Default Mode Network Oscillatory Coupling Is Increased Following Concussion

Benjamin T. Dunkley1,2,3*, Karolina Urban4, Leodante Da Costa5, Simeon M Wong1, Elizabeth W. Pang2,6 and Margot J. Taylor1,2,3,7

Concussion is a common form of mild traumatic brain injury. Despite the descriptor “mild,” a single injury can leave long-lasting and sustained alterations to brain function, including changes to localized activity and large-scale interregional communication. Cognitive complaints are thought to arise from such functional deficits. We investigated the impact of injury on neurophysiological and functionally specialized resting networks, known as intrinsic connectivity networks (ICNs), using magnetoencephalography. We assessed neurophysiological connectivity in 40 males, 20 with concussion and 20 without. Regions-of-interest that comprise nodes of ICNs were defined, and their time courses derived using a beamformer approach. Pairwise fluctuations and covariations in band-limited amplitude envelopes were computed reflecting measures of functional connectivity. Intra-network connectivity was compared between groups using permutation testing and correlated with symptoms. We observed increased resting spectral connectivity in the default mode network (DMN) and motor networks (MOTs) in our concussion group when compared with controls, across alpha through gamma ranges. Moreover, these differences were not explained by power spectrum density within the ICNs. Furthermore, this increased coupling was significantly associated with symptoms in the DMN and MOTs—but once accounting for comorbidities (including, depression, anxiety, and ADHD) only the DMN continued to be associated with symptoms. The DMN plays a critical role in shifting between cognitive tasks. These data suggest even a single concussion can perturb the intrinsic coupling of this functionally specialized network in the brain, and may explain persistent and wide-ranging symptomatology.

Keywords: concussion, mild traumatic brain injury, magnetoencephalography, resting-state, functional connectivity, neural oscillations, synchrony

INTRODUCTION

Concussion is a common form of mild traumatic brain injury (mTBI), and while symptoms are often acute and the majority of patients make a full recovery, a single injury can leave long-lasting and sustained alterations to brain structure and function, even in the absence of symptomatology. A single concussive event has been shown to perturb neurophysiological function, including...
localized activity (1) and large-scale interregional interactions (2, 3), with cognitive sequelae manifesting from these phenomena. Resting functional connectivity is known to be affected, with observed changes in inter-areal spectral correlations, a mechanism that subserves dynamic brain networks for cognition (4), across multiple frequency scales replicated in several magnetoencephalography (MEG) studies (5–7). However, the impact of injury on the coordination of neural activity by oscillations in spontaneous and defined intrinsic connectivity networks’ (ICNs), such as the default mode network (DMN), vision, attention, and motor networks (MOTs), has received little consideration. These networks are critical in coordinating and routing information in the brain, and serve functionally defined and specialized purposes, such as visual perception (8, 9), directed attention (10), and self-referential processes in the DMN (11), among others.

Characterizing changes in spectral ICNs after concussion could help our understanding of the functional phenotypes of injury and improve diagnostics. Early imaging studies examined alterations to functionally segregated brain regions and the contribution of these areas to symptoms and specific cognitive deficits (12). However, concussion is beginning to be considered an example of disturbed neuronal network communication (13). Specifically, there has been a gradual paradigm shift toward thinking of the injury as one affecting interregional integration and segregation—in other words, the coordinated action of areas critical in cognition. The compromised communication within and between networks could lead to a better understanding of the sequelae of concussion. Recent research supports this view and connectivity studies have shown that atypical synchronous network interactions can help describe the disorder, in both task-free resting-state and task dependent, cognitive-behavioral paradigms (3, 6, 7, 14). The majority of disturbances to ICN connectivity have been found in concussion using fMRI (15), however, this technique is limited to measuring ultra-slow fluctuations in blood flow and their regional dynamics. In contrast to fMRI, electrophysiological techniques, such as electroencephalographic (EEG) and MEG, have the capability to measure higher frequency neurophysiological oscillations and the synchrony of these networks which operate at behaviorally relevant time-scales required for goal-directed cognition and action (16). Specifically, EEG and MEG are sensitive to the electrophysiological interactions of primary and secondary currents in the brain and can elucidate their frequency composition and dynamics (4, 17, 18) as EEG and MEG captures neuronal activity at the millisecond temporal resolution. Rather than simple epiphenomenology, neuronal oscillations are thought to gate information and coordinate the functional coupling of brain areas (19–25). Importantly, perturbations to cortical oscillations and synchronization are abnormal and atypical in a variety of neuropsychiatric disorders, and characterizing them provides new understanding of neuropsychopathology. In terms of the rationale for the choice of technique here, when compared with EEG, MEG benefits from improved source localization and its ability to disentangle high-frequency physiological artifacts (such as intermingled ocular or muscular contributions to source signals) from veridical, brain-based, physiological measures (26).

In concussion studies, MEG has revealed abnormal local changes in neuronal function, including source amplitude (27) and atypical interactions among brain areas, while other experiments have shown that pattern classification can differentiate those with the disorder from control groups (3, 28). A recent study of persistent concussion symptom patients showed decreased functional connectivity, mediated via phase locking and synchrony, across multiple frequency bands in the DMN (29). Moreover, converging evidence from longitudinal EEG has revealed progressive restoration of EEG functional connectivity within the DMN, which was also paralleled by significant functional recovery (30). Together, this evidence suggests brain oscillations contribute to symptoms and can track recovery in the disorder, and large-scale neuronal oscillatory connectivity may explain emergent cognitive sequelae and comorbidities. In a previous study, we took an atlas-guided region-of-interest approach to characterize these metrics and examined how individual regions and connections were atypical in their graph properties; in this paper, we investigated how atypicalities in specialized ICNs and their connectivity are expressed following injury and related to the presence of symptoms.

Our aim was to determine changes in resting brain connectivity mediated by oscillations in established intrinsic brain networks after a single concussion—we predicted that connectivity would be reduced in concussion across multiple frequency scales, and particularly that of the DMN given recent findings (29). We explored whether these interactions were associated with primary symptoms and secondary conditions (attention, anxiety, and depression). We predicted that those with a concussion would express atypical and reduced ICN oscillatory connectivity and that neurophysiological network interactions would be negatively associated with the presence of primary and secondary symptoms.

**MATERIALS AND METHODS**

**Participants**

Resting-state MEG data were recorded from 26 male participants with a single concussive episode (scanned <3 months post-injury, mean days since injury = 32.20, SD = 17.98, mean age at injury = 31.4 years, SD = 6.87). Six datasets were excluded from the final analysis due to artificial data (two due to dental work and four due to excessive head motion during the scan), for a total of 20 participants. The control group consisted of 24 age- and sex-matched participants (mean age = 27.0 years, SD = 5) without any self-reported history of head injury; for final analysis a subset of 20 participants who were most closely matched to the concussion group on age and IQ were used. All participants signed an informed written consent form, after receiving a description of the study. The Research Ethics Board of the Hospital for Sick Children, Toronto, ON, Canada, gave institutional approval for the study.

Participants with concussion were identified at the emergency department of Sunnybrook Health Science Centre (Toronto, ON, Canada). Inclusion criteria were between 20 and 40 years...
MEG Data Processing
Seed Definition and Virtual Electrode Output
Magnetoecephalography data were processed using a mixture of the FieldTrip toolbox (36) and in-house analysis scripts. Time-series were band-pass filtered offline at 1–150 Hz, a Discrete Fourier Transform notch filter applied at the 60 Hz powerline frequency and second harmonic, and a third-order spatial gradient environmental noise-cancellation was applied to the recording. A priori sources (seeds) of interest in cortical and sub-cortical regions were identified using coordinates from de Pasquale et al. (4) [ventral attention network (VAN), dorsal attention network, DMN, MOT, and visual network]. Figure 1A shows the node locations, Figure 1B shows the analysis pipeline.

Time-series data were reconstructed from these seed locations using a linearly constrained minimum variance (vector) beamformer (37) for each subject and filtered into five canonical bandwidths for further analysis: theta (4–7 Hz), alpha (8–14 Hz), beta (15–30 Hz), gamma (30–55 Hz), and high-gamma (65–80 Hz). A beamformer is a spatial filter used to suppress signals from extrinsic neural and noise sources, while maintaining unit gain for activity in a target brain location. Individual weight vectors are applied to each sensor signal and summed to give estimated source activity at target seed locations effectively suppressing physiological artifacts not of interest (38, 39).

Statistical Analysis
Each of the extracted time courses for each frequency band from each subject had amplitude envelope correlations (AEC) calculated across each of the 10 s epochs—the envelope was based on the instantaneous amplitude estimate for each sample from the filtered time-series using the Hilbert transform. The magnitude of AEC between all pairwise combinations of the seeds varied between 1 (perfect correlation) and −1 (perfect anti-correlation). These values quantify the time-varying correlation in the envelope between any two sources, referred to henceforth as functional connectivity.

Connectivity matrices with AEC values acting as edge weights for all sources pairs were constructed, and the matrix of weighted undirected graphs in each analyzed frequency band for each participant were averaged to characterize the magnitude of spontaneous intra-network coupling. These were then either averaged over the 12 epochs (2-min run) to derive time-averaged connectivity, or the SD was calculated to define temporal dynamism (39, 40), albeit in network connectivity, rather than local source oscillatory amplitude. Connectivity matrices were then divided into the respective groups and inferential statistics investigating group differences for mean edge weight were implemented using non-parametric permutation testing (20,000 iterations), which do not require the data distributions to be normal. False positives due to multiple comparisons were controlled using Bonferroni-correction across frequency bands. Cognitive-behavioral correlation analyses were conducted using the MATLAB Statistics Toolbox (The Mathworks, Inc.). Networks were visualized and figures produced using BrainNet Viewer (41).
RESULTS

Comorbid Symptoms in Concussion

All clinical outcome measures were greater in the concussion group than the control group (Conners, $t = 2.52, p = 0.02$; GAD7, $t = 2.44, p = 0.02$; PHQ9, $t = 3.36, p = 0.002$; SCAT2 symptoms, $t = 4.53, p < 0.001$; SCAT2 severity, $t = 3.09, p = 0.004$), while being matched on the WASI ($t = 1.79, p = 0.08$). Table 1 shows the outcome scores for the concussion group.

Table 1 | Outcome scores for the concussion group.
| ID | Age | SCAT2 symptoms | SCAT2 severity | Days since injury | LOC | GCS |
|----|-----|----------------|----------------|------------------|-----|-----|
| Mean | 31.40 | 9.30 | 21.75 | 32.20 | NA | 14.45 |
| SD | 6.86 | 6.11 | 20.88 | 17.98 | NA | 0.60 |

SCAT2, Sports Concussion Assessment Tool 2; LOC, loss of consciousness; GCS, Glasgow Coma Scale.

TABLE 1 | Outcome scores for the concussion group.
Increased DMN and MOT Resting Connectivity Following Concussion

Significantly increased DMN connectivity was observed in the alpha and beta ranges for the concussion group compared to controls (Bonferroni-corrected within frequency bands at \( p < 0.05 \); null distributions generated using 20,000 permutations, Figure 2). Connections between the ventro-medial prefrontal cortex (vmPFC), and the dorso-medial prefrontal cortex (dmPFC) and right medial prefrontal cortex (rmPFC) appeared to drive this difference, exhibiting the greatest degree of hypercoupling in the concussion group compared to controls. Elevated coupling in concussion was also found in the MOT across the alpha, beta, and gamma ranges (\( p_{\text{corrected}} < 0.05 \)). No significant differences were observed in the SD of internal coupling across epochs (all \( p > 0.05 \)).

Resting-State Spectral Power Does Not Explain Differences in ICN Coupling

To determine the extent to which changes in intra-network coupling were dependent on oscillatory power, the mean internal power spectrum for each of the ICNs was calculated and divided into canonical frequency ranges—qualitative assessment of the spectrum show an apparent increase in low-frequency power/an alpha peak shift toward low-frequencies, particularly within the DMN (Figure 3). Mixed ANOVAs on each of the ICNs independently revealed a main effect of band \( p < 0.001 \), as expected, but not of group or any interaction \( p > 0.05 \). Post hoc contrasts between groups within bands revealed no significant differences (all \( p > 0.05 \)). This suggests connectivity in the bands exhibiting between group differences is not explained by raw spectral power.

DMN Connectivity Correlates With Symptoms

In addition to the main MEG findings, we also conducted follow-up analyses of the relation between network connectivity

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**Figure 2** | Intrinsic connectivity network spectral power content, averaged over node regions that comprise a network. Mean whole-network spectral power content with \( \pm 1 \) SE bars for the concussion (green) and control groups (blue). Of note is the 10 Hz alpha peak, prominent in the VIS. Abbreviations: DAN, dorsal attention network; VAN, ventral attention network; MOT, motor network; DMN, default mode network; VIS, visual network.
and concussion symptoms (Figure 4 shows scatter plots of connectivity versus symptom presence, and test statistics for full and partial correlations are detailed in Table 2). Specifically, we examined brain-behavior relations in the DMN and MOTs across frequency ranges where differences were observed in between groups contrasts; the alpha, beta, and gamma bands (Bonferroni-corrected across frequencies). Significant correlations (non-parametric Spearman’s Rho) with symptoms were observed in the DMN and MOT across alpha, beta, and low gamma ranges; however, partial correlations with comorbidity symptom scores (Conner’s, GAD7, and PHQ9) entered as covariates revealed that the variance in MOT connectivity was not solely driven by concussion symptoms. Factoring in these covariates reduced the full correlation coefficients, such that they were found to no longer be significant—critically, the DMN correlations remained significant at the alpha and beta frequencies (Figure 4 shows original scatter plots linear least squares regression line).

**DISCUSSION**

**Summary**

In this study, we used MEG to investigate frequency-specific interactions within functional ICNs in adults with a single concussion compared to a matched control group. We found that a single concussion was associated with increased functional connectivity mediated via band-limited AEC—specifically, elevated coupling within DMN and MOTs, and importantly, in the absence of canonical band power spectrum differences. Intra-DMN connectivity was positively associated with concussion symptoms, even when controlling for secondary/comorbid outcomes (depression, anxiety, and attentional problems), which suggests that the internal coupling of this task-negative (42) and dynamic “cortical-core” network (4) is particularly prone to the effects of even relatively mild traumatic brain injuries. In addition, elevated MOT connectivity was also associated with symptoms and secondary sequelae.

**Elevated Default Mode Coupling in Concussion**

We found altered oscillatory-mediated connectivity in the DMN in concussion patients. These results appear in opposition to previous fMRI literature examining BOLD fluctuations (13, 15, 43, 44). The DMN, known as the primary resting-state network, involves coordinated action between the posterior cingulate cortex (PCC), bilateral angular gyri, ventro-medial prefrontal cortex (vmPFC), dorso-medial prefrontal cortex (dmPFC), and...
inferior temporal gyri. Studies evaluating the slow frequency hemodynamic components have shown overall reductions in connectivity of the DMN in mTBI, especially in posterior regions such as the PCC, inferior parietal, and precuneus (13, 45). By contrast, we found overall increased mean coupling within the default mode. Further evaluation of internal edge weights found that these changes were mainly driven by hypercoupling between the vmPFC, dmPFC, and rmPFC frontal regions, in contrast to the posterior bias reported in fMRI work.

This study shows the value of using MEG to determine which neurophysiological mechanisms underlying resting-state networks are impacted by concussion. While it has been shown that the ultra-slow BOLD is recapitulated and positively correlated with AEC in alpha and beta bands in MEG (18, 46, 47), this is possibly not true in brain injury where the mechanisms of inter-regional coupling (that is phase based or envelope coupled) do not function as expected. Apparently conflicting observations—that DMN connectivity in fMRI and MEG positively correlate in healthy participants, but in concussion, patients show differential connectivity across modalities, decreased in fMRI and increased in MEG—could be due to the impact of injury on distinct mechanisms, such as hemodynamics and neurovascular coupling, changes in regional or global cerebral perfusion, disruption to the neurometabolic balance, and oxidative stress (i.e., endogenous changes in neuronal excitability). Other recent electrophysiological studies have found reduced functional connectivity based on synchronization in the DMN, in a case study of severe TBI using EEG (30), and in a study of chronic mTBI patients using MEG. Together, these further suggest that brain injury, across the severity spectrum, affects neurophysiological fingerprints. These varying results should be considered in light of the fact that all of these measures of connectivity differ (amplitude envelope coupling versus phase synchrony and BOLD correlations), the severity of injury [severe TBI in the case of Ref. (30)] and capture distinct neural mechanisms in brain communication that are either more closely associated with inner mental state and cognition (phase ICNs) or the underlying structural connectivity (21, 48). Moreover, the time since injury to scan was different in all studies, capturing either acute/subacute (as here), or chronic stages (29). These different results could perhaps be explained by compensation mechanisms—that during the acute/subacute recovery, the hyperconnectivity is a reflection of an attempt to reorganize networks. Clearly, these results suggest a multimodal imaging and a synergistic approach to connectivity is required to explain the complexity of pathology in concussion.

The DMN is a task-negative network involved in self-referential processes, such as introspection and experiential memory (11, 49–52), that contains “hubs” that also facilitate task-switching and engagement of other functional networks (4), such as those

**TABLE 2 | Correlations of band-limited connectivity in the default mode network (DMN) and motor network (MOT) against symptoms.**

|                | DMN | MOT | DMN | MOT |
|----------------|-----|-----|-----|-----|
| **Full correlation** (symptoms versus connectivity) |  |  |  |  |
| p              | 0.462 | 0.008** | 0.421 | 0.020* |
| **Partial correlation** (comorbid symptoms as covariates) |  |  |  |  |
| p              | 0.388 | 0.053 | 0.249 | 0.411 |
| p              | 0.421 | 0.028* | 0.173 | 0.920 |
| **Bonferroni-corrected** |  |  |  |  |
| p              | 0.318 | 0.165 | 0.258 | 0.371 |

*Bonferroni-corrected at **p < 0.01, *p < 0.05.* Bold indicates a significant correlation (p < 0.05).
linked to memory, attention, and executive function (53, 54). These are cognitive domains often reported to be dysfunctional in concussion (55–57), and in light of the DMN’s role in cognition and network toggling, the hyperconnectivity we report might reflect an inability to disengage the DMN in response to shifting task demands, and explain some of the emergent cognitive deficits seen here. The DMN’s critical role in neuropsychopathology and cognitive deficits is further supported by studies of other disorders, including ADHD (58), Alzheimer’s disease (59, 60), PTSD (28, 61), ASD (62, 63), depression (64), and schizophrenia (65).

Oscillations underlie communication processes between brain regions (i.e., within or between brain network connectivity) (21, 23, 66). The complex interplay among regions that comprise the DMN, and ICNs more generally, and how they are mediated by frequency-specific connectivity mechanisms, further highlights the important role of oscillations and their contribution to network architecture and interregional communication—perhaps most importantly, these results show that they are susceptible to perturbations through injury. These neurophysiological processes are intrinsically linked to the topological patterns of communication that constitute functional resting networks (18, 67). Any disruption in the internal balance of these networks may impact the ability for them to switch, engage, or separate—altering cognitive efficiency or recruitment processes. For example, the task-positive executive network is active during externally directed behavior and requires communication between bilateral DLFC and PCC. However, in the concussion cohort, the connectivity patterns of these brain regions were altered and thus we speculate that task related activity would also be effected. We believe these observations show dysfunctional integration within networks, and an inability to efficiently segregate/decouple areas (6). Thus, a disruption in the internal balance could lead to altered cognition, consistently shown to occur following concussion (56, 68, 69).

Increased MOT Connectivity

In addition to our DMN observations, we also found that the MOT showed multiscale network dysfunction, including the beta band. Beta oscillations serve a critical role in long-range synchrony (70), with the connectivity of these ICNs related to structural connections linking distinct anatomical areas (71); these connections rely on white matter tracts to facilitate signal conduction and increase velocity (72). In patients with Parkinson’s disease, increases in resting-state MOT beta connectivity has been related to slower reaction times during visual-motor-related tasks (73) and similar changes to reaction time are evident in concussion (74). However, the increased MOT connectivity could be a general indicator of functional changes following concussion (e.g., fatigue) and not specific to the symptoms we used in this study.

Increased beta in the MOT may be due to a variety of neural circuitry changes, possibly related to GABAergic action and concentration (75, 76). Changes to spectral connectivity could cause myriad neurophysiological changes, including altered inhibitory input and changes to excitatory threshold which could alter the connectivity and oscillatory patterns among the brain regions within the MOT. In the motor cortex, beta oscillatory power is high during rest and decreases during movement, known as the event-related-beta desynchronization, related to local processing during movement (73).

As neural oscillations are thought to be a managed through a relation between excitatory and inhibitory neurotransmission and related to resting GABA concentration (76), the increased beta amplitude coupling within the MOT could reflect an increase in cross-regional inhibitory processes, that could be the cause of increased motor threshold (77), and inhibition and excitability in motor cortex, as measured by transcranial magnetic stimulation in concussion (78). Furthermore, increased GABA concentration, an inhibitory neurotransmitter in the motor cortex has been reported in animal and human studies of concussion (79, 80). Although these changes in circuitry are evident at the neuronal level, they will also impact short and long-range connectivity patterns to which MEG is sensitive.

Local alpha oscillations and their regional coupling are thought to facilitate information integration and segregation within and across neural populations via modulation and gating of local inhibition and excitation (81, 82). These multi-frequency abnormalities suggest disruption to communication channels and align with mechanisms of injury where high tensile and shearing forces have been shown to alter white matter connections and therefore local neural activity and large-scale synchrony. Thus, the functional deficits from injury may alter the coordination of information transfer and integration across a variety of complex processes, including oscillatory coupling (investigated here), and phase-amplitude coupling and cross-frequency interactions to which MEG is sensitive (26, 83) and have shown to be affected by concussion (84). As such, the heterogeneous nature of concussion can lead to various changes in brain function on local and global scales, which aligns with the results we found of spectral connectivity changes.

Relations Between Functional Connectivity and Structural Architecture

Cartography of the human “connectome” has seen a surge in recent years, but progress has been slow in elucidating the association between electrophysiological connectivity and structural connectivity. Preclinical work using optogenetics to stimulate neuronal (electrical) activity has shown that this promotes adaptive myelination (85), and a recent human study has proposed that there is a strong link between neural connectomics, their dynamics, and cortical white matter structure [or “myeloarchitecture” (67)]. It seems reasonable to posit, given these findings, that our observations in altered connectivity of cortical ICNs could be related to neuromorphological changes (86), and more specifically microscopic white matter pathology following concussion, including demyelination and/or differentiation (87, 88), reductions in cortical thickness (89–91), and Wallerian degeneration (92, 93).

Several hypotheses have been proposed to better understand the underlying neurophysiological causes of increases in resting-state connectivity. One frame of thought suggests that
connectivity increases could be a result of compensation for injury. Specifically, hyperconnectivity could be representative of recruitment of additional resources to maintain cognitive function—the elevated connectivity in frontal regions of the DMN in the concussion group aligns to the general findings of frontal susceptibility to injury [for a review, see Ref. (94)]. The disruption to white matter tracts could cause changes in the long-range connections (such as between PCC and frontal regions) and result in increases in small-world connectivity. This can be seen in our results across the DMN, particularly that increases in spectral connectivity can be attributed to the hypercoupling in frontal regions.

CONCLUSION

A particular focus in concussion research is to better understand the link between symptom severity/presence and altered brain function, both in the short and long term. We found a significant relation between symptoms and increases in spectrum connectivity in the DMN and MOT. The association between DMN and symptoms was maintained even while controlling for secondary factors as anxiety and depression. Given the critical role of the DMN in cognitive functions, these abnormal patterns may well underlie the cognitive difficulties so often reported following concussion. These results, when combined with observations from other studies, suggest that MEG may be able to identify electrophysiological changes along the temporal continuum of recovery, from the short term, acute stages of injury, through to later, chronic phases. In conclusion, longitudinal MEG studies of neurophysiological function may be able to link symptoms with intrinsic function and predict the course of recovery in individuals.

ETHICS STATEMENT

All participants signed an informed written consent form, after receiving a description of the study. The Research Ethics Board of the Hospital for Sick Children gave institutional approval for the study.

AUTHOR CONTRIBUTIONS

BD, LC, EP, and MT conceived and designed the study, and collected the data. BD, KU, and SW analyzed the data. BD, KU, LC, EP, and MT interpreted the data and wrote the manuscript.

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