NeuroImage 84 (2014) 76–96

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Disrupted modular organization of resting-state cortical functional connectivity in U.S. military personnel following concussive 'mild' blast-related traumatic brain injury☆

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ARTICLE INFO

Article history:
Accepted 9 August 2013
Available online 20 August 2013

Keywords:
Functional connectivity
Traumatic brain injury
Graph theory
Modularity
Functional magnetic resonance imaging (fMRI)
Blast injury

ABSTRACT

Blast-related traumatic brain injury (TBI) has been one of the "signature injuries" of the wars in Iraq and Afghanistan. However, neuroimaging studies in concussive 'mild' blast-related TBI have been challenging due to the absence of abnormalities in computed tomography or conventional magnetic resonance imaging (MRI) and the heterogeneity of the blast-related injury mechanisms. The goal of this study was to address these challenges utilizing single-subject, module-based graph theoretic analysis of resting-state functional MRI (fMRI) data. We acquired 20 min of resting-state fMRI in 63 U.S. military personnel clinically diagnosed with concussive blast-related TBI and 21 U.S. military controls who had blast exposures but no diagnosis of TBI. All subjects underwent an initial scan within 90 days post-injury and 65 subjects underwent a follow-up scan 6 to 12 months later. A second independent cohort of 40 U.S. military personnel with concussive blast-related TBI served as a validation dataset. The second independent cohort underwent an initial scan within 30 days post-injury. 75% of the scans were of good quality, with exclusions primarily due to excessive subject motion. Network analysis of the subset of these subjects in the first cohort with good quality scans revealed spatially localized reductions in the participation coefficient, a measure of between-module connectivity, in the TBI patients relative to the controls at the time of the initial scan. These group differences were less prominent on the follow-up scans. The 15 brain areas with the most prominent reductions in the participation coefficient were next used as regions of interest (ROIs) for single-subject analyses. In the first TBI cohort, more subjects than would be expected by chance (27/47 versus 2/47 expected, $p < 0.0001$) had 3 or more brain regions with abnormally low between-module connectivity relative to the controls on the initial scans. On the follow-up scans, more subjects than expected by chance (5/37, $p = 0.044$) but fewer subjects than on the initial scans had 3 or more brain regions with abnormally low between-module connectivity. Analysis of the second TBI cohort validation dataset with no free parameters provided a partial replication; again more subjects than expected by chance (8/31, $p = 0.006$) had 3 or more brain regions with abnormally low between-module connectivity on the initial scans, but the numbers were not significant (2/27, $p = 0.276$) on the follow-up scans. A single-subject, multivariate analysis by probabilistic principal component analysis of the between-module connectivity in the 15 identified ROIs, showed that 31/47 subjects in the first TBI cohort were found to be abnormal relative to the controls on the initial scans. In the second TBI cohort, 9/31 patients were found to be abnormal in identical multivariate analysis with no free parameters. Again, there were not substantial differences on the follow-up scans. Taken together, these results indicate that single-subject, module-based graph theoretic analysis of resting-state fMRI provides potentially useful information for concussive blast-related TBI if high quality scans can be obtained. The underlying biological mechanisms and consequences of disrupted between-module connectivity are unknown, thus further studies are required.

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1053-8119/$ – see front matter
http://dx.doi.org/10.1016/j.neuroimage.2013.08.017

Introduction

Traumatic brain injury (TBI) has been called a "signature injury" in the wars of Iraq and Afghanistan (Okie, 2006). As of the first quarter of 2012, the total incidence of TBI in U.S. military personnel since 2000 is 244,217 with 76.8% of these incidents concussive or 'mild' TBI (Defense Medical Surveillance System and Theater Medical Data Store, http://www.health.mil/Libraries/TBI-Numbers-Current-Reports/dod-tbi-worldwide-2000-2012Q1-as-of-120516.pdf). Concussive or 'mild' TBI is characterized by loss of consciousness up to 30 min, altered consciousness and mental state up to 24 h, post-traumatic amnesia up to 24 h and the absence of abnormalities in computed tomography or conventional magnetic resonance imaging (MRI) (Casscells, 2007). However, utilizing advanced neuroimaging techniques such as functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), magnetoencephalography and electroencephalography, reports have described abnormalities in concussive TBI subjects (e.g., fMRI: Scheibel et al. (2012), Shumskaya et al. (2012), Slobounov et al. (2011), Tang et al. (2011); DTI: Levin et al. (2010), Mac Donald et al. (2011), Niogi et al. (2008), Niogi and Mukherjee (2010), Shenton et al. (2012); fMRI and DTI: Mayer et al. (2011); magnetoencephalography: Castellanos et al. (2010, 2011); electroencephalography and DTI: Sponheim et al. (2011)).

Most of these previous functional neuroimaging studies in TBI have focused on group comparisons and have adopted hypothesis-driven approaches with predefined regions of interest, seed, or networks of interests. However, high individual variability of functional topology (van Essen and Dierker, 2007) is a major source of variability in group analysis in healthy normal subjects. In TBI populations, the heterogeneity of injury types and locations (Doppenberg and Bullock, 1997; Saatman et al., 2008) further increases between-subject variability. In blast-related TBI (bTBI), the heterogeneity is further increased by the variety of blast-related injury mechanisms. Blast-related injuries may occur by (1) blast overpressure inducing mechanical damage to the brain, (2) having the head struck by debris or other objects set in motion by the blast, (3) being thrown to the ground or against another stationary object or (4) inhaling toxic fumes, smoke or dust (Finkel, 2006; Warden, 2006). Different combinations of these injury types and other variables such as direction, distance and open field versus enclosed space associated with the blast exposures may make group analysis insufficient for the assessment of bTBI. The aforementioned heterogeneity of concussive bTBI also increases the chance for hypothesis-driven approaches with predefined regions or networks of interest to miss regions or networks with alterations of functional connectivity in concussive bTBI patients. Thus, single-subject based, data-driven approaches would be more meaningful in these heterogeneous concussive bTBI populations.

Recently, graph theory has become increasingly popular in neuroimaging research (see Rubinov and Sporns (2010) and Bullmore and Sporns (2009) for reviews), offering new insights into the understanding of the brain as a complex network. Several studies (Achard et al., 2006; He et al., 2007; Salvador et al., 2005; van den Heuvel et al., 2008) have found that the brain network has economical 'small world' properties having high levels of clustering and a short path length for efficient global and local communications (Latora and Marchiori, 2001; Watts and Strogatz, 1998). Early studies of graph theoretic analysis in clinical populations have demonstrated disrupted 'small world' properties in patients with dementia of the Alzheimer's type (Stam et al., 2006), schizophrenia (Micheloyannis et al., 2006) and epilepsy (Ponten et al., 2007). Taking advantage of the 'small world' properties of the brain network, subsequent studies (Chen et al., 2008; Hagmann et al., 2008; He et al., 2009; Power et al., 2011; Valencia et al., 2009; Yeo et al., 2011b) have identified a modular or community structure of the normal, healthy human brain. With regard to clinical populations, Valencia et al. (2009) raised the possibility that characterizing the modular structure of the brain may be important to understand the brain organization during different pathological or cognitive states. Indeed, graph theoretic analysis of magnetoencephalography data has revealed a disrupted modular structure in patients with dementia of the Alzheimer's type (de Haan et al., 2012).

Another advantage of graph theoretic analyses over simple network approaches is that they do not require assumptions regarding hypothesized (thus predefined) seed regions or networks of interest. Thus, in this regard, graph theoretic analyses are useful in heterogeneous populations. With this advantage in heterogeneous populations over simple network approaches, recent studies (Caeyenberghs et al., 2012; Castellanos et al., 2011; Nakamura et al., 2009; Pandit et al., 2013) have utilized graph theoretic analyses to provide a more comprehensive understanding of abnormal functional connectivity in TBI patients. In particular, Nakamura et al. (2009) demonstrated disrupted 'small worldness', defined as the level of clustering relative to path length, of functional networks in patients with moderate to severe TBI. To our knowledge, there are no previous studies that have investigated modular structure in resting-state functional connectivity MRI in patients with bTBI or any other concussive 'mild' TBI populations (though Pandit et al. (2013) included a wide range of injury severities).

In this study, we posited that module-based connectivity in patients with concussive bTBI may be disrupted. In our previous report (Mac Donald et al., 2011), we demonstrated DTI 'abnormalities' in white matter integrity of active duty U.S. military personnel with concussive bTBI relative to controls who had blast exposure but no diagnosis of TBI. At the time of the DTI and structural MRI collections in each of these subjects, resting-state blood oxygenation level dependent (BOLD) fMRI scans were also acquired. Here, we assessed modular organization of these active duty U.S. military personnel with concussive bTBI, utilizing whole brain, module-based graph theoretic analysis of these resting-state BOLD fMRI scans. Because of the heterogeneity of the concussive bTBI patients, we investigated module-based resting-state network properties at both the group and single-subject levels.

Materials and methods

Subjects

Three groups (controls and two TBI cohorts) of active duty U.S. military personnel deployed to the wars in Iraq and Afghanistan participated in this study. All of them had been exposed to blasts in a combat environment. The two TBI cohorts had sustained clinically diagnosed bTBI. The 21 controls (20 males; 19–49 years old with median = 29; 11–17.5 years of education with median = 12.5) had other injuries but screened negative for TBI (Dempsey et al., 2009). The first TBI cohort (TBI I cohort) consisted of a subset of the subjects about which we have reported previously (Mac Donald et al., 2011). Screening, enrollment, and initial scans were performed at the Landstuhl Regional Medical Center (LRMC), a U.S. Military hospital in Landstuhl, Germany. 63 TBI patients (all males; 19–57 years old with median = 25; 8–17 years of education with median = 12) were diagnosed with mild, uncomplicated traumatic brain injury based on the criteria from the Department of Defense (Casscells, 2007), marked by less than 30 min of loss of consciousness and the absence of abnormalities in conventional MRI and CT. Post blast exposure time on the initial scans at LRMC were within 90 days (median = 14). After 6–12 months from their initial scans, 65 of these subjects traveled to Washington University in St. Louis for follow-up scans. More details and demographics of this cohort are in Mac Donald et al. (2011).

The same screening criteria as on the TBI I cohort and controls allowed the second TBI cohort (TBI II cohort) to comprise 40 additional concussive bTBI patients (37 males; 19–44 years old with median = 23; 9–16 years of education with median = 12). The TBI II cohort underwent the initial scans within 30 days (median = 7) after the blast exposure. After 6–12 months from their initial scans, 32 out of these subjects underwent follow-up scans at Washington University in St. Louis. The first cohort