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Comparison of panic disorder with and without comorbid major depression by using brain structural magnetic resonance imaging

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ABSTRACT

Background: Strong lifetime and current comorbidity occur between panic disorder and depression. However, no study has examined the influence of comorbid depression on brain structural characteristics in panic disorder patients. We aimed to compare gray matter (GM) volume and white matter (WM) connectivity in panic disorder patients with and without depression.
Methods: Twenty-one panic disorder patients without comorbid major depression (PD − D) and seventeen panic disorder patients with major depression (PD + D) were investigated. The Panic Disorder Severity Scale (PDSS) and Beck Depression Inventory (BDI) were assessed for all subjects. Voxel Based Morphometry 5 toolbox and Tract-Based Spatial Statistics were used.
Results: Compared to the PD − D group, GM volumes of patients with PD + D were significantly increased in a cluster located across the left cingulate gyrus, right medial frontal gyrus, and left paracentral lobule. Clinical symptom severity such as PDSS and BDI scores showed positive correlation with GM volumes in the PD + D group. Of the highlighted regions, the left posterior cingulate gyrus demonstrated both a GM volume difference between the groups and a positive correlation of GM volume with symptom severity in the PD + D group. Fractional anisotropy values were significantly higher across almost all the WM tracts in the PD + D group compared to the PD − D group.
Conclusion: Alteration of GM volume and WM connectivity was associated with comorbid depression in panic disorder patients in this study. These findings suggest that distinct structural characteristics may be related to comorbid depression occurring in the context of panic disorder.

1. Introduction

Panic disorder with another psychiatric comorbidity appears to be more common than panic disorder alone (Roy-Byrne et al., 1999). In particular, strong lifetime and current comorbidity were found between panic disorder and depression (Kessler et al., 1998). Comorbid depression in panic disorder leads to more severe psychiatric symptoms, a higher frequency of other comorbid conditions, a higher rate of suicide attempts, increased risk of academic, occupational, and interpersonal difficulties and a poorer response to treatment (Roy-Byrne et al., 2000). However, currently little is known in terms of the underlying pathophysiological mechanisms of depression suffered by panic disorder patients.

The notion of a shared etiology between anxiety disorders and depression has been supported by previous studies (Heninger et al., 1988; Hettema et al., 2006, 2008; Levinson et al., 2003; van Tol et al., 2012). However, other studies have reported that depression and anxiety may be related to specific neurobiological backgrounds.

Abbreviations: ACC, anterior cingulate cortex; AC–PC, anterior commissure–posterior commissure; ANCOVA, analysis of covariance; ASSET, array spatial sensitivity encoding techniques; BA, Brodmann area; BDI, Beck Depression Inventory; CSF, cerebrospinal fluid; DTI, Diffusion-tensor image; EPI, echo planar imaging; FA, fractional anisotropy; FOV, field of view; FWE, family-wise error; GM, gray matter; ICV, intracranial volume; MRI, magnetic resonance imaging; OCD, obsessive–compulsive disorder; PCC, posterior cingulate cortex; PDSS, Panic Disorder Severity Scale; PD − D, panic disorder without comorbid major depression; PD + D, panic disorder with comorbid major depression; PTSD, posttraumatic stress disorder; SCID-I, Structured Clinical Interview to assess DSM-IV Axis I disorders; SENSE, sensitivity encoding; SPM, Statistical Parametric Mapping; SSRI, selective serotonin re-uptake inhibitor; TBSS, Tract-Based Spatial Statistics; TE, echo time; TFCE, threshold-free cluster enhancement; TR, repetition time; VBM, Voxel Based Morphometry; WM, white matter; 3D T1-FSPGR, three-dimensional T1-weighted fast spoiled gradient recalled echo.

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According to a quantitative electroencephalographic study, specific symptom features of depression and anxiety are related to different patterns of regional brain activity (Bruder et al., 1997). Moreover, it was suggested that brain volume alteration of each specific region in depression and anxiety disorders without comorbid depression could reflect disorder-specific symptom clusters (van Tol et al., 2010).

With regard to the neural correlates of comorbid depression in anxiety disorders, distinct structural characteristics or brain activation patterns were related to comorbid depression occurring in the context of anxiety disorders (Kroes et al., 2011; Lanius et al., 2007). For example, an influence of comorbid depression was associated with less amygdala activity in posttraumatic stress disorder (PTSD) patients with depression than in patients without depression (Kemp et al., 2007). In neuroimaging studies of obsessive–compulsive disorder (OCD) and comorbid depression, gray matter (GM) volume alteration of the medial frontal gyrus, insula, and amygdala was associated with comorbid depression in OCD patients (Cardoner et al., 2007). Further, compared to OCD patients free from depression, discrete basal ganglia-thalamic abnormalities, and different regional cortical thickness were associated with comorbid depression in OCD patients (Fallucca et al., 2011; Saxena et al., 2001).

According to prior functional magnetic resonance imaging (MRI) data, brain structures, such as the prefrontal cortex, cingulate cortex, amygdala, and brainstem structures, might play a major role in the panic circuitry (Pillay et al., 2006; van den Heuvel et al., 2005). GM volume alterations of panic disorder have appeared inconsistently. GM volume reductions were found in fronto-temporal regions including the amygdala, insula, prefrontal, temporal and cingulate cortex (Asami et al., 2009; Lai and Wu, 2012; Sobanski et al., 2010). In contrast, other studies observed a relative increase in GM volume in the insula, superior temporal gyrus, midbrain, and pons (Protopopescu et al., 2006; Uchida et al., 2008). In addition, a diffusion tensor imaging study found increased white matter (WM) connectivity in left anterior and right posterior cingulate regions in panic disorder (Han et al., 2008).

According to meta-analyses of structural and functional alterations in depression, the most consistently identified regions include areas involved in emotional processing, such as the prefrontal cortices, cingulate cortex, hippocampus, amygdala, and basal ganglia (Fitzgerald et al., 2008; Koolschijn et al., 2009; Sacher et al., 2012). In a similar context, altered WM connectivity has been consistently identified in the tracts connecting the prefrontal cortex to cortical and subcortical (amygdala and hippocampus) areas in patients with major depression (Liao et al., 2012).

Brain structural and functional abnormalities related to panic disorder or depression have been investigated separately. However, no study has examined the influence of comorbid depression on brain structural characteristics in panic disorder patients. We hypothesized that brain structural characteristics could be different depending on the presence or absence of comorbid depression in panic disorder. Therefore, the present study aimed to analyze the alterations of GM volume and WM connectivity in panic disorder patients with comorbid depression compared to panic disorder patients without depression. In addition, we planned to examine if the regions showing structural alterations associated with comorbid depression would be correlated with clinical severity.

2. Methods

2.1. Subjects and clinical assessment

Twenty-one patients with panic disorder free of comorbid major depression (PD − D) and seventeen patients with panic disorder comorbid with major depression (PD + D) were recruited from the outpatient units of the Department of Psychiatry, CHA Bundang Medical Center, CHA University. Subjects were 18 to 60 years old who primarily met the DSM-IV criteria for panic disorder with or without agoraphobia, as diagnosed by experienced psychiatrists using the structured clinical interview to assess DSM-IV Axis I disorders (SCID-I) (First et al., 1996). We defined the presence of comorbid major depression with a clinical diagnosis of a current major depressive episode by experienced psychiatrists using the SCID-I. All patients were recruited from our outpatient clinic where they were being treated for their panic symptoms. We identified patients who exhibited current comorbid major depressive episodes as assessed via a diagnostic interview. There was no history of treatment for major depression among our patients.

All subjects were of Korean descent and right-handed. Exclusion criteria for all subjects included any current diagnosis or lifetime history of schizophrenia, bipolar disorder, anxiety disorders other than panic disorder, alcohol or substance dependence, mental retardation, serious medical or neurological disorders, or contraindications to MR scanning including metal implants or pregnancy. Prior to enrollment into this study, the majority of patients were treated with a selective serotonin re-uptake inhibitor (SSRI) including paroxetine or escitalopram (n = 36), and benzodiazepines as anxiolytics including alprazolam or clonazepam (n = 36) within the previous 1 week (mean ± SD, 3.95 ± 1.58 days).

Subjects were assessed for clinical severity of panic symptoms using the Panic Disorder Severity Scale (PDSS) (Lim et al., 2007a; Shear and Maser, 1994), and comorbid depressive symptoms using the Beck Depression Inventory (BDI) (Beck et al., 1961; Hahn et al., 1986). Items of the PDSS can measure almost all of the dimensions of panic disorder, including frequency of panic attacks, distress caused by panic attacks, anticipatory anxiety, agoraphobic fear/avoidance, panic-related sensation fear/avoidance, and work and social impairment (Shear et al., 1997). The PDSS has been reported to perform well and to meet the need for a reliable global assessment (Lim et al., 2007b). Assessment of the reliability of the PDSS yielded an overall Cronbach's α of .83, an interrater reliability of .88, and a test–retest reliability of .96. Similarly, the BDI is one of the most widely used self-report instruments for measuring the severity of depression. The BDI was developed to assess the type and degree of depression based on symptoms. The questionnaire contains questions about emotional, cognitive, motivational, physiological, and other symptoms, reflecting how participants have felt over the past week. Many studies have shown the reliability and validity of the BDI (Beck et al., 1988; Jo et al., 2007). The BDI showed significant positive Cronbach's α (.88) and test–retest reliability (.60). Both scales were assessed within the 3 days prior to or following the MRI scan.

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

2.2. MRI acquisition

All scans were performed on the same 3 T GE Signa HDxt scanner (GE Healthcare, Milwaukee, WI, USA) equipped with an eight-channel phase array head coil at CHA Bundang Medical Center, CHA University. Parameters for three-dimensional T1-weighted fast spoiled gradient recalled echo (3D T1-FSPGR) images were as follows: repetition time (TR) 16 ms, echo time (TE) 4.3 ms, flip angle 10°, slice thickness 1.7 mm, field of view (FOV) 25.6 cm, 256 × 256 matrix, isotropic voxel size $1 \times 1 \times 1$ mm^3. Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence, with the following parameters: TR 17,000 ms, TE 108 ms, FOV 24 cm, 144 × 144 matrix, slice thickness 1.7 mm, voxel size $1.67 \times 1.67 \times 1.7$ mm^3. A double echo option was used to reduce eddy-current related distortions. To reduce the impact of EPI spatial