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Altered cross-frequency coupling in resting-state MEG after mild traumatic brain injury

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ABSTRACT

Cross-frequency coupling (CFC) is thought to represent a basic mechanism of functional integration of neural networks across distant brain regions. In this study, we analyzed CFC profiles from resting state Magnetoencephalographic (MEG) recordings obtained from 30 mild traumatic brain injury (mTBI) patients and 50 controls. We used mutual information (MI) to quantify the phase-to-amplitude coupling (PAC) of activity among the recording sensors in six nonoverlapping frequency bands. After forming the CFC-based functional connectivity graphs, we employed a tensor representation and tensor subspace analysis to identify the optimal set of features for subject classification as mTBI or control. Our results showed that controls formed a dense network of stronger local and global connections indicating higher functional integration compared to mTBI patients. Furthermore, mTBI patients could be separated from controls with more than 90% classification accuracy. These findings indicate that analysis of brain networks computed from resting-state MEG with PAC and tensorial representation of connectivity profiles may provide a valuable biomarker for the diagnosis of mTBI.

1. Introduction

Mild traumatic brain injury (mTBI) is the most common cause of brain insult. Typically, patients experience an initial brief change in mental state or consciousness that is followed by post-concussion symptoms (PCS) (Cassidy et al., 2004), such as headaches, fatigue, and dizziness, which usually emerge on the day of injury and persist for at least the first few days thereafter (Boccaletti et al., 2006). In most patients, cognition recovers and PCS resolve within three months. However, up to 25% of patients (Sigurdardottir et al., 2009) suffer residual PCS, long-term impairment, and sometimes disability (Levin, 2009), so that efficient identification of alterations due to mTBI becomes particularly important. Several cognitive functions are affected by mTBI, including attention (De Monte et al., 2006; Vanderploeg et al., 2005) working memory (Vanderploeg et al., 2005), episodic memory (Tsirka et al., 2011), verbal learning (De Monte et al., 2006; Ruff et al., 1989), and visual memory (Levin et al., 1987; Raskin, 2000; Ruff et al., 1989).

Conventional neuroimaging techniques, such as acute magnetic source imaging (MRI) and computed tomography (CT), have limited sensitivity in detecting physiological alterations caused by mTBI (Bigler and Orrison, 2004; Johnston et al., 2001; Kirkwood et al., 2006). Magnetoencephalography (MEG) on the other hand, is a noninvasive functional imaging technique that measures directly neuronal currents in gray matter with extraordinary (<1 ms) temporal resolution and excellent (2–3 mm) spatial localization accuracy (Leahy et al., 1998). Consequently, during the past several years, numerous studies have attempted to develop reliable biomarkers of mTBI based on MEG (see reviews by Jeter et al., 2013, and Huang et al., 2009, Eierud and Fletcher, 2014). Of particular interest is the analysis of resting-state

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MEG activity either alone (Luo et al., 2013; Zouridakis et al., 2012; Dimitriadis et al., 2015a; Li et al., 2015) or combined with diffusion tensor imaging (DTI) MRI (Huang et al., 2009).

Recent approaches to study brain function view the brain as an intricate network of complex systems with abundant interactions between local and distant areas, having the capacity to combine local specialization (segregation) with global integration (Tononi et al., 1994; Tognoli and Scott Kelso, 2014). Fluctuations of spontaneous activity are strongly synchronized among spatially distributed neuronal subsystems (Contreras and Steriade, 1997; Destexhe et al., 1999), suggesting that processing of stimuli is influenced by the dynamics of coherently active networks. These spatiotemporal patterns involve not only low-frequency activity within the δ (1–4 Hz) band or below (Contreras and Steriade, 1997; Destexhe et al., 1999), but also higher frequencies in the θ (4–8 Hz), α (8–12 Hz), β (13–30 Hz), and γ (>30 Hz) ranges (Steriade et al., 1996a, b; Destexhe et al., 1999). Oscillations in these frequency bands are known to be involved in a variety of cognitive processes (Engel and Fries, 2010; Siegel et al., 2012).

One approach to understanding the dynamic nature of connections between local and distant neural assemblies is the analysis of functional and effective connectivity (Friston et al., 1994): the former captures patterns of statistical dependence, whereas the latter attempts to extract networks of causal influences of one physiological time series over another (Aertsen et al., 1989). Several studies have demonstrated changes in functional connectivity patterns after brain tumor resection (Douw et al., 2008), recovery from stroke (Gerloff et al., 2006), and traumatic brain injury (Castellanos et al., 2010; Zouridakis et al., 2012), suggesting that functional connectivity graphs (FCGs) of brain activity are sensitive to changes due to brain insult.

The MEG is a complex signal containing different interacting frequency components. Power spectrum analysis based on the Fourier, wavelet, or Gabor transform can uncover amplitude modulations within the above-defined frequencies across time. Intrinsic coupling modes (ICMs) in ongoing activity are thought to reflect the action of two different coupling mechanisms (Engel et al., 2001): one that arises from phase coupling of band-limited oscillatory signals, and another one that results from coupled aperiodic fluctuations of signal envelopes. When studying ICMs, apart from exploring the relationship between same frequency signals, it is highly interesting to also quantify functional relationships between signals of different frequencies (Jensen and Colgin, 2007; Palva and Palva, 2011; Jirsa and Müller, 2013; Dimitriadis et al., 2015c, 2015d, in press), as this cross-frequency coupling (CFC) has been hypothesized to represent the mechanism of interaction between local and global processes and therefore it is directly related to the integration of distributed information.

Recently, different forms of cross-frequency interactions were described (Jensen and Colgin, 2007), namely power-to-power, phase-to-phase, phase-to-frequency, and phase-to-power. There is ample evidence that the last type of CFC, also called phase–amplitude modulation, occurs very often in both animals and humans in the prefrontal cortices, the hippocampus, and other distributed cortical areas (Osipova et al., 2008; Tort et al., 2008, 2009, 2010; Cohen et al., 2009a, 2009b; Colgin et al., 2009; Axmacher et al., 2010a, 2010b; Voytek et al., 2010).

Only a few MEG studies have considered CFC interactions at rest or during execution of active tasks. An early study (Osipova et al., 2008) reported that γ power was phase-locked to α activity over occipital brain regions at rest with eyes closed (EC). Interestingly, there was no peak in the gamma activity estimated by Fourier transform, but a clear peak was evident only when studied in relation to the alpha phase. In another MEG study (Palva et al., 2005), cross-frequency of phase synchrony was identified as the main communication mechanism between frequencies from 3 to 80 Hz. In particular, enhanced CFC phase synchrony was revealed among the α, β, and γ frequency bands during a continuous mental arithmetic task. This enhancement of CFC phase synchrony could be attributed to the integration needed among different brain areas activated during the task that were synchronized in the dominant frequency (Palva et al., 2005).

The human brain can be divided into distinct and spatially distributed functional networks (Eierud et al., 2014). These brain networks exist at a range of spatial scales extending from microscopic neuronal networks of individual neurons and local synaptic interactions to large-scale networks of brain areas interconnected by large white matter tracts. In the present study, we focus on how large-scale intrinsic connectivity networks (ICNs) change due to mild traumatic brain injury, considering that interactions between large-scale brain networks are significant for high-level cognitive functions, such as memory and attention (Mesulam, 1998). Moreover, neuroimaging techniques, including electroencephalography (EEG), MEG, fMRI, and DTI, have recently enabled investigation of these networks in clinical populations (for a review see Eierud et al., 2014). ICNs are composed of brain regions that are characterized by temporally coordinated activity (Beckmann et al., 2005; Smith et al., 2009). The functional architecture of these networks possibly reflects the underlying structural brain connectivity, since brain areas strongly connected via white-matter tracts are likely to present strong functional connections. This linkage supports the assumption that ICN function is vulnerable to the effects of mTBI, considering that diffuse axonal injury (DAI) usually damages long-distance white-matter tracts that connect key brain areas (known as hubs) in these networks (Smith et al., 2003; Gentleman et al., 1995).

ICN abnormalities after TBI have been widely observed in resting-state fMRI, demonstrating both increase and decrease of connectivity in a number of networks, including the default mode network (DMN) and salience network (SN) (Sharp et al., 2011; Stevens et al., 2012). Several studies have also reported that these abnormalities correlate with cognitive impairment or post-concussive symptoms (Messé et al., 2013; Caeyenberghs et al., 2014). Recent studies based on EEG and MEG, which provide higher temporal resolution than fMRI, have further demonstrated disrupted functional connectivity related to TBI for different types of injury severity (Castellanos et al., 2010; Tarapore et al., 2013; Han et al., 2014; Dimitriadis et al., 2015b).

Based on the aforementioned evidence from previous studies, we investigate the hypothesis that exploring ICMs in terms of cross-frequency coupling can provide better understanding of how mTBI alters the integration of information exchange at resting-state networks. Such alterations of oscillations, referred to as “oscillopathies” or “dysrhythmias,” could reflect malfunction and disruption of brain networks in mTBI subjects. Thus, they could assist in defining alternative or complementary connectomic biomarkers (Buzsáki and Draguhn, 2004).

In the present study, we demonstrate how the phase of low frequency spontaneous MEG activity modulates higher frequency activity in mTBI subjects (Florin and Baillet, 2015). Then, adopting a phase-to-amplitude coupling (PAC) estimator to quantify CFC between pairs of frequencies, we construct cross-frequency FCGs in mTBI patients and controls. We hypothesize that PAC at rest can capture intrinsic network interactions that play a crucial role in information exchange and integration. Finally, we examine the proposition that mTBI can affect functional integration, mainly the communication between different cell assemblies that function on a prominent frequency, and these functional changes of intrinsic networks can be captured by CFC.

The remainder of this paper is structured as follows: the next section, Methods, describes the study participants and the MEG recording procedures, the preprocessing steps for artifact detection and elimination, the dimensionality reduction algorithm, and the various classification schemes applied on the filtered FCGs. Furthermore, several methods for comparing the CFC pairs between the two groups are discussed. The following section, Results, presents the performance of each classification scheme on the current dataset and examines the differences between the two groups as potential biomarkers. The final section, Discussion, summarizes our findings, provides concluding remarks about the CFC metric and its potential use as a biomarker for mTBI, and suggests future analysis directions.