EBioMedicine 4 (2016) 176–183

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Research Paper

White Matter Abnormalities in Post-traumatic Stress Disorder Following a Specific Traumatic Event

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ARTICLE INFO

Article history:
Received 3 October 2015
Received in revised form 27 November 2015
Accepted 11 January 2016
Available online 13 January 2016

Keywords:
Posttraumatic stress disorder
Mental disorders
Diffusion tensor imaging
Magnetic resonance imaging
Neuroimaging
Psychoradiology

ABSTRACT

Studies of posttraumatic stress disorder (PTSD) are complicated by wide variability in the intensity and duration of prior stressors in patient participants, secondary effects of chronic psychiatric illness, and a variable history of treatment with psychiatric medications. In magnetic resonance imaging (MRI) studies, patient samples have often been small, and they were not often compared to similarly stressed patients without PTSD in order to control for general stress effects. Findings from these studies have been inconsistent. The present study investigated whole-brain microstructural alterations of white matter in a large drug-naive population who survived a specific, severe traumatic event (a major 8.0-magnitude earthquake). Using diffusion tensor imaging (DTI), we explored group differences between 88 PTSD patients and 91 matched traumatized non-PTSD controls in fractional anisotropy (FA), as well as its component elements axial diffusivity (AD) and radial diffusivity (RD), and examined these findings in relation to findings from deterministic DTI tractography. Relations between white matter alterations and psychiatric symptom severity were examined. PTSD patients, relative to similarly stressed controls, showed an FA increase as well as AD and RD changes in the white matter beneath left dorsolateral prefrontal cortex and forceps major. The observation of increased FA in the PTSD group suggests that the pathophysiology of PTSD after a specific acute traumatic event is distinct from what has been reported in patients with several years duration of illness. Alterations in dorsolateral prefrontal cortex may be an important aspect of illness pathophysiology, possibly via the region's established role in fear extinction circuitry. Use-dependent myelination or other secondary compensatory changes in response to heightened demands for threat appraisal and emotion regulation may be involved.

1. Introduction

Posttraumatic stress disorder (PTSD) is a response to traumatic experiences characterized by four main symptom clusters: re-experiencing symptoms (e.g. flashback and nightmares), avoidance symptoms, negative cognitions and mood, and arousal symptoms (e.g. hypervigilance and exaggerated startle). Given its high lifetime prevalence of 6.8% in the American general population, and its significant morbidity (Kessler et al., 2005), there is an urgent need to better understand its neurobiology.

A recent meta-analysis from our group showed that PTSD is associated with gray matter abnormalities (Li et al., 2014). Fewer studies have investigated white matter integrity (for a recent review (Daniels et al., 2013)). Results of these studies have been inconsistent, with reports of decreased fractional anisotropy (FA) in corpus callosum (Kitayama et al., 2007; Villarreal et al., 2004), prefrontal cortex (PFC) (Schuff et al., 2011), anterior cingulum (Kim et al., 2005; Schuff et al., 2011; Zhang et al., 2011) and posterior cingulum (Fani et al., 2012b), but also of increased FA in anterior cingulum (Abe et al., 2006) and superior frontal gyrus (Zhang et al., 2011).

There are important methodological issues regarding imaging protocols and patient sample characteristics that may contribute to the variability in study findings. Most early white matter studies in PTSD used manual tracing analysis in predefined regions of interest

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http://dx.doi.org/10.1016/j.ebiom.2016.01.012

(ROI) (Daniels et al., 2013). Although this method can be sensitive, results are highly reliant on anatomically specific prior hypotheses (Lee et al., 2009). This ROI-bias is avoided by whole-brain voxel-based analysis (Bandettini, 2009). Second, most previous voxel-based studies had small patient samples, and this might limit the reliability of results and sensitivity to illness effects (Abe et al., 2006; Fani et al., 2012b; Kim et al., 2005; Schuff et al., 2011; Zhang et al., 2012). Third, most studies have examined chronically ill patients treated with psychotropic medications, so that multiple secondary factors might differentially impact neuroanatomic measurements in the PTSD patients. Fourth, most prior studies compared PTSD patients to non-traumatized healthy controls, making it difficult to determine whether observed effects were related to PTSD per se or simply to traumatic stress exposure (Li et al., 2014). Only a few studies have compared PTSD patients to controls who experienced similar psychological trauma but did not develop PTSD (Abe et al., 2006; Schuff et al., 2011), and those studies often were complicated by psychotropic medication. Fifth, the nature, intensity and duration of trauma often varied widely among study participants. Studies using voxel based approaches with large samples of individuals with PTSD who experienced discrete stress compared to similarly stressed healthy individuals may better clarify PTSD neurobiology.

Diffusion tensor imaging (DTI) is particularly powerful for evaluating microstructural integrity of white matter by analyzing the restricted diffusion of water molecules (Catani, 2006). It can detect early neuropathological changes using quantitative indicators such as FA, which is thought to reflect fiber density, axonal diameter and myelination in white matter (Basser et al., 1994a; Basser et al., 1994b). Other DTI parameters that in combination determine FA, such as axial diffusivity (AD, along the axon) and radial diffusivity (RD, perpendicular to the main axonal axis) yield potentially more specific information. In animal studies, AD and RD have been identified as reflecting axonal and myelin integrity, respectively, that underlie changes in FA (Song et al., 2003; Song et al., 2002). Although methodological factors qualify their interpretation (Wheeler-Kingshott and Cercignani, 2009), these parameters provide potentially useful insight into the neurobiology of brain disorders. Few previous DTI studies of PTSD exploited the specific directional diffusivities (AD and RD), or used deterministic tractography to delineate the origins of fibers passing through regions with altered white matter anisotropy.

This study used DTI to investigate whole-brain microstructural alterations of white matter in a large sample of PTSD patients and controls, both of whom had survived a major 8.0-magnitude earthquake that occurred near a highly populated region of West China. Those diagnosed with PTSD were compared to those who did not develop the disorder ('non-PTSD') to control for general stress effects. The potential power of this study to illuminate the neuropathophysiology of PTSD is enhanced by several factors: 1) the unique characteristic of the trauma event involving a single, discrete period of acute emotional distress, 2) the relatively homogeneous demographic characteristics of the trauma survivors, 3) the use of non-PTSD controls exposed to similar trauma to control for general stress effects, 4) a relatively large study population free from psychotropic medication, and 5) the use of advanced techniques for analyzing the DTI data including the separation of radial and axial diffusivity and deterministic DTI tractography. Our previous functional magnetic resonance imaging (fMRI) studies using some of the present study participants found altered function in prefrontal-limbic system (Jin et al., 2014; Lei et al., 2015a; Yin et al., 2012; Yin et al., 2011a; Yin et al., 2011b). However, anatomic alterations underlying the functional abnormalities were not examined. Based on prior findings from our sample and other laboratories, we hypothesized that there are white matter abnormalities in prefrontal cortex in PTSD patients, and that they are related to PTSD severity.

2. Materials and Methods

2.1. Subjects

We recruited subjects who survived a severe earthquake (magnitude 8.0) in Sichuan Province of western China. A large-scale PTSD survey was conducted among 4200 survivors who were screened with the PTSD checklist (PCL) (Weathers et al., 1993). To be included in our study, the survivors needed to have (i) physically experienced the earthquake, and (ii) personally witnessed death, serious injury or the collapse of buildings, but (iii) suffered no physical injury, head trauma or loss of consciousness for >5 min. These criteria ensured that all survivors were exposed to generally similar traumatic stress intensity. Survivors with PCL scores ≥35 points were screened using the clinician-administered PTSD scale (CAPS) (Blake et al., 1995) and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (SCID) to confirm the PTSD diagnosis. Four hundred and fifteen eligible PTSD patients were identified from the survey. The SCID was also used to exclude individuals with current or past psychiatric illness, and any history of alcohol or drug abuse ($n = 134$). Participants also were excluded with any history of or current brain injury ($n = 12$), any significant medical or neurological conditions ($n = 58$), pregnancy ($n = 0$), any MRI contraindication ($n = 81$), left handed ($n = 16$), brain lesions identified at the MRI examination ($n = 5$), CAPS scores <50 points ($n = 11$) or age ≤18 years ($n = 10$). All patients included had no psychotropic medication use in the prior two months (to limit possible confounding effects on brain structure). Finally, 88 PTSD and 91 demographically matched non-PTSD study-eligible individuals were selected for this study. This study was approved by the local university ethics committee. Written fully-informed consent was obtained from all participants.

2.2. Imaging Acquisition

MRI data were acquired on a 3 T MRI system (EXCITE; General Electric) at the Department of Radiology in West China Hospital using an 8-channel phased-array head coil. The head was stabilized with cushions and ear plugs were used. DTI data, with 15 noncollinear directions ($b = 1000$ s/mm^2), as well as a reference image without diffusion weighting ($b = 0$), were acquired using a single-shot spin-echo echo planar image (SE-EPI) sequence. Array spatial sensitivity encoding was used to reduce susceptibility and eddy-current artifacts. Scan parameters were as follows: repetition time (TR) = 12,000 ms; echo time (TE) = 70.8 ms; matrix = 128×128 mm^2 on 240×240 mm^2 field of view (FOV); slices 3 mm without gap. Pairs of images during acquisition were averaged to increase resolution of MRI data.

2.3. Image Analysis

DTI preprocessing, including skull stripping using the Brain Extraction Tool (BET, http://fsl.fmrib.ox.ac.uk/fsl/bet2/) and eddy current correction for distortions induced by the head movement and eddy currents, were performed using the FMRIB Software Library (FSL 4.1, Oxford, U.K., http://www.fmrib.ox.ac.uk/fsl/). A diffusion tensor model was fitted to each voxel to create FA and eigenvalue ($\boldsymbol{\lambda}_{i,\,i} = 1, 2, 3$) images. The parametric map of eigenvalue $\boldsymbol{\lambda}_1$ represents that of AD ($\boldsymbol{\lambda}_{||} = \boldsymbol{\lambda}_1$), while RD was calculated by using the image manipulation subroutine (ImCalc) function in SPM8 [$\boldsymbol{\lambda}_{\perp} = (\boldsymbol{\lambda}_2 + \boldsymbol{\lambda}_3) / 2$].

A whole-brain voxel-wise analysis was then performed with SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/) running in MATLAB 2010 (MathWorks, Natick, Mass). For each subject, the FA, AD and RD images were normalized to the standard Montreal Neurological Institute (MNI) space, based on the deformation information generated from the unweighted image (B_0 image) and using the echo-planar imaging (EPI) template supplied with SPM8, each voxel being $2 \times 2 \times 2$ mm^3. The