuable advice on MEG processing and analyses during the early stages of this study. This work was supported by Defence Research and Development Canada (DRDC), the Canadian Forces Health Services awarded to authors M.J.T. and E.W.P. (contract # W7719-135182/001/TOR), and the Ontasian Imaging Lab which supported P.P.S. (Dr. Manohar Shroff, Director Ontasian Imaging Lab) at The Hospital for Sick Children.

Author Disclosure Statement

No competing financial interests exist.

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