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RECONFIGURATION OF DOMINANT COUPLING MODES IN MILD TRAUMATIC BRAIN INJURY MEDIATED BY δ-BAND ACTIVITY: A RESTING STATE MEG STUDY

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Abstract—During the last few years, rich-club (RC) organization has been studied as a possible brain-connectivity organization model for large-scale brain networks. At the same time, empirical and simulated data of neurophysiological models have demonstrated the significant role of intra-frequency and inter-frequency coupling among distinct brain areas. The current study investigates further the importance of these couplings using recordings of resting-state magnetoencephalographic activity obtained from 30 mild traumatic brain injury (mTBI) subjects and 50 healthy controls. Intra-frequency and inter-frequency coupling modes are incorporated in a single graph to detect group differences within individual rich-club subnetworks (type I networks) and networks connecting RC nodes with the rest of the nodes (type II networks). Our results show a higher probability of inter-frequency coupling for (δ–γ_1), (δ–γ_2), (θ–β), (θ–γ_2), (α–γ_2), (γ_1–γ_2) and intra-frequency coupling for (γ_1–γ_1) and (δ–δ) for both type I and type II networks in the mTBI group. Additionally, mTBI and control subjects can be correctly classified with high accuracy (98.6%), whereas a general linear regression model can effectively predict the subject group using the ratio of type I and type II coupling in the (δ, θ), (δ, β), (δ, γ_1), and (δ, γ_2) frequency pairs. These findings support the presence of an RC organization simultaneously with dominant frequency interactions within a single functional graph. Our results demonstrate a hyperactivation of intrinsic RC networks in mTBI subjects compared to controls, which can be seen as a plausible compensatory mechanism for alternative frequency-dependent routes of information flow in mTBI subjects.

Key words: magnetoencephalography (MEG), mild traumatic brain injury (mTBI), cross-frequency coupling, intrinsic networks, brain network models.

INTRODUCTION

While traumatic brain injury (TBI) is one of the most serious brain disorders, mild TBI (mTBI) is one of the most frequent, and accounts for almost 90% of all brain injuries (Levin et al., 1987; Len and Neary, 2011; Huang et al., 2014). The symptomatology of brain injury is characterized by headaches, fatigue, memory loss, sleep disturbances, loss of balance, seizures, depression, and visual and emotional disturbances (Huang et al., 2014). It is estimated that 5–20 percent of irremediable patients (Bharath et al., 2015) have symptoms that persist for one year or more after the injury (Huang et al., 2014). Based on these findings, a number of research groups have worked on developing robust biomarkers for highly accurate differentiation of mTBI patients from healthy controls using resting state magnetoencephalographic (MEG) recordings and functional brain connectivity analysis (Huang et al., 2009, 2014; Zouridakis et al., 2012; Dimitriadis et al., 2015a; Antonakakis et al., 2016a; Zouridakis et al., 2016; Mvula et al., 2017).

In terms of brain communication, both structural and functional imaging studies have shown (Van de Heuvel and Sporns, 2011; Palva and Palva, 2011; Vértes and Bullmore, 2015) that the highest amount of information

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Abbreviations: CFCG, cross-frequency functional connectivity graphs; DoD, Department of Defense; FDR, false discovery rate; ICs, independent components; IER, information exchange rate; IFCG, Intra-frequency functional connectivity graphs; MEG, magnetoencephalography; MI, mutual information; mTBI, mild traumatic brain injury; PAC, phase-to-amplitude coupling; PC, principal component; RC, rich-club; SW, small-world; TBI, traumatic brain injury.

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flows within a backbone of the brain network consisting of a subset of main nodes, or hubs, known as rich club (RC) that often follows a small-world (SW) topology. The SW network model has been investigated in Alzheimer's disease (Stam et al., 2007), schizophrenia (Micheloyannis et al., 2006), and autism (Liu et al., 2008; Rubinov and Sporns, 2010; Tsiaras et al., 2011), whereas the RC organization has been observed both in computer simulations (Senden et al., 2014) and human studies involving healthy subjects (Van de Heuvel and Sporns, 2011; Bullmore and Sporns, 2012; Mišić et al., 2014), as well as brain ischemia (Fornito et al., 2012; Van den Heuvel et al., 2013; Watanabe and Rees, 2015; Alawieh et al., 2015; Crossley et al., 2016) and mTBI patients (Antonakakis et al., 2015). RC nodes play a significant role in communication and information integration among brain areas that are distinct and distant. Thus, it is important to explore how this integration of information is affected by various brain diseases and disorders (Van de Heuvel and Sporns, 2011; Bullmore and Sporns, 2012; Mišić et al., 2014).

Functionally, the human brain consists of several specialized subsystems, each oscillating in a dominant frequency. Communication between a small and a larger system is facilitated via intra-frequency coupling, whereas communication between two larger systems, whereby each system oscillates with its own prominent frequency, is realized via cross-frequency coupling (Canolty et al., 2006). A key feature of ongoing brain activity is its intrinsic coupling mode which exhibits multiple spatio-temporal patterns and supports rich information processing (Varela et al., 2001). There is significant evidence that these intrinsic coupling modes are negatively affected by brain diseases and positively reinforced by cognition and learning (Engel et al., 2013).

Important issues stemming from previous analyses on the study of mTBI using Granger causality (Zouridakis et al., 2012), phase synchronization (Dimitriadis et al., 2015b), cross-frequency coupling (Antonakakis et al., 2015, 2016a,c), complexity (Antonakakis et al., 2016b), as well as brain activation patterns of both EEG and MEG at the sensor (Li et al., 2015) and source (Zouridakis et al., 2016; Li et al., 2017) levels relate to the following key questions: (1) Is there a group difference in intra-frequency and inter-frequency coupling within the RC networks (type I network) and between the RC hubs and the rest of the brain network (type II network)? (2) If so, in which intra-frequency and inter-frequency intrinsic coupling modes does the ratio of probability distributions between the two types of networks show group differences? (3) Are the theoretical information exchange rate (IER), the weighted IER (WIER), and the ratio of probabilities between the two types of networks altered in mTBI? (4) Can the ratio of probability distribution of the prominent intrinsic coupling modes between the two types of networks discriminate the two groups? To address these questions, in the current study we explore both intra-frequency and inter-frequency coupling using resting-state MEG obtained from mTBI patients and healthy controls under the distinction of brain network nodes as RC and non-RC hubs.

The present study is structured as follows: the next section describes the Experimental Procedures including the subjects and analysis methods, the subsequent section presents the analysis results, whereas the last section discusses advantages and limitations of the proposed methodology and describes further future improvements.

EXPERIMENTAL PROCEDURES

Participants and procedure

Thirty right-handed mTBI patients (29.33 ± 9.2 years of age) (Levin, 2009) and fifty age- and gender-matched neurologically intact healthy controls (29.25 ± 9.1 years of age) participated in the study. The control group was drawn from a normative data repository at UTHSC-Houston, whereas the mTBI patients were recruited from three trauma centers in the greater Houston metropolitan area. Those centers were part of a larger study (Levin, 2009) supported by Department of Defense (DoD). mTBI was defined according to the guidelines of DoD (Assistant Secretary, 2007) and the American Congress of Rehabilitation Medicine (Kay, 1993). Demographic details about the mTBI patients are presented in the Supplementary Material, which includes all information provided by the clinicians. Previous head injuries, history of neurologic or psychiatric disorder, substance abuse, and extensive dental work and implants incompatible with MEG were used as exclusion criteria for the control group. The project was approved by the Institutional Review Boards (IRBs) at the participating institutions and the Human Research Protection Official's review of research protocols for DoD. All procedures were compliant with the Health Insurance Portability and Accountability Act (HIPAA).

The MEG acquisition included ten minutes of resting-state activity for each subject lying on a bed with eyes closed, using a whole-head Magnes WH3600 system with 248 channels (4D Neuroimaging Inc., San Diego, CA). Data were acquired using a sampling rate of 1017.25 Hz and online bandpass filters between 0.1 and 200 Hz. Five minutes of data were artifact contaminated (Dimitriadis et al., 2015a) and thus the rest five minutes were used in the current analysis. The original axial gradiometer recordings were transformed to planar gradiometer field approximations using the *sincos* method implemented in the software package Fieldtrip (Oostenveld et al., 2011).

MEG preprocessing

Reduction of non-cerebral activity was based on an automated blind detection and elimination strategy applied to the raw MEG data, due to the lack of independent ocular and cardiac activity monitoring, using the Fieldtrip toolbox (Oostenveld et al., 2011) and MATLAB (The MathWorks, Inc., Natick, MA, USA). In particular, the following iterative procedure was applied to all datasets individually: First, correction of activity from bad MEG channels was performed using interpolation (Oostenveld et al., 2011) on the four closest channels surrounding the bad one, whereas notch filtering was used to