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Decreased gray matter volume of the medial orbitofrontal cortex in panic disorder with agoraphobia: A preliminary study

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ABSTRACT

Background: Patients with panic disorder with agoraphobia (PDA) have clinical symptoms such as the fear of being outside or of open spaces from which escape would be difficult. Although recent neurobiological studies have suggested that fear conditioning and extinction are associated with PDA, no study has examined the possible structural abnormalities in patients with PDA.
Methods: This preliminary study compares the gray matter volume among patients with PDA, those with panic disorder without agoraphobia (PDW), and healthy controls (HC) using high-resolution 3.0 T magnetic resonance imaging (MRI) with voxel-based morphometry (VBM).
Results: Compared with HC, patients with PDA showed decreased gray matter volume in their left medial orbitofrontal gyrus. However, differences were not found in the gray matter volumes of patients with PDW and whole panic disorder compared with HC.
Conclusions: These findings suggest that the phobic avoidance found in patients with PDA arise from abnormalities in the medial orbitofrontal cortex, which plays an important role in fear extinction. Future studies should investigate the neuroanatomical substrates of PDA and distinguish them from those of PDW.

1. Introduction

Panic disorder (PD) is characterized by unexpected and recurrent panic attacks that are accompanied by feelings of intense distress or fear and various physical symptoms (American Psychiatric Association, 1994). Although several volumetric studies have revealed that abnormalities in several brain structures are associated with PD, inconsistent results remain. The amygdala (Hayano et al., 2009; Massana et al., 2003b), parahippocampal gyrus (Massana et al., 2003a), cingulate (Asami et al., 2008; Lai et al., 2010), medial frontal area (Roppongi et al., 2010; Sobanski et al., 2010), insula (Lai and Wu, 2012; Uchida et al., 2008), temporo-occipital regions (Asami et al., 2009; Lai and Hsu, 2011; Lai and Wu, 2012; Sobanski et al., 2010), and cerebellum (Kessler et al., 1998; Lai and Hsu, 2011; Sheehan et al., 1998) have been associated with PD. The inconsistencies among these studies might be partially due to clinical factors such as comorbid Axis I disorders (Asami et al., 2008; Hayano et al., 2009; Lai et al., 2010; Protopopescu et al., 2006; Roppongi et al., 2010; Uchida et al., 2008), current or past psychiatric medications (Asami et al., 2008, 2009; Hayano et al., 2009; Roppongi et al., 2010; Uchida et al., 2008), and patient age at onset (Lai and Wu, 2012).

However, little is known about the role of agoraphobia with regard to the subtypes of PD. PD is a heterogeneous disease with various subtypes (Roberson-Nay and Kendler, 2011). Although agoraphobia is not an independent Diagnostic and Statistical Manual for Mental Disorders, fourth edition (DSM-IV) (American Psychiatric Association, 1994) diagnosis, panic disorder with agoraphobia (PDA) might be the best subtype example. Agoraphobia refers to abnormal feelings of anxiety and fear associated with being at places or in situations from which escape is difficult (American Psychiatric Association, 1994). Since Klein suggested that agoraphobia can be conceptualized as the psychopathology that results from recurrent panic attacks (Klein, 1980), subsequent studies

Abbreviations: PD, Panic Disorder; PDA, Panic Disorder with Agoraphobia; DSM-IV, Diagnostic and Statistical Manual for Mental Disorders, Fourth edition; PDW, Panic Disorder without Agoraphobia; fMRI, functional Magnetic Resonance Imaging (fMRI); HC, Healthy Controls; MINI, Mini-International Neuropsychiatric Interview; SPSS, Statistical Package for the Social Sciences; MRI, Magnetic Resonance Imaging; PDSS, Panic Disorder Severity Scale; API, Acute Panic Inventory; STAI, Spielberger State-Trait Anxiety Inventory; ASI-R, Anxiety Severity Index, revised version; MP-RAGE, Magnetization Prepared Rapid Acquisition Gradient Echo; VBM, Voxel-Based Morphometry; DARTEL, Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra; ANOVA, Analysis of Variance; TIV, Total Intracranial Volume; ROIs, Regions of Interest; FWE, Family-Wise Error; MNI, Montreal Neurological Institute; DMN, Default Mode Network.

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have supported the notion that agoraphobia should be viewed in the context of recurrent panic attacks (Kikuchi et al., 2005). However, other studies have argued that agoraphobia is a distinct psychiatric disorder (Bienvenu et al., 2006; Fava et al., 1988; Wittchen et al., 2008). Although whether agoraphobia is an independent diagnosis remains controversial, a growing body of literature reports that PDA has discriminative clinical and prognostic features compared with PD without agoraphobia (PDW). Patients with PDA are typically female, have poor psychosocial functioning, a high comorbidity with other psychiatric disorders, and high non-specific anxiety levels compared with patients with PDW (Grant et al., 2006; Hayward et al., 2003; Kessler et al., 2006; Kikuchi et al., 2005; Slaap and den Boer, 2001).

These epidemiological and clinical findings strongly suggest that PDA has a distinct neurobiological etiology. For example, genetic (Rothe et al., 2004) and neurophysiological (McTeague et al., 2011) studies have revealed that PDA might have its own etiological characteristics. Although few neuroimaging studies have been conducted, recent functional magnetic resonance imaging (fMRI) studies have consistently reported that PDA is associated with activation in brain structures that belong to the so-called 'fear circuitry'. Activations of the medial orbitofrontal cortex, anterior cingulate, insula, and amygdala are associated with agoraphobia-specific stimuli (Wittmann et al., 2011) and responses to cognitive behavioral therapy (Kircher et al., 2013) in patients with PDA. This neurobiological evidence for PDA suggests that characteristic structural abnormality may exist in patients with PDA. However, to the best of our knowledge, no structural MRI studies have examined the possible differences in gray matter volumes in patients with PDA.

This study hypothesized that decreased gray matter volume in the structures involved in a fear conditioning process would indicate a characteristic neuroanatomical substrate among patients with PDA but not those with PDW.

2. Methods

2.1. Participants and procedures

The study sample consists of 18- to 65-year-old patients with PD as well as age- and gender-matched HC recruited from the Department of Psychiatry at Korea University Anam Hospital. All the participants were right-handed according to the Edinburgh Handedness Test (Oldfield, 1971).

Patients who were diagnosed with PD using the DSM-IV were consecutively recruited. To diagnose psychiatric disorders between the patient and healthy participant groups, board-certified psychiatric professionals used the Korean version of the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; Yoo et al., 2006).

Patients with PD were excluded if they (1) had any past or current comorbid psychiatric diagnosis including mood disorders, psychotic disorders, anxiety disorders, substance-related disorders, and personality disorders; (2) had an IQ under 80; (3) had a clinically significant general or neurological disease that might influence the structural brain image; (4) were pregnant or nursing; or (5) had any contraindicated factors for magnetic resonance imaging (MRI), such as a pacemaker.

After completely explaining the study to all participants, written informed consent was obtained. The Institutional Review Board of Korea University Anam Hospital approved the study procedures. This study was conducted in accordance with the 1989 revision of the Declaration of Helsinki.

2.2. Psychopathology assessments

To assess panic symptom severity, the Panic Disorder Severity Scale (PDSS) (Lim et al., 2007b; Shear et al., 2001) and the Acute Panic Inventory (API) (Dillon et al., 1987) were used. To evaluate general anxiety symptoms, the Spielberger State-trait Anxiety Inventory (STAI) (Hahn et al., 1996; Spielberger et al., 1970) and the Anxiety Sensitivity Index, revised version (ASI-R) (Lim et al., 2007a; Reiss et al., 1986) were used.

2.3. MRI

Structural brain images were obtained from three-dimensional MRI scans using a 3.0 T Magnetom Trio Tim System (Siemens Medical Solutions, Inc., Iselin, NJ, USA) in the Korea University Brain Imaging Center. The images were taken using a high-resolution T1-weighted magnetization prepared rapid acquisition gradient echo (MP-RAGE) sequence (1900-ms repetition time, 2.6-ms echo time, 220-mm field of view, 256×256 matrix size, 176 coronal slices without a gap, $1 \times 1 \times 1$ mm3 voxels, 16° flip angle, number of excitations $= 1$).

2.4. VBM

Data were analyzed using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8) with the default parameters of the statistical parametric mapping software package (SPM8, http://www.fil.ion.ucl.ac.uk/spm) executed using Matlab 7.7.0 (R2008b) (MathWorks, Natick, MA, USA).

For a more accurate registration of the MRI images, we used diffeomorphic anatomical registration using exponentiated lie algebra (DARTEL) (Ashburner, 2007). DARTEL is one of the most outstanding nonlinear registering methods (Klein et al., 2009). The optimization in DARTEL is based on the Levenberg–Marquardt strategy, which enables DARTEL to be more sensitive than the standard VBM (Bergouignan et al., 2009). All imaging analysis processes were conducted as described in the VBM Tutorial (Ashburner, 2010). We briefly summarize the process here: First, the images were automatically segmented into gray matter, white matter, and cerebrospinal fluid using the standard option implemented in SPM8. Second, a DARTEL approach was applied for registration, normalization, and modulation. Finally, the gray matter probability values were smoothed using an 8-mm full-width half-maximum isotropic Gaussian kernel.

2.5. Statistical analysis

Demographic and clinical variables were compared across groups using an analysis of variance (ANOVA) or independent *t*-tests for continuous variables and χ^2 tests for dichotomous variables. When variables were not normally distributed according to a Kolmogorov–Smirnov test, appropriate non-parametric tests were used. All statistical analyses for demographic and clinical data were conducted using Statistical Package for the Social Sciences (SPSS) 17.0 (Chicago, IL, USA). The smoothed gray matter images were analyzed with an analysis of covariance model using SPM8. Age, gender, and total intracranial volume (TIV) were included as covariates. TIV was calculated as the sum of the segmented images of modulated gray matter, white matter, and cerebrospinal fluid.

The gray matter volumes of patients with PD were compared with those of HC. Patients with PDA and those with PDW were also compared with corresponding age- and gender-matched HC. As mentioned above, structural abnormalities have been found in nearly all brain regions of patients with PD, including the frontal, limbic, occipito-temporal, and cerebellar areas. Hence, the difference in gray matter volume between patients with PD and HC was analyzed across the whole brain. With regard to the subgroup analysis that primarily explored the possible association between PDA and fear conditioning structures, however, regions of interest (ROIs) using a priori hypotheses were created. The ROIs included the structures of the fear circuit (i.e., the medial prefrontal cortex including medial orbitofrontal cortex and anterior cingulate cortex, amygdala, hippocampus, parahippocampal gyrus, thalamus, and insula) (de Carvalho et al., 2010).

A family-wise error (*FWE*)-corrected statistical threshold of $p < 0.05$ was applied. Multiple regression models that adjusted for