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Low-frequency connectivity is associated with mild traumatic brain injury

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A B S T R A C T

Mild traumatic brain injury (mTBI) occurs from a closed-head impact. Often referred to as concussion, about 20% of cases complain of secondary psychological sequelae, such as disorders of attention and memory. Known as post-concussive symptoms (PCS), these problems can severely disrupt the patient's quality of life. Changes in local spectral power, particularly low-frequency amplitude increases and/or peak alpha slowing have been reported in mTBI, but large-scale connectivity metrics based on inter-regional amplitude correlations relevant for integration and segregation in functional brain networks, and their association with disorders in cognition and behaviour, remain relatively unexplored. Here, we used non-invasive neuroimaging with magnetoencephalography to examine functional connectivity in a resting-state protocol in a group with mTBI ($n = 20$), and a control group ($n = 21$). We observed a trend for atypical slow-wave power changes in subcortical, temporal and parietal regions in mTBI, as well as significant long-range increases in amplitude envelope correlations among deep-source, temporal, and frontal regions in the delta, theta, and alpha bands. Subsequently, we conducted an exploratory analysis of patterns of connectivity most associated with variability in secondary symptoms of mTBI, including inattention, anxiety, and depression. Differential patterns of altered resting state neurophysiological network connectivity were found across frequency bands. This indicated that multiple network and frequency specific alterations in large scale brain connectivity may contribute to overlapping cognitive sequelae in mTBI. In conclusion, we show that local spectral power content can be supplemented with measures of correlations in amplitude to define general networks that are atypical in mTBI, and suggest that certain cognitive difficulties are mediated by disturbances in a variety of alterations in network interactions which are differentially expressed across canonical neurophysiological frequency ranges.

1. Introduction

Mild traumatic brain injury (mTBI) is due to considerable changes in acceleration and resultant impact forces on the brain (Niogi et al., 2008; Xu et al., 2007). These forces may damage white matter, comprising stretching, inflammation, disruption, and separation from grey matter structures (Ball et al., 1977; Gloor et al., 1977; Huang et al., 2007) and may also induce changes in cholinergic transmission (Huang et al., 2014). Commonly referred to as concussion, mTBI is reported in emergency rooms in less than 2% of the overall population, although it encompasses about 75% of all head injuries, with the additional 25% including moderate and more severe TBI. Post-concussive symptoms (PCS) are often observed (Levin et al., 1987), broadly defined by three psychological clusters in the behavioural, cognitive, and emotional domains. Particularly prevalent are complaints such as irritability and fatigue, inattention, impulsivity and memory deficits, and anxiety and depression (Ryan and Warden, 2003). These symptoms spontaneously subside in about 80% of cases in less than 3 months post-injury; however, the other 20% continue to experience secondary, chronic psychological sequelae that can fail to attenuate (Binder et al., 1997), severely disrupting the patient's quality of life.

Despite these psychological problems, *structural* neuroimaging is unremarkable and often fails in diagnostics due to the lack of conspicuous neural lesions. However, *functional* neuroimaging has proven its

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efficacy in delineating indicators of the disorder (Huang et al., 2007). One of the macroscopic functional imaging markers that tend to distinguish sufferers of mTBI is changes in local spectral power measured using electroencephalography (EEG) and magnetoencephalography (MEG), as low-frequency amplitude increases, and/or peak alpha oscillatory slowing, have been reported by multiple groups (Huang et al., 2009; Lewine et al., 2007; Lewine et al., 1999; Tarapore et al., 2013).

Technological advances in the analyses of intrinsic brain connectivity, examined using resting-state paradigms have proven suitable for mapping functional connectivity (FC) among brain regions. Using this translatable and readily operationalised protocol, researchers have mapped the intrinsic and dynamic communication patterns underlying the spatio-temporal coordination of information (Damoiseaux et al., 2006) required for complex goal-directed behaviour. FC is reflected in the coordination of neurophysiological activity among neural populations relevant for cortical computation and information integration (Wang, 2010) has shown to be useful in exploring cortical pathophysiology as well as neurological and neuropsychiatric disorders and their symptoms (Tewarie et al., 2013). MEG has proven particularly fruitful in this regard, and allows the patterns of brain activity from direct neural firing to be mapped with millisecond precision (Hari and Salmelin, 2012), supporting accurate noninvasive interrogation of coordinated oscillatory activity in the human brain relevant for cognition (Palva et al., 2005). Coordinated fluctuations in band-limited oscillatory amplitudes across brain regions have recently been shown to be an effective means for mapping the functional networks of the brain using MEG (Brookes et al., 2011a; Brookes et al., 2011b; Hipp et al., 2012). This technique provides an ideal opportunity, as there is little evidence of how mTBI modifies large-scale electrophysiological connectivity patterns of brain integration and segregation, and how this impacts cognition and behaviour. Given the hypothesised role of deafferentation of white matter in the disorder, axonal structures that mediate brain communication, changes in FC might be expected to be one of the principal outcomes and aetiology for PCS.

Prior studies have not investigated neurophysiological network connectivity in mTBI, or potential associations between altered network interactions in specific frequency ranges and the cognitive, affective and behavioural sequelae associated with this condition. To address this knowledge gap, we used non-invasive neuroimaging with MEG to examine FC in a resting-state protocol in a group with mTBI compared to a matched control group. We tested the hypotheses that mTBI patients would express atypical resting-state network amplitude correlations. Furthermore we performed an exploratory, data-driven analysis examining individual variability in certain cognitive-behavioural measures, and whether they correlated with connectivity measures and graph theoretical metrics. We selected connection weight, node strength and degree as our graph properties of interest, as they most directly correspond to network hyperconnectivity or hypoconnectivity, and thus correspond most closely with our hypothesis that patients with mTBI would show alterations in network-level neurophysiological interactions.

2. Methods and materials

2.1. Participants

Resting-state MEG data were recorded from 20 male participants with mTBI (less than 3 months post-injury, mean days since injury = 32.20, SD = 17.98, mean age at injury = 31.4 years, SD = 6.87). An age- and sex-matched control group without any history of TBI comprising 21 participants (mean age = 27.0 years, SD = 5) was also recruited.

Participants with mTBI were recruited from the emergency department of Sunnybrook Health Science Centre, Toronto. Inclusion criteria were: between 20 and 40 years of age; concussion symptoms whilst in emergency; less than 3 months since injury; if loss of consciousness occurred, then less than 30 min; if post-traumatic amnesia occurred, then less than 24 h; causes of head injury were clear (e.g. sustaining a force to the head); Glasgow Coma Scale ≥ 13 (within 24 h of injury); no skull fracture; unremarkable CT scan; no previous incidence of concussion. Every participant in the mTBI group completed the Symptom Checklist and Symptom Severity Score (Sports Concussion Assessment Tool 2; SCAT2); was able to tolerate enclosed space for MR brain imaging; English speaking, to comply with instructions to complete tasks during MEG and MR scans and able to give informed consent. The control group had no history of TBI (mild, moderate or severe) or neurological disorders. Exclusion criteria included ferrous metal inside the body that might be classified as MRI contraindications, or items that might interfere with MEG data acquisition; presence of implanted medical devices; seizures or other neurological disorders, or active substance abuse; certain ongoing medications (anticonvulsants, benzodiazepines, and/or GABA antagonists) known to directly or significantly influence electroencephalographic (EEG) findings.

All participants underwent cognitive-behavioural testing in addition to the MEG resting-state scan. These assessments included: estimates of IQ from the Wechsler Abbreviated Scale of Intelligence (WASI); the Alcohol Use Disorders Identification Test (AUDIT); Conners Attention-Deficit Hyperactivity Disorder Test; the Generalised Anxiety Disorder 7 test (GAD-7); Patient Health Questionnaire (PHQ9); and the Sports Concussion Assessment Tool 2 (SCAT2).

2.2. Procedure and MEG data acquisition

Resting-state MEG data were collected whilst participants were lying supine, and instructed to rest with eyes open and maintain visual fixation on an X within a circle on a screen 60 cm from the eyes. MEG data were collected inside a magnetically-shielded room on a CTF Omega 151 channel system (CTF Systems, Inc., Coquitlam, Canada) at The Hospital for Sick Children, at 600 Hz for 300 s. Throughout the run, head position was continuously recorded by three fiducial coils placed on the nasion, and left and right pre-auricular points.

After the MEG session, anatomical MRI images were acquired using the3 T MRI scanner (Magnetom Tim Trio, Siemens AG, Erlangen, Germany) in a suite adjacent to the MEG. Structural data were obtained as T1-weighted magnetic resonance images using resolution 3D MPRAGE sequences (repetition time [TR] = 2300 ms; echo time [TE] = 2.9 ms; flip angle [FA] = 9°; Field-of-view [FOV] = 28.8 × 19.2 cm; 256 × 256 matrix; 192 slices; 1 mm isovoxel) on a 12-channel head coil. MEG data were coregistered to the MRI structural images using the reference fiducial coil placements. A multi-sphere head model was constructed for each individual and brain space was normalised to a standard Montreal Neurological Institute (MNI) brain using SPM2.

2.3. MEG data processing

2.3.1. Seed definition and virtual electrode recording

MEG data were band-pass filtered offline at 1–150 Hz, a notch filter applied at 60 Hz (8 Hz bandwidth) and a third-order spatial gradient environmental noise-cancellation applied to the recording. *A priori* sources (seeds) of interest in the cortex and sub-cortical regions were identified from the Automated Anatomical Labeling AAL (Tzourio-Mazoyer et al., 2002) atlas giving 90 locations for time-series to be extracted and analysed. Broadband time-series ('virtual electrodes') from these voxels were reconstructed using a vector beamformer on the basis of the 90 AAL coordinates for each subject and filtered into 'classical' EEG bandwidths for further analysis: Delta (1–4 Hz), theta (4–7 Hz), alpha (8–14 Hz), beta (15–30 Hz), low gamma (30–80 Hz) and high gamma (80–150 Hz) (see Fig. 1).

Continuous time series were reconstructed from each of the 90 cortical and subcortical locations using beamformer analysis. Beamformers are a type of spatial filter used to suppress signals from unwanted noise