Journal of Affective Disorders 220 (2017) 139–146

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Fornix microalterations associated with early trauma in panic disorder

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ARTICLE INFO

Keywords:
Panic disorder
Early trauma
Fornix
Neural correlates
Neuroimaging

ABSTRACT

Background: It is well accepted that panic disorder (PD) is associated with early trauma, and that the limbic systems are one of the main structures involved in PD pathophysiology. However, previous studies have not addressed the relationship between early trauma and major limbic white-matter (WM) structures in PD.

Methods: Participants enrolled in the study consisted of 53 right-handed patients with PD and 21 healthy controls (HC). The Early Trauma Inventory Self Report-Short Form (ETISR-SF), Anxiety Sensitivity Inventory-Revised (ASI-R), and the Albany Panic and Phobia Questionnaire (APPQ) were applied in the study. Tract-based spatial statistics were used for diffusion tensor magnetic resonance imaging analysis.

Results: Among the patients with PD, the fractional anisotropy (FA) values of the fornix body in major limbic WM regions showed significant negative correlation with the ETISR-SF total score, while the scores of mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) in the same region of fornix had significant positive correlation with those scores ($p < 0.05$; FWE corrected). Further significant correlation was observed between these four scores and the measures of symptom severity in PD, such as that in ASI-R and APPQ in the same region.

Limitations: Recall bias is possible in evaluating early trauma in the participants.

Conclusions: The current study suggests a significant association of early trauma with the fornix body possibly through axons and myelin disruptions within major limbic structures in PD. A multi-centered large sample will be needed to confirm these findings.

1. Introduction

Childhood trauma is defined as any act or series of acts by a parent or caregiver that results in harm, potential for harm, or threat of harm to a child (Hamburger et al., 2008). Almost 76% of adults reporting child physical abuse and neglect have experienced at least one psychiatric disorder in their lifetime, while nearly 50% have developed three or more psychiatric disorders (Borger et al., 2005). Adults with a history of abuse also present with medical, social, and behavioral problems more frequently than those who have not experienced abuse (Draper et al., 2008).

The human brain develops during childhood through the process of synaptic remodeling, activity dependent myelination, and programmed cell death, which affects both gray and white matter (WM) organization (de Graaf-Peters and Hadders-Algra, 2006). Therefore, childhood maltreatment can be a stressor that leads to the development of psychiatric problems and affects the structure and function of the brain until midlife (Teicher et al., 2006).

Structural neuroimaging studies have provided evidence of an association between child abuse and deficits in brain volume and gray matter in several regions, most prominently the hippocampus and amygdala (Hart and Rubia, 2012). In particular, Diffusion tensor imaging (DTI) studies have reported evidence for deficits in the structural interregional connectivity between these areas, suggesting neural network abnormalities in the uncinate fasciculus, cingulum bundle, and fornix (Choi et al., 2009; Eluvathingal et al., 2006; Seidman et al., 2005).

Individuals who have experienced childhood abuse are more likely to experience psychiatric disorders including generalized anxiety or panic disorder (PD) (Goodwin et al., 2005). In traumatized children, the fear system tends to become increasingly responsive to relatively minor stimuli by means of the processes of sensitization and kindling (Post

Abbreviations: AS, anxiety sensitivity; PD, panic disorder; SSRI, selective serotonin re-uptake inhibitor; WM, white matter; SD, standard deviation; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; MR, magnetic resonance; ETISR-SF, Early Trauma Inventory Self Report-Short Form; ASI-R, Anxiety Sensitivity Inventory-Revised; APPQ, Albany Panic and Phobia Questionnaire; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; EPI, echo planar imaging; DTI, Diffusion tensor image; FA, fractional anisotropy; MD, Mean Diffusivity; AD, Axial Diffusivity; RD, Radial Diffusivity; TBSS, Tract-Based Spatial Statistics; TFCE, threshold-free cluster enhancement; ICV, intracranial volume; fMRI, functional magnetic resonance imaging

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http://dx.doi.org/10.1016/j.jad.2017.05.043
Received 31 January 2017; Received in revised form 25 April 2017; Accepted 28 May 2017
Available online 30 May 2017

et al., 1998). Fear and avoidance of trigger cues are common in many anxiety disorders and resemble the arousal and avoidance responses displayed by healthy individuals in response to conditioned fear cues. It has been reported that the limbic structures are chiefly involved in these fear responses (Etkin and Wager, 2007).

The limbic system consists of a group of interconnected nuclei and cortical structures that mediate emotion, memory, and behavior (Patestas and Gartner, 2006). The classical circuit described by Papez (1937) includes important WM pathways interlinking the hippocampus, mammillary bodies, anterior thalamic nuclei, cingulate gyrus, and parahippocampal gyrus, which forms a closed loop in each hemisphere. Major tracts of the limbic system were described based on in vivo MRI of the human brain (Mori and Aggarwal, 2014). Based on this study, the major limbic tracts were defined as the cingulum, fornix, and stria terminalis.

However, there is no study addressing the relationship between early trauma and structural neural correlates in PD to date, particularly the major limbic WM structures. Thus, it is necessary to conduct a study to examine the relationship between early trauma and the major limbic tracts in PD. Based on previous reports, we have developed two hypotheses. First, an exposure to early trauma may be correlated with the integrity of major limbic WM structures in PD. Second, the measures of symptom severity in PD may be related to the microalteration levels in these WM structures.

The objective of this study is to investigate the major limbic WM correlates associated with early trauma in PD and the nature of the link between these WM regions and measures of symptom severity.

2. Materials and methods

2.1. Subjects and clinical assessments

Subjects were recruited from patients with PD who were treated at the Department of Psychiatry of CHA Bundang Medical Center between January 2011 and June 2015. The study sample consisted of 53 patients with PD (24 men and 29 women) with an average age of 36.70 ± 10.84 years (mean ± standard deviation [SD]). A total of 21 age- and sex-matched healthy control (HC) subjects (10 men and 11 women; aged, 33.71 ± 9.43 years) were recruited for the study through advertisements. All subjects were between 18 and 60 years of age, Korean, and right-handed. Only subjects without a personal or family history of psychiatric disorders among their first-degree relatives were regarded as HCs in this study. The personal and family histories of the subjects were established through interviews.

Patients with PD met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for PD with or without agoraphobia, as diagnosed by experienced psychiatrists using the structured clinical interview to assess DSM-IV-TR Axis I disorders. Only patients with primary PD were included; secondary lifetime diagnoses were major depression in seven patients and generalized anxiety disorder in three patients. Exclusion criteria for all subjects included any current diagnosis or lifetime history of schizophrenia, bipolar disorder, anxiety disorders other than PD, alcohol and substance abuse or dependence, mental retardation, serious medical or neurological disorders, pregnancy, or contraindications to brain magnetic resonance (MR) scanning, including metal implants. After the commencement of the study, the majority of the patients began treatment with a minimal dosage of selective serotonin reuptake inhibitors (SSRIs) including escitalopram or paroxetine (n = 27; escitalopram equivalence dosage, 7.69 ± 2.59 mg/day), and benzodiazepines including alprazolam or clonazepam as anxiolytics (n = 21; alprazolam equivalence dosage, 0.81 ± 0.60 mg/day). Brain MR scans of all patients were obtained within 10 days (4.12 ± 2.64 days) of the initiation of medication use.

A shortened version of the Early Trauma Inventory Self Report (ETISR-SF) has been previously developed for measuring early trauma (Bremner et al., 2007). To measure the childhood trauma, we used the Korean version of ETISR-SF (Jeon et al., 2012), which consists of 27 items in the four domains of physical, emotional, and sexual abuse, as well as general trauma before the age of 18 years. Each of the items is answered by either 'yes' or 'no'.

All subjects' anxiety sensitivity (AS) levels were assessed using the Korean version of the Anxiety Sensitivity Inventory-Revised (ASI-R) (Lim et al., 2007; Taylor and Cox, 1998), which is the most commonly used measure of AS and consists of fear of a respiratory symptom, fear of a cardiovascular symptom, fear of a publicly observable anxiety reaction, and fear of cognitive dyscontrol. The ASI-R is an expanded version of the ASI (Peterson and Reiss, 1987). Each item has a scale ranging from 0 (very little) to 4 (very much) and yields total scores ranging from 0 to 144. The internal consistency coefficient of the Korean version is 0.92 and its test-retest reliability is 0.82.

To measure the clinical severity of the patients' anxiety and depressive symptoms, we also applied the Albany Panic and Phobia Questionnaire (APPQ) (Rapee et al., 1994), the Beck Anxiety Inventory (BAI) (Beck et al., 1988), and the Beck Depression Inventory (BDI) (Beck et al., 1961) at the same time. The APPQ was developed to assess the fear of activities that may induce physical sensation in panic patients. Twenty-seven items were rated on a 9-point scale ranging from 1 (not at all) to 8 (extremely), with the total score obtained corresponding to the summed score of all items. We used the Korean version of the APPQ, which shows a good internal consistency (Cronbach's alpha = 0.95) and a high test-retest reliability (r = 0.77) (Kim, 2004).

All study procedures complied with the Institutional Review Board regulations of the CHA Bundang Medical Center, the Declaration of Helsinki, and the principles of Good Clinical Practice. After a complete description of the study was presented to the subjects, their written informed consent was obtained.

2.2. Magnetic Resonance Imaging procedures

Diffusion data were acquired on a 3.0 T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA). Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence, with the following parameters: repetition time (TR) of 17,000 ms, echo time (TE) of 108 ms, field of view (FOV) of 24 cm, 144 × 144 matrix, 1.7 mm slice thickness, and voxel size of $1.67 \times 1.67 \times 1.7\ mm^3$. A double-echo option was used to reduce eddy current-related distortions. To reduce the impact of EPI spatial distortions, an 8-channel coil and an array of spatial sensitivity encoding techniques (ASSET, GE Healthcare) with a sensitivity encoding (SENSE) speed-up factor of two were used. Seventy axial slices parallel to the anterior commissure–posterior commissure (AC-PC) line covering the whole brain were acquired in 51 directions with b-value = 900 s/mm^2. Eight baseline scans with b = 0 s/mm^2 were also acquired. Diffusion tensor images (DTIs) were estimated from the diffusion-weighted images using the least-squares method (approximate scan time = 17 min).

2.3. Tract-based spatial statistics

Voxel-wise statistical analysis of the fractional anisotropy (FA) data was performed using Tract-Based Spatial Statistics (TBSS) version 1.2, implemented in the Oxford functional MRI of the brain (FMRIB) Software Library (FSL version 4.1, Oxford, UK, http://www.fmrib.ox.ac.jk/fsl) according to the standard procedure published elsewhere (Smith et al., 2006). First, DTI preprocessing, including skull stripping using the Brain Extraction Tool (BET) and eddy current correction, were performed using the FSL. Subsequently, FA images were created by fitting a tensor model to the raw diffusion data (Smith, 2002). All subjects' FA data were aligned in the standard space (Montreal Neurologic Institute 152 standard) using the FMRIB's nonlinear image registration tool (FNIRT). All transformed FA images were combined and applied to the original FA map, resulting in a standard-space version of