NeuroImage: Clinical 5 (2014) 377–384

Contents lists available at ScienceDirect

NeuroImage: Clinical

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

Resting-state hippocampal connectivity correlates with symptom severity in post-traumatic stress disorder

B.T. Dunkley[a,b,*], S.M. Doesburg[a,b,c,d], P.A. Sedge[e], R.J. Grodecki[f], P.N. Shek[g], E.W. Pang[b,h], M.J. Taylor[a,b,c,d]

[a]Department of Diagnostic Imaging, The Hospital for Sick Children, Toronto, Canada
[b]Neuroscience & Mental Health Program, The Hospital for Sick Children Research Institute, Toronto, Canada
[c]Department of Medical Imaging, University of Toronto, Toronto, Canada
[d]Department of Psychology, University of Toronto, Toronto, Canada
[e]Directorate of Mental Health, Canadian Forces Health Services, Ottawa, Canada
[f]Canadian Forces Environmental Medicine Establishment, Toronto, Canada
[g]Defence Research and Development Canada, Toronto, Canada
[h]Division of Neurology, The Hospital for Sick Children, Toronto, Canada

ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 7 July 2014
Accepted 30 July 2014
Available online 1 August 2014

Keywords:
Post-traumatic stress disorder
Magnetoencephalography (MEG)
Resting-state
Functional connectivity
Neural network

ABSTRACT

Post-traumatic stress disorder (PTSD) is a serious mental health injury which can manifest after experiencing a traumatic life event. The disorder is characterized by symptoms of re-experiencing, avoidance, emotional numbing and hyper-arousal. Whilst its aetiology and resultant symptomology are better understood, relatively little is known about the underlying cortical pathophysiology, and in particular whether changes in functional connectivity may be linked to the disorder. Here, we used non-invasive neuroimaging with magnetoencephalography to examine functional connectivity in a resting-state protocol in the combat-related PTSD group ($n = 23$), and a military control group ($n = 21$). We identify atypical long-range hyperconnectivity in the high-gamma-band resting-state networks in a combat-related PTSD population compared to soldiers who underwent comparable environmental exposure but did not develop PTSD. Using graph analysis, we demonstrate that apparent network connectivity of relevant brain regions is associated with cognitive-behavioural outcomes. We also show that left hippocampal connectivity in the PTSD group correlates with scores on the well-established PTSD Checklist (PCL). These findings indicate that atypical synchronous neural interactions may underlie the psychological symptoms of PTSD, whilst also having utility as a potential biomarker to aid in the diagnosis and monitoring of the disorder.

1. Introduction

Post-traumatic stress disorder (PTSD) is a mental health problem, characterized by anxious and depressive features, which develops after exposure to a traumatic life event. It is placed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) trauma and stressor-related disorders category, and PTSD is principally comprised of four symptom clusters: re-experiencing; avoidance; emotional numbing; and hyperarousal (American Psychiatric Association, 2013). Incidence of the disorder in the general population is around 5–10% (Kessler et al., 2005), and is thought to be much higher in some military populations returning from recent combat deployments in hazardous regions (Richardson et al., 2010). Knowledge remains scant, however, regarding the neurobiological basis of PTSD, limiting our understanding of the disorder and hampering the search for reliable biomarkers.

Structural and functional neuroimaging studies of PTSD using magnetic resonance imaging (MRI and fMRI) and positron emission tomography (PET) have reported atypical neuroanatomy and differential activation patterns in a number of cortical and subcortical structures (Hull, 2002). Known to play a role in episodic memory, the hippocampi show both structural and functional abnormalities (Bremner et al., 2003). Additionally, the amygdalae (Etkin and Wager, 2007), ventromedial prefrontal (Gold et al., 2011), and the dorsal anterior cingulate cortices (Shin et al., 2011) have been reported to show atypical function in the disorder (for an extensive biological review of PTSD, see Pitman et al., 2012).

In recent years, advances in the analyses of resting-state networks and the functional connectivity among brain regions have allowed researchers to map ongoing and spontaneous communication required for the temporal coordination of cognitive and sensory processing (Damoiseaux et al., 2006). In particular, changes in functional connectivity defined by ongoing oscillatory synchrony (Wang, 2010) have proven to be useful in mapping cortical pathophysiology, thought to underlie a number of neurophysiological disorders (Tewarie et al., 2013),

* Corresponding author at: Department of Diagnostic Imaging, 555 University Ave., Toronto M5G 1X8, Canada.
E-mail address: ben.dunkley@sickkids.ca (B.T. Dunkley).

http://dx.doi.org/10.1016/j.nicl.2014.07.017

including magnetoencephalographic (MEG) studies of PTSD. The technique of MEG allows spatiotemporal patterns of brain activity to be mapped with millisecond precision, elucidating functional brain changes on time scales to which fMRI is blind (Hari and Salmelin, 2012); fMRI only images ultra-low frequencies. Furthermore, MEG benefits from being able to directly record ongoing brain activity, as opposed to changes in the haemodynamics associated with neural firing.

MEG studies of PTSD suggest enhanced slow wave generators in left temporal regions, and decreased oscillations in parieto-occipital cortex are related to PTSD (Kolassa et al., 2007). Georgopoulos et al. (2010) suggested that patterns of abnormal synchronous oscillations could differentiate PTSD from control subjects, particularly poor communication between right temporo-parietal areas and other brain regions (Engdahl et al., 2010). This group also linked decorrelations in small networks, most evident in the right superior temporal gyrus, with resilience to lifetime trauma in control veterans, but not those with PTSD (James et al., 2013). The above studies collectively suggest that abnormal coherent brain oscillations might contribute to symptoms of the disorder.

Prior studies, however, have not investigated frequency-specific interactions in source-resolved networks, or their association with exposure to stressful stimuli or symptom severity. Here we used source-analysed MEG and graph theoretical analysis to test the hypotheses that veterans with PTSD would express atypical resting-state network synchrony; that these atypical inter-regional interactions would be exacerbated by exposure to stressful, combat-related imagery; and that an aberrant organization of neurophysiological networks is associated with the severity of PTSD symptoms and associated cognitive-behavioural outcomes. We selected strength and degree as our graph properties of interest, as they most directly correspond to network hyperconnectivity or hypoconnectivity when comparing two populations, and thus correspond most closely with our hypothesis that veterans with PTSD would show alterations in the intensity of network-level neurophysiological interactions. Specifically, node strength represents the weighted magnitude of the relation between a seed node and the network, which is the sum of all connections, and node degree indicates the number of connections between a given node and other nodes in the network (Bullmore and Sporns, 2009), which would capture differential network synchrony between veterans with PTSD and their matched controls.

2. Methods and materials

2.1. Participants

MEG data were recorded from 23 Canadian Armed Forces soldiers, who deployed in support of the Afghan mission and were subsequently diagnosed with PTSD (all male, mean age = 37.4, SD = 6.8, age range 22–48). Twenty-one soldiers (all male, mean age = 33.05, SD = 5.26, age range 18–45) who also participated in the Afghan mission but did not develop PTSD were recruited as a control group.

Participants were included in the PTSD group if they met the following criteria: they have a diagnosis of combat-related PTSD from an operational trauma stress support centre (OTSSC); PTSD symptoms were present from 1 to 4 years prior to participation in the study; they were engaged in regular mental health follow-up; and they had moderate or greater severity on the PTSD Checklist (PCL > 50). The diagnosis was determined by a psychiatrist or psychologist specializing in trauma-related mental health injuries and conducted through a comprehensive, semi-structured interview based upon DSM-IV-TR diagnostic criteria (American Psychiatric Association, 2000), along with Canadian Armed Forces (CAF) standardized psychometric testing. Interview-based clinician diagnosis of mental disorders is considered superior to pen and paper or self-administered screening methods. All participants in the PTSD group were recruited from one of the CAF OTSSCs, which are centres of excellence for the diagnosis and treatment of trauma-related mental health injuries. There were usually more than one DSM-IV-TR 'A1' stressor-related criteria (American Psychiatric Association, 2000) identified as a traumatic event contributing to the development of PTSD (direct personal experience of an event that involves actual or threatened death or injury), with diagnosis related to operational exposure. Control soldiers were matched on rank, education level, handedness and military experience.

Additional inclusion criteria applied to both groups included: no history of a traumatic brain injury (TBI), screened by a psychiatrist through a review of their electronic health record, telephone interview, and administration of the Defence and Veteran's Brain Injury Centre (DVBIC) 3 item screening tool; English-speaking and able to understand task instructions and give informed consent. 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. As this was a naturalistic sample, however, all PTSD patients were on evidenced-based psychotropic medication(s), such as selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and Prazosin.

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); Conner's Attention-Deficit Hyperactivity Disorder Test; the Generalized Anxiety Disorder 7 (GAD-7) test; Patient Health Questionnaire (PHQ9); and the Post Traumatic Stress Disorder Checklist (PCL). Within the PTSD group, there were significant rates of co-morbid mental disorders, including major depressive disorder (MDD; 74% of the PTSD group). These findings are consistent with prevalence rates established through large scale studies in military populations (Garber et al., 2012).

2.2. Procedure and MEG data acquisition

Resting-state MEG data were collected in two separate runs. Participants were supine and instructed to rest with eyes open and maintain visual fixation on an x within a circle on the screen. Following the first resting-state run, the participants completed a number of imaging protocols, with a memory-related paradigm containing trigger images, such as scenes of traumatic events (e.g. battlefield casualties) intermixed with neutral images, an emotional faces task, and a verbal task that contained neutral as well as salient trigger words (such as 'Kandahar' and 'grenade'). They then completed a second resting-state run. We expected the affective stimuli to induce arousal and attentional mechanisms, and perhaps differentially activate the PTSD group compared to the controls. We refer to the initial scan as the pre-triggering resting-state run and the subsequent acquisition as the post-triggering resting-state run.

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 per resting-state run. 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 the 3 T MRI Research 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