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The relationship between self-referential processing-related brain activity and anhedonia in patients with schizophrenia

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ABSTRACT

Despite the possible relationship between impaired self-referential processing and anhedonia, it has not yet been investigated. This study investigated an abnormality in brain activation associated with self-referential processing and its relationship with anhedonia in schizophrenia, specifically in self-related brain regions of interest. Twenty patients with schizophrenia and 25 controls underwent functional magnetic resonance imaging while rating the degree of relevance between faces (self, familiar other, or unfamiliar other) and words (positive, negative, or neutral). Brain activation in self-related regions, including the ventral and dorsal medial prefrontal cortices, anterior cingulate cortex (ACC), posterior cingulate cortex, precuneus, and insula, were compared between groups and their correlations with anhedonia level were calculated. Compared to controls, patients were less likely to rate negative words as irrelevant for the self face. Patients showed significantly increased activation in the ACC and precuneus compared to controls, irrespective of conditions. ACC activity in the self-neutral word condition was positively correlated with anhedonia score in patients. These results suggest that patients with schizophrenia may have an abnormality in the self-related cortical midline structures and particularly, abnormal ACC activation may be involved in anhedonia. Disrupted self-referential processing may be a possible cause of anhedonia in schizophrenia.

1. Introduction

Anhedonia, a diminished or lack of ability to experience pleasure in normally pleasurable situations, is one of the cardinal features of schizophrenia (Blanchard et al., 1998). As a component of negative symptoms, anhedonia is a significant determinant of long-term functional outcome in schizophrenia (Milev et al., 2005). Negative symptoms of schizophrenia have been suggested to be closely related to impairments in the reward system, including the ventral striatum, anterior cingulate cortex (ACC), and orbitofrontal cortex (Haber and Knutson, 2010). A recent fMRI study showed that reduced activation in the ventromedial prefrontal cortex (VMPFC) was related to increased severity of anhedonia in patients with schizophrenia (Dowd and Barch, 2012). Our research group reported that resting state metabolic activity in the dorsomedial prefrontal cortex (DMPFC) was reduced in patients with schizophrenia and was correlated with other anhedonia-related brain regions, such as the VMPFC and precuneus (Park et al., 2009). We also demonstrated that gray matter volumes of the precuneus and posterior cingulate cortex (PCC) were negatively correlated with severity of anhedonia in patients with schizophrenia (Lee et al., 2011).

Self-referential processing refers to the evaluation process used to determine whether certain environmental cues apply to one's self, and it concerns stimuli that are experienced as strongly related to one's self (van der Meer et al., 2010). To address self-referential processing, neuroimaging studies usually employ a behavioral paradigm in which subjects are presented with trait adjectives or sentences and are asked whether the trait or sentence applies to them. Brain imaging studies using this paradigm have consistently reported that the cortical midline structures,

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including the VMPFC, DMPFC, ACC, PCC, and precuneus, are involved in self-referential processing (Northoff et al., 2006). These regions are also part of the default mode network (DMN) that is preferentially active when individuals do not focus on the external environment (Buckner et al., 2008). In addition, the insula has been found to be activated during self-referential processing (Northoff et al., 2011). Although all of these regions play an important role in self-referential processing, each brain region may be involved in a distinct process depending on the information domain (Araujo et al., 2015). The VMPFC and DMPFC have been reported to be specifically associated with self- processing as a core region (van der Meer et al., 2010; Kim et al., 2016) and differently involved in a mentalizing process for self- and other judgments (Denny et al., 2012). The ACC and insula together constitute the salience network, which is an intrinsic large-scale network responsible for detecting and orienting to both external and internal salient stimuli and events (Seeley et al., 2007); thus, these two regions are important for directing attention to the self (van der Meer et al., 2010). The PCC/precuneus is responsible for the integration of autobiographical information regarding the self (Kircher et al., 2000; van der Meer et al., 2010).

The similarity between the neural correlates of anhedonia and self-referential processing, i.e., involvement of the cortical midline structures, suggests a possible relationship between these two phenomena. In the tradition of phenomenological psychiatry, schizophrenia is fundamentally a self-disorder that is characterized by complementary distortions of hyper-reflexivity and diminished self-affection (Sass, 2014), which refers to an exaggerated self-consciousness and a weakened vitality of subjective self-presence, respectively. Several studies have demonstrated deficient self-referential processing in schizophrenia (Brebion et al., 2000; Lindner et al., 2005). Recently, it has been reported that self-disturbance is more prominent in negative symptom-predominant schizophrenia patients than in paranoid-type schizophrenia patients (Maeda et al., 2013). Furthermore, anhedonia in schizophrenia has been suggested to be a facet of fundamental and pervasive abnormality of self (Juckel et al., 2003; Raballo et al., 2011). Given that pleasure seems to require a normal sense of self, a disrupted sense of self-presence can be accompanied by a loss of vital contact with the external world, eventually leading to anhedonia (Juckel et al., 2003). Despite the possible relationship between anhedonia and self-referential processing, however, no study has yet been conducted to search for evidence of this relationship in patients with schizophrenia.

The current study was designed to investigate the neural basis of the relationship between anhedonia and self-referential processing in schizophrenia using functional magnetic resonance imaging (fMRI). We hypothesized that patients with schizophrenia would exhibit abnormal activation in regions related to self-referential processing, and that the degree of abnormal activation would be correlated with the severity of anhedonia. To test these hypotheses, we calculated the percent signal change in the predefined regions of interest (ROIs), including the VMPFC, DMPFC, ACC, PCC, precuneus, and insula, and we examined the correlations between the percent signal change in the ROIs and anhedonia score.

2. Methods

2.1. Participants

The participants consisted of 20 patients with schizophrenia (14 males, 6 females, 43.9 ± 6.2 years of age) who were recruited from psychiatric outpatient clinics and 25 healthy controls (16 males, 9 females, 41.5 ± 4.6 years of age) who were recruited through advertisement at a local hospital and via the Internet. The exclusive diagnosis of schizophrenia in patients and the exclusion of any psychiatric disorder in controls were assured by a skilled psychiatrist using the Structural Clinical Interview for DSM-IV (First et al., 1996). Exclusion criteria were the presence of a neurological or significant medical illness and current or past substance abuse or dependence. Additionally, all participants were right-handed, as assessed by the Annett Handedness Inventory (Anett, 1970). The study was approved by the Yonsei University Severance Hospital Institutional Review Board. Written informed consent was obtained from all participants before the study began.

Table 1
Demographic and clinical data.

	Patients (n=20)	Controls (n=25)	χ^2/t^a	p-value
Gender (M/F)	14/6	16/9	0.18	0.67
Age (years)	43.9 ± 6.2	41.5 ± 4.6	1.49	0.14
Education (years)	13.0 ± 1.5	15.9 ± 1.7	−5.87	< 0.001
Raven's Progressive Matrices	39.4 ± 11.5	54.0 ± 4.8	−5.38	< 0.001
Physical Anhedonia Scale	19.8 ± 9.4	10.4 ± 6.5	3.80	0.001
Social Anhedonia Scale	15.0 ± 7.7	9.1 ± 4.7	3.00	0.005

[a] Pearson's chi-square test or two-sample t-test.

As shown in Table 1, there was no statistically significant difference in gender or age between the patient and control groups. Level of education and intellectual function, assessed using Raven's Progressive Matrices (Raven et al., 1988), were significantly lower in patients than in controls ($t = -5.87$, $df = 43$, $p < 0.001$; $t = -5.38$, $df = 24.50$, $p < 0.001$, respectively). Level of anhedonia, assessed by the Physical Anhedonia Scale (PAS) and the Social Anhedonia Scale (SAS) (Chapman et al., 1976), was significantly higher in patients than in controls ($t = 3.80$, $df = 32.62$, $p = 0.001$; $t = 3.00$, $df = 30.10$, $p = 0.005$, respectively). Patients' mean duration of illness was 14.0 ± 7.3 years, and the level of clinical symptoms rated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was 12.4 ± 3.7 for positive, 16.7 ± 6.4 for negative, and 29.5 ± 5.2 for general. All patients were taking one or two combinations of antipsychotic regimens, and the mean chlorpromazine-equivalent dose was 542.1 ± 312.1 mg.

2.2. Experimental task

Patients underwent fMRI scanning while performing the face–word relevance rating task, in which visual stimuli consisting of a face in the upper position and a word in the lower position were serially presented. A face stimulus was one of three types (self, familiar other, and unfamiliar other) with neutral expression. The self face was photographed under uniform lighting conditions prior to scanning, using a Samsung VLUU WB650 digital camera. The familiar other face was a picture of a famous Korean athlete. The unfamiliar other face was a male or female picture selected from Korean Facial Expressions of Emotion (Park et al., 2011). The background of all photographs was converted into light gray. The word stimulus was a Korean abstract noun referring to an idea, concept, or emotion with positive (e.g., victory), negative (e.g., crime), or neutral (e.g., analysis) valence. The words were matched to one another for frequency and number of letters (Han and Kang, 2000).

Thirty words per valence were presented in each type of facial stimuli; thus, a total of 270 trials were arranged in an event-related design and were divided into two sessions. The order of presentation was randomized and counterbalanced across participants. Each stimulus was presented for 2.5 s. The null events of crosshair fixation varied from 625 ms to 5625 ms. The total task time was 15 min. Participants were asked to press a button that