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Neural correlate of impulsivity in subjects at ultra-high risk for psychosis

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ABSTRACT

Objective: Impulsivity is one of the most commonly reported behavioral characteristics of patients with schizophrenia. Although there is accumulating evidence regarding behavioral problems in individuals at ultra-high risk (UHR) for psychosis, as yet, no study has reported on impulsivity in this population. The aim of the present study was to assess impulsivity in UHR subjects and to investigate the associated gray matter correlates.
Method: This study included 32 UHR subjects and 32 age- and gender-matched healthy controls (HCs). The Barratt Impulsiveness Scale version-11 (BIS-11) was employed to assess impulsivity. Differences between the groups in gray matter volume in the anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), and orbitofrontal cortex (OFC) were assessed. Then, a correlational analysis between the BIS-11 scores and significant clusters of gray matter volume was conducted in UHR subjects.
Results: UHR subjects were more impulsive than HC subjects in terms of attention ($t = 3.5187$, $p < 0.01$), motor ($t = 3.1751$, $p < 0.01$), and non-planning ($t = 4.4154$, $p < 0.01$) scores. The gray matter volume of the ACC was negatively correlated with the motor ($r = -0.472$, $p < 0.01$) and non-planning ($r = -0.354$, $p = 0.04$) scores of the BIS-11 in UHR subjects.
Conclusion: These results suggest that impulsivity in UHR subjects may reflect altered integrated conflict processing, which likely stems from abnormalities in the ACC, rather than altered reward/punishment processing or executive control.

1. Introduction

Impulsivity is one of the most commonly reported behavioral characteristics of patients with schizophrenia (Gut-Fayand et al., 2001; Hoptman et al., 2002; Ouzir, 2013). Because impulsivity is associated with serious behavioral problems including substance abuse, violence, and suicide attempts, early intervention before psychosis develops is critical for relieving these adverse manifestations and improving patient prognosis (Kooyman et al., 2007). The term "ultra-high risk for psychosis" (UHR) refers to those who have sub-threshold psychotic symptoms that can be regarded as a risk factor for developing schizophrenia, and accordingly, this population has become the focus of early intervention strategies (Yung and McGorry, 1996). Previous research has found a high prevalence of substance use, risk factors for violence, and suicide risk in UHR subjects (Dragt et al., 2010; Hutton et al., 2011) as well as impaired ability to control emotional expression and aggression (Lee et al., 2008). Although there is accumulating evidence regarding behavioral problems in UHR individuals, as yet, no study has specifically investigated impulsivity in these subjects.

Higher impulsivity is seen in patients with attention-deficit hyperactivity disorder (ADHD), borderline personality disorder (BPD), and substance dependence as well as those with schizophrenia. Previous studies have indicated that specific brain regions, including the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), mediate impulsivity in schizophrenia (Narayan et al., 2007; Schiffer et al., 2010). The ACC, OFC, and dorsolateral prefrontal cortex (DLPFC) are also affected in individuals with ADHD, BPD, and substance dependence,

Abbreviations: UHR, subjects at ultra-high risk for psychosis; ADHD, attention-deficit hyperactivity disorder; BPD, borderline personality disorder; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; OFC, orbitofrontal cortex; HC, healthy controls; SCID-I, Structured Clinical Interview for DSM-IV Axis I; SIPS, Structured Interview of Prodromal Symptoms; APS, attenuated positive symptoms state; BIPS, brief intermittent psychotic symptoms state; GRD, genetic risk with deterioration state; SCID-NP, Structured Clinical Interview for DSM-IV Axis I Non-Patient version; BIS-11, Barratt impulsiveness scale, version-11; K-WAIS, Korean version of the Wechsler Adult Intelligence Scale; VBM, voxel-based morphometry; ROI, regions of interest.

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and these defects are correlated with impulsivity (Berlin et al., 2005; Matsuo et al., 2009; Passarotti et al., 2010). All of these brain regions are related with impulsivity, but the main functions of each region, such as executive control, regulation of internal conflict, and decision making, slightly differ. Moreover, the main regional abnormalities in each disorder are different and may be correlated with the behavioral characteristics (Hazlett et al., 2005, Schoenbaum et al., 2006, Seidman et al., 2005). Several studies have found that UHR subjects also have reduced gray matter volume in the ACC, DLPFC, and OFC (Fusar-Poli et al., 2011; Koutsouleris et al., 2012; Witthaus et al., 2009). Given that these regions may mediate impulsivity these findings suggest that UHR subjects may be more impulsive, similar to patients with schizophrenia. However, it is not clear whether the impulsivity in UHR subjects is related to defects in brain regions similar to those in patients with schizophrenia or other related disorders.

In this study, we used the Barratt Impulsiveness Scale version-11 (BIS-11) to estimate impulsivity and a voxel-based morphometry (VBM) analysis to measure gray matter volume associated with impulsivity. We hypothesized that UHR subjects would be more impulsive than healthy controls (HCs). Moreover, we expected that impulsivity would be correlated with a reduction in gray matter volume in UHR subjects. To our knowledge, no previous study has focused on impulsivity in UHR subjects. Therefore, improving knowledge concerning the neural underpinnings of impulsivity in UHR subjects will be crucial for understanding the pathophysiology and the characteristics of the disorder.

2. Methods

2.1. Subjects and clinical assessments

This study recruited 32 UHR subjects from the Seoul Youth Clinic in Seoul, South Korea. All UHR subjects participated in an intensive clinical interview administered by experienced psychiatrists, who used the Structured Clinical Interview for DSM-IV Axis I (SCID-I) disorders to identify past and current psychiatric illnesses. These subjects were also assessed using the Structured Interview of Prodromal Symptoms (SIPS; Miller et al., 2003). All subjects had to fulfill at least one of the three established criteria for prodromal psychosis state: present attenuated positive symptoms state (APS); have a brief intermittent psychotic symptoms state below the threshold required for a DSM-IV axis I psychotic disorder diagnosis (BIPS); and/or show a 30% decline in global functioning over the past year, as well as having a diagnosis of schizotypal personality disorder or a first-degree relative with psychosis (genetic risk with deterioration state; GRD). The Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) was administered to all subjects to provide an estimated IQ. The exclusion criteria for all subjects included the following: lifetime diagnosis of a psychotic disorder; substance use disorder; neurological disease or significant head injury; evidence of a medical illness that could manifest as psychiatric symptoms; and intellectual disability. Additionally, 32 age- and gender-matched healthy controls (HCs) were recruited through internet advertisement. Exclusion criteria for HCs were: (1) past or current SCID-I Non-patient Edition (SCID-NP) axis I diagnoses and (2) any first- to third-degree biological relative with a psychiatric disorder. Informed consent forms were obtained from all subjects; the present study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the Seoul National University Hospital.

2.2. Behavioral measures

The BIS-11 (Patton et al., 1995) was employed to estimate impulsivity. The BIS-11 is the most widely used self-report measure of impulsive personality traits and has three higher-order factors: attention impulsiveness, which measures the tendency to not focus on the task at hand; motor impulsiveness, which measures the tendency to act on the spur of the moment; and non-planning impulsiveness, which measures the tendency to not engage in careful thinking or planning.

2.3. Image acquisition

All structural magnetic resonance imaging (MRI) scans were acquired in the sagittal plane using a 3-T scanner (MAGNETOM Trio Tim Syngo MR B17; Siemens, Erlangen, Germany) and T_1-weighted 3-D magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence. Parameters were as follows: TR/TE = 1670/1.89 ms, voxel size = $0.98 \times 0.98 \times 1$ mm^3, FOV = 250 mm, flip angle = 9°, 208 slices, and matrices = 256×256.

2.4. Image processing

The VBM analysis was performed with the FSL software package (www.fmrib.ox.ac.uk/fsl/), v. 5.0. First, structural images were brain-extracted using the Brain Extraction Tool (BET), and then tissue-type segmentation was performed using FMRIB's automated segmentation tool (FAST). Next, the gray matter partial volume images were aligned with the Montreal Neurological Institute's 152 reference spaces using FMRIB's linear image registration tool (FLIRT). The resulting images of all participants were averaged to create a study-specific template to which the native gray matter images were then nonlinearly registered using the FSL nonlinear registration tool (FNIRT). The registered partial volume images were modulated by methods of division using the Jacobian warp field to correct for local contraction or enlargement. All the modulated segmented images were smoothed with a Gaussian kernel with a sigma of 3 mm.

2.5. Regions of interest definition

Regions of interest (ROIs) were defined by considering previous impulsivity studies (Lee et al., 2008; Schiffer et al., 2010). Gray matter ROIs were defined in the ACC, DLPFC, and OFC. The ROI regions were defined by the Harvard–Oxford cortical structural atlas.

2.6. Statistical analysis

First, differences in demographics and clinical variables between the groups were analyzed using independent *t*-tests and Fisher's exact test. Second, differences in gray matter volume in the ACC, DLPFC, and OFC between the groups were assessed by a voxel-wise general linear model applied using permutation-based non-parametric testing with 5000 permutations. A voxel-wise statistical analysis was performed with a threshold-free cluster enhancement (TFCE) correction for multiple comparisons. The significance level with corrected family-wise error (FWE) was set at $p < 0.05$. Third, significant clusters were defined as ROIs. Then, a correlational analysis between the BIS-11 scores and the gray matter volume in the significant clusters was performed. Statistical significance was defined as $p < 0.05$, and statistical analyses were performed using Stata, v. 12.0 (StataCorp; College Station, TX, US).

3. Results

3.1. Demographic and psychological data

The demographic and clinical characteristics of UHR and HC subjects were collected (Table 1). Of the UHR subjects, 32 met the criteria for APS, five subjects met the criteria for GRD, and five subjects met the criteria for both APS and GRD. None of the UHR subjects was taking antipsychotics. Among those who were taking psychotropics, four were taking antidepressants at baseline assessment: 75 mg venlafaxine ($n = 1$), 10 mg lexapro ($n = 1$), 80 mg prozac ($n = 1$), and 25 mg clomipramine ($n = 1$). There were no significant differences in age, gender,