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Cognitive clustering in schizophrenia patients, their first-degree relatives and healthy subjects is associated with anterior cingulate cortex volume

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ABSTRACT

Cognitive impairments are a core feature in schizophrenia patients (SCZ) and are also observed in first-degree relatives (FR) of SCZ. However, substantial variability in the impairments exists within and among SCZ, FR and healthy controls (HC). A cluster-analytic approach can group individuals based on profiles of traits and create more homogeneous groupings than predefined categories. Here, we investigated differences in the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery (six subscales) among SCZ, unaffected FR and HC. To identify three homogeneous and meaningful cognitive groups regardless of categorical diagnoses (SCZ, FR and HC), cognitive clustering was performed, and differences in the BACS subscales among the cognitive cluster groups were investigated. Finally, the effects of diagnosis and cognition on brain volumes were examined. As expected, there were significant differences in the five BACS subscales among the diagnostic groups. The cluster-analytic approach generated three meaningful subgroups: (i) neuropsychologically normal, (ii) intermediate impaired and (iii) widespread impaired. The cognitive subgroups were mainly affected by the clinical diagnosis, and significant differences in all BACS subscales among clusters were found. The effects of the diagnosis and cognitive clusters on brain volumes overlapped in the frontal, temporal and limbic regions. Frontal and temporal volumes were mainly affected by the diagnosis, whereas the anterior cingulate cortex (ACC) volumes were affected by the additive effects of diagnosis and cognition. Our findings demonstrate a cognitive continuum among SCZ, FR and HC and support the concept of cognitive impairment and the related ACC volumes as intermediate phenotypes in SCZ.

1. Introduction

Schizophrenia is a common and complex psychiatric disorder with a lifetime morbidity rate of 0.5–1.0% and is characterized by clinical and genetic heterogeneity. Family, twin, and adoption studies of schizophrenia patients (SCZ) have indicated that the risk of occurrence is increased approximately 10-fold in first-degree relatives (FR) of SCZ (Cardno and Gottesman, 2000; Tsuang, 2000) and that there is a strong genetic component, with an estimated heritability of approximately 80% (Sullivan et al., 2003). Although the risk for developing schizophrenia is commonly accepted to be mediated by many genes or genetic variants, previous genome-wide association studies (GWASs) on schizophrenia only explain a small aspect, approximately up to 20%, of the genetic architecture of the disorder (O'Donovan et al., 2008; Ripke et al., 2011; Stefansson et al., 2009). To resolve this difference and to minimize clinical and genetic heterogeneity, intermediate phenotypes, such as those based on cognitive functions, rather than the diagnosis of schizophrenia have been emphasized (Ohi et al., 2015; Rasetti and Weinberger, 2011).

Cognitive impairments are a core feature and reasonable treatment target for SCZ (Mohamed et al., 1999; Saykin et al., 1994), and they contribute to social dysfunction and life outcomes (Green, 1996; Green et al., 2000; Kahn and Keefe, 2013). Substantial evidence suggests that most cognitive functions have a genetic basis and are heritable (h^2 = 0.33–0.85) (Berrettini, 2005; Chen et al., 1998; Husted et al., 2009; Posthuma et al., 2001). The latest and largest GWAS on cognitive function has also explained approximately 20% of the genetic architecture of cognitive impairments (Trampush et al., 2017). A substantial portion of the phenotypic correlation between schizophrenia and cognitive function is caused by identical genetic effects (Toulopoulou et al., 2010; Trampush et al., 2017). Polygenic cognitive scores have been associated with a risk of schizophrenia, whereas polygenic

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schizophrenia risk scores have been associated with lower cognitive ability (Lencz et al., 2014). The cognitive domains that show differential impairments in SCZ include attention/vigilance, executive function, long-term and learning memory, working memory and verbal fluency (Green, 1996; Green et al., 2000; Hill et al., 2013; Rund and Borg, 1999). These impairments are present at illness onset, stable and minimally affected by antipsychotic medications and cognitive remediation interventions (Bilder et al., 2000; Hill et al., 2004; Hodge et al., 2010; Hoff et al., 1999; Revell et al., 2015; Wexler and Bell, 2005; Wykes et al., 2007). In addition, these impairments are typically stronger in SCZ and have also been observed in unaffected FR or unaffected twin siblings of SCZ (Green, 2006; Hill et al., 2013; Toulopoulou et al., 2010). The cognitive impairments in unaffected FR are very similar to those in SCZ but somewhat less pronounced, indicating that cognitive impairments are in a genetic continuum among SCZ, FR and healthy controls (HC). These findings suggest that the cognitive impairments are thought to be trait dependent and may be useful intermediate phenotypes to understand the genetic mechanisms implicated in the pathophysiology of schizophrenia. Therefore, the assessment of cognitive function is an important step to evaluate SCZ. The Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery was developed to be easily and quickly administered (in approximately 30 min) by a variety of testers, including nurses, clinicians, psychiatrists, neurologists, social workers, and other mental health personnel, is fully portable (Keefe et al., 2004; Keefe et al., 2008), and is sensitive to the profile of generalized impairments observed in SCZ. The cognitive domains assessed by the BACS include verbal memory, working memory, motor speed, verbal fluency, attention, and executive function. However, few studies have examined the degree of cognitive impairment across the BACS neuropsychological battery among SCZ, FR and HC (Hill et al., 2013).

Although cognitive dysfunction is a core feature of SCZ, substantial variability may exist within and among diagnostic groups (SCZ, FR and HC). A cluster-analytic approach can group individuals based on patterns or profiles of traits and create more homogeneous groupings than predefined categories (Lewandowski et al., 2014), providing an opportunity to classify individuals using a data-driven approach rather than pre-determined grouping criteria (*e.g.*, SCZ, FR and HC). Cluster-analytic studies of cognition within SCZ have successfully generated meaningful subtypes with at least three clusters: those that are neuropsychologically normal and those with intermediate cognitive deficits and widespread deficits (Allen et al., 2003; Goldstein et al., 1998; Heinrichs and Awad, 1993; Hill et al., 2002; Lewandowski et al., 2014; Seaton et al., 1999; Seaton et al., 2001). To date, no study has examined cognitive variability, *i.e.*, heterogeneity, among SCZ, FR and HC using the cluster-analytic approach based on the BACS subscales without using clinical diagnosis (SCZ, FR and HC). Given the evidence that cognitive functions are in a genetic continuum among SCZ, FR and HC and that impairments are intermediate phenotypes for SCZ, we hypothesized that the cluster-analytic approach would generate three meaningful subgroups derived from three clinical diagnoses (SCZ, FR and HC). Furthermore, we hypothesized that the cognitive clusters would be related to brain volume reductions, such as those in frontal, temporal and limbic areas, observed in SCZ (Glahn et al., 2008).

In this study, we first investigated differences in the BACS subscales among SCZ, FR and HC. Next, cognitive clustering was performed to identify three meaningful cognitive groups regardless of diagnosis. Then, we investigated differences in the BACS subscales among the cognitive cluster groups. Finally, the effects of the diagnosis and cognition on brain volumes were examined.

2. Methods

2.1. Subjects

Subjects consisted of 81 SCZ (36 males/45 females, mean age ± SD: 37.6 ± 10.4 years), 20 of their unaffected FR (11 parents/8 siblings/1 offspring, 3 males/17 females, 52.4 ± 13.0 years) and 25 HC (14 males/11 females, 36.2 ± 11.8 years). All subjects were of Japanese descent. Patients and their unaffected FR were recruited from both the outpatient and inpatient populations at Kanazawa Medical University Hospital. Each of the SCZ was diagnosed by at least two trained psychiatrists on the basis of unstructured clinical interviews, medical records and clinical conferences (Ohi et al., 2016; Ohi et al., 2017; Yasuyama et al., 2016). The patients were diagnosed according to the criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Their unaffected FR were evaluated using the non-patient version of the Structured Clinical Interview for DSM-IV (SCID) to exclude individuals who had current or past contact with psychiatric services or had received psychiatric medication. HC were recruited through local advertisements and from among hospital staff at Kanazawa Medical University and were also evaluated using the non-patient version of the SCID to exclude individuals who had current or past contact with psychiatric services, had received psychiatric medication or had family history of any neuropsychiatric diseases within the second-degree relatives. Subjects were excluded from the analysis if they had neurological or medical conditions that could affect the central nervous system, including atypical headache, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, active cancer, cerebrovascular disease, thyroid disease, epilepsy, seizures, substance-related disorders, current steroid use or mental retardation. The demographic information among the three diagnostic groups (SCZ, FR and HC) is summarized in Table 1A. The mean age, gender ratio, years of education and estimated premorbid intelligence quotient (IQ) differed significantly among the groups ($P < 0.05$). Current clinical symptoms in SCZ were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Written informed consent was obtained from all subjects after the procedures were fully explained. This study was performed according to the World Medical Association's Declaration of Helsinki and was approved by the Research Ethical Committee of Kanazawa Medical University.

2.2. Cognitive functions

We administered the Japanese version of the BACS battery (Kaneda et al., 2007) in all subjects. The BACS battery provides a brief (30 min), reliable, and valid test of global neuropsychological function (Keefe et al., 2004; Keefe et al., 2008) and is widely used in schizophrenia research (Hill et al., 2013; Keefe et al., 2007). The BACS battery consists of 6 subtests: (i) Verbal Memory (verbal memory): score range, 0–75, (ii) Digit Sequencing (working memory): score range, 0–28, (iii) Token Motor (motor speed): score range, 0–100, (iv) Verbal Fluency (verbal fluency): score range, 0–Inf, (v) Symbol Coding (attention): score range, 0–110, and (vi) Tower of London (executive function): score range, 0–22. Each cognitive function assessed by the BACS is indicated by parentheses. All tests were scored by a trained psychologist, and some cases were randomly reviewed for scoring accuracy by another psychologist and a psychiatrist. In the BACS analysis, each raw score was corrected for covariates of age and gender by taking the unstandardized residuals of the scores using linear regression in the total group. For each subject, the unstandardized residual was added to the intercept + $\text{beta}_i \times \text{mean}_i$, where $_i$ represents the different covariates. Therefore, we used age- and gender-corrected scores in the BACS analysis.

2.3. Magnetic resonance imaging procedure

Brain magnetic resonance imaging (MRI) scans using a Siemens 3 T Magnetom Trio, a Tim System (Siemens, Erlangen, Germany) were performed in SCZ ($N = 76$), FR ($N = 17$) and HC ($N = 24$) who all participated in the BACS analysis. High-resolution T1-weighted images were acquired with a 3D Magnetization Prepared-RApid Gradient Echo