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White matter correlates of anxiety sensitivity in panic disorder

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ABSTRACT

Background: Anxiety sensitivity (AS) refers to a fear of anxiety-related sensations and is a dispositional variable especially elevated in patients with panic disorder (PD). Although several functional imaging studies of AS in patients with PD have suggested the presence of altered neural activity in paralimbic areas such as the insula, no study has investigated white matter (WM) alterations in patients with PD in relation to AS. The objective of this study was to investigate the WM correlates of AS in patients with PD.

Methods: One–hundred and twelve right-handed patients with PD and 48 healthy control (HC) subjects were enrolled in this study. The Anxiety Sensitivity Inventory-Revised (ASI-R), the Panic Disorder Severity Scale (PDSS), the Albany Panic and Phobia Questionnaire (APPQ), the Beck Anxiety Inventory (BAI), and the Beck Depression Inventory (BDI) were administered. Tract-based spatial statistics were used for diffusion tensor magnetic resonance imaging analysis.

Results: Among the patients with PD, the ASI-R total scores were significantly correlated with the fractional anisotropy values of the WM regions near the insula, the splenium of the corpus callosum, the tapetum, the fornix/stria terminalis, the posterior limb of the internal capsule, the retrolenticular part of the internal capsule, the posterior thalamic radiation, the sagittal striatum, and the posterior corona radiata located in temporo-parieto-limbic regions and are involved in interoceptive processing ($p < 0.01$; threshold-free cluster enhancement [TFCE]-corrected). These WM regions were also significantly correlated with the APPQ interoceptive avoidance subscale and BDI scores in patients with PD ($p < 0.01$, TFCE-corrected). Correlation analysis among the HC subjects revealed no significant findings.

Limitations: There has been no comparative study on the structural neural correlates of AS in PD.

Conclusions: The current study suggests that the WM correlates of AS in patients with PD may be associated with the insula and the adjacent temporo-parieto-limbic WM regions, which may play important roles in interoceptive processing in the brain and in depression in PD.

1. Introduction

Anxiety sensitivity (AS) has been suggested to be a risk factor for the development of anxiety disorders and plays a particularly important role in panic disorder (PD)(McNally, 2002). AS refers to the fear of anxiety-related bodily sensations, such as increased breathing rate, palpitation, pain, numbness, and dizziness. This fear is based on the erroneous belief that these sensations are signs of impending harmful physical, social, or cognitive consequences (McNally, 2002). Individuals with high AS believe ambiguous body sensations to be dangerous and experience increased anxiety arousal and aggravated fear sensations, which result in further catastrophic misinterpretations of the sensations, and finally lead to panic attacks (Cox, 1996). Therefore, high AS is related to an increased likelihood of experiencing panic attacks. Patients with PD generally have higher levels of AS than healthy subjects or those with other anxiety disorders (Asmundson and Norton, 1993; Deacon and Abramowitz, 2006). In addition, prior studies have reported that reductions in AS following cognitive-behavioral therapy are associated with improvements in panic symptoms and better treatment responses (Smits et al., 2004). Previously, our group had reported that improvements in AS following Mindfulness-Based Cognitive Therapy (MBCT) may predict treatment response and remission after MBCT in patients with PD (Kim et al., 2013a). Therefore, high AS is considered a major component of the

Abbreviations: AS, anxiety sensitivity; PD, panic disorder; MBCT, Mindfulness-Based Cognitive Therapy; SSRI, selective serotonin re-uptake inhibitor; HC, healthy control; WM, white matter; SD, standard deviation; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; MR, magnetic resonance; ASI-R, Anxiety Sensitivity Inventory-Revised; PDSS, Panic Disorder Severity Scale; 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; TBSS, Tract-Based Spatial Statistics; TFCE, threshold-free cluster enhancement; ICV, intracranial volume; fMRI, functional magnetic resonance imaging

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development and maintenance of PD.

In accordance with this cognitive model of PD, recent studies have suggested that cognitive vulnerability is mediated through a neural circuit in which the insula plays a central role and may be a risk factor for PD (Gasquoine, 2014; Kircher et al., 2013; Klucken et al., 2015; Wittmann et al., 2014). Individuals with high AS perceive exaggerated interoceptive prediction signals, which may be caused by altered information processing in the above brain circuit (Critchley et al., 2004; Paulus and Stein, 2006). Prior studies have shown that neural circuits related to the modulation of interoceptive processing in the brain involve major afferent and efferent connections between the insula and other cortical or subcortical structures, such as the thalamus, amygdala, entorhinal cortex, temporo-parietal cortex, orbitofrontal cortex, and anterior cingulate cortex (Paulus and Stein, 2006). These regions have been proposed to serve essential roles in sensorimotor integration, object-/spatial-specific associations, memory formation, and the detection, valuation, and monitoring of internal body sensations, which are fundamentally related to stimulus processing in the brain (Owen et al., 2013; Paulus and Stein, 2006; Tyll et al., 2011). In particular, there is evidence that the reciprocal connections between the insular cortex and the limbic regions may be involved in altered homeostatic physiological sensations and sympathetic hyperarousal, which may then lead to panic attacks (Craig, 2009; Paulus and Stein, 2006).

AS has also been linked to other anxiety disorders and depression. Specifically, strong lifetime and current comorbidity was found between PD and depression, whose severity is thought to be related to the symptom severity of the PD (Ch-ro et al., 1995; Roy-Byrne et al., 2000). Depressed individuals tend to have higher levels of AS than healthy subjects in psychological factors concerning a fear of cognitive dyscontrol when they are anxious (Cox et al., 2001). In addition, among depressive symptoms, AS was most strongly related to dysfunctional attitudes. In fact, the severity of somatic symptoms and AS scores decline after treatment with selective serotonin re-uptake inhibitor (SSRI) medication to levels seen in healthy control (HC)(Ch-ro et al., 1995). Taken together, the above results indicate that some neural substrates of AS may be common to both PD and depression.

One of the most well-known neuroanatomical hypotheses for PD is the ‘fear network’ model. Panic attack and related responses are mediated by the fear network in the brain, which is centered in the amygdala and linked to its interactions with limbic or paralimbic structures, including the hippocampus and the insula (Gorman et al., 2000). This same fear matrix is also implicated in the interoceptive processing of the brain (Garfinkel and Critchley, 2014). Because the feeling of fear is associated with a substantial physiological or interoceptive component, the neural circuit of interoceptive processing partially overlaps with these fear network structures (Kleint et al., 2015; Pfleiderer et al., 2014).

This study examined the hypothesis that the structural neural correlates of AS in patients with PD are associated with the neural circuits involved in the modulation of interoceptive processing related to the fear network in PD. To test this hypothesis, we investigated the white matter (WM) correlates of AS in patients with PD. In addition, we examined the relationship between structural WM alterations and the clinical severity of the panic and depressive symptoms in patients with PD.

2. Materials and methods

2.1. Subjects and clinical assessments

Subjects were recruited from patients with PD who were treated in the Department of Psychiatry of CHA Bundang Medical Center between January 2011 and June 2015. The study sample consisted of 112 patients with PD(69 women and 43 men; age, 37.27 ± 11.66 [mean ± SD] years) recruited at the Department of Psychiatry of CHA Bundang Medical Center and 48 age- and sex-matched HC subjects (26 women and 22 men; age, 36.31 ± 10.38 [mean ± SD] years) recruited through advertisements. All subjects were between 18 and 60 years old, 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. 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, a majority of the patients began treatment with a minimal dosage of SSRIs including escitalopram or paroxetine (n=59; escitalopram equivalence dosage, 7.54 ± 3.39 [mean ± SD] mg/day), and benzodiazepines including alprazolam or clonazepam as anxiolytics (n=71; alprazolam equivalence dosage, 0.81 ± 0.60 [mean ± SD] mg/day). Brain MR scans of all patients were obtained within 10 days (4.12 ± 4.64 [mean ± SD] days) of the initiation of medication use.

All subjects’ 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) and includes 36 items. Each item has a scale ranging from “very little” (0) to “very much” (4) 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 severities of the patients’ anxiety and depressive symptoms, we also administered the Panic Disorder Severity Scale (PDSS) (Shear and Maser, 1994), 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 clinician-administered PDSS is a questionnaire developed to measure the severity of PD. The APPQ was developed to assess 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 as the summed score of all items. We use the Korean version of the APPQ, which shows good internal consistency (Cronbach’s alpha=0.95) and high test-retest reliability (r=0.77)(Kim et al., 2004). There are three subscales, which are interoceptive avoidance, agoraphobia, and social phobia (Brown et al., 2005). The APPQ interoceptive avoidance subscale scores were used to evaluate each subject's level of interoceptive fear, which is a reflection of the state of the neural circuit involved in interoceptive processing in the brain.

All study procedures complied with CHA Bundang Medical Center's Institutional Review Board regulations, 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. MRI procedures

Diffusion data were acquired on a 3 T GE SignaHDxt 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 1.67×1.67×1.7 mm^3. A double-echo