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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

Table 1
Demographic variables among the diagnostic groups (**A**) and three cognitive cluster groups (**B**).

(A)	HC	FR	SCZ	*P* values (*F* or χ^2)	*Post hoc*
Variables	(*N* = 25)	(*N* = 20)	(*N* = 81)		
Age (years)	36.2 ± 11.8	52.4 ± 13.0	37.6 ± 10.4	**8.82×10^{-7} (15.6)**	HC < FR, FR > SCZ
Gender (male/female)	14/11	3/17	36/45	**0.017 (8.2)**[a]	–
Education (years)	15.8 ± 2.3	13.3 ± 1.9	12.9 ± 2.1	**5.00×10^{-8} (19.3)**	HC > FR, SCZ
Estimated premorbid IQ	107.3 ± 6.8	98.6 ± 9.8	100.7 ± 10.5	**5.07×10^{-3} (5.5)**	HC > FR, SCZ
CPZ-eq (mg/day)	0	0	495.6 ± 425.0	–	–
Age at onset (years)	–	–	26.2 ± 9.1	–	–
Duration of illness (years)	–	–	11.5 ± 10.3	–	–
PANSS Positive symptoms	–	–	15.8 ± 6.1	–	–
PANSS Negative symptoms	–	–	16.7 ± 6.4	–	–
(B)	Cluster 1	Cluster 2	Cluster 3	*P* values (*F* or χ^2)	*Post hoc*
Variables	(*N* = 36)	(*N* = 60)	(*N* = 30)		
Diagnosis (HC/FR/SCZ)	19/8/9	6/11/43	0/1/29	**5.33×10^{-10} (46.7)**[b]	–
Age (years)	39.3 ± 12.0	40.6 ± 13.3	38.2 ± 11.1	0.69 (0.4)	–
Gender (male/female)	16/20	22/38	15/15	0.50 (1.4)[a]	–
Education (years)	14.9 ± 2.6	13.3 ± 2.0	12.4 ± 2.0	**1.44×10^{-5} (12.2)**	1 > 2, 3
Estimated premorbid IQ	107.7 ± 9.6	100.5 ± 9.0	96.6 ± 9.4	**1.63×10^{-5} (12.1)**	1 > 2, 3
CPZ-eq in SCZ (mg/day)	541.7 ± 573.6	358.8 ± 279.7	684.0 ± 488.3	**4.74×10^{-3} (5.7)**	3 > 2
Age at onset (years)	27.4 ± 9.5	27.6 ± 9.9	23.7 ± 7.4	0.19 (1.5)	–
Duration of illness (years)	10.9 ± 8.4	9.4 ± 9.5	14.8 ± 11.4	0.09 (2.4)	–
PANSS Positive symptoms	16.4 ± 6.1	15.1 ± 6.5	16.4 ± 5.5	0.63 (0.5)	–
PANSS Negative symptoms	18.3 ± 8.0	15.2 ± 5.5	18.4 ± 6.8	0.08 (2.6)	–

HC, healthy controls; FR, first-degree relatives of schizophrenia patients; SCZ, schizophrenia patients; IQ, intelligence quotient; and CPZ-eq; chlorpromazine equivalents of total antipsychotics. Means ± SD are shown. Complete demographic information was not obtained for all subjects (estimated premorbid IQ in SCZ, *N* = 77; in Cluster 2, *N* = 58; in Cluster 3, *N* = 28). *P* values < 0.05 are shown in boldface and underlined, and *post hoc* analysis was performed.
[a] χ^2 test.
[b] Fisher's exact test.

(MP-RAGE TR = 1420 ms, inversion time = 800 ms, echo time = 2.08 ms, flip angle = 9°, resolution = 1 × 1 × 1 mm^3, matrix size = 256 × 256), yielding 192 contiguous slices of 1.0-mm thickness in the sagittal plane (Ohi et al., 2016), providing high-resolution T1-weighted images with good contrast between gray matter (GM) and white matter (WM) using this scanner in our scanning environment. Subjects with MRI abnormalities, such as infarcts, hemorrhages, or brain tumors, were screened out prior to inclusion in this study as part of the routine clinical diagnosis and treatment procedures; therefore, there were no gross abnormalities in any of the subjects. Each image was visually examined to eliminate images with motion or metal artifacts, and the anterior commissure-posterior commissure line was adjusted.

The MR images were processed using the voxel-based morphometry (VBM) 8 toolbox in the Statistical Parametric Mapping 8 program (SPM8; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running on MATLAB R2014b (MathWorks, Natick, MA, USA) according to the VBM8-Toolbox Manual (http://dbm.neuro.uni-jena.de/vbm8/VBM8-Manual.pdf) and previous studies (Hashimoto et al., 2014; Ohi et al., 2012a; Ohi et al., 2014). The T1 images were normalized and segmented into GM, WM and cerebrospinal fluid using the VBM8-Toolbox with defaults for the extended options (Ashburner, 2007; Wilke et al., 2008). The voxel values of the normalized GM images were modulated according to the non-linear component of the transformation, which resulted in approximately total brain volume adjusted GM volumes while preserving local volume changes (Good et al., 2001). Lastly, the images were smoothed with an 8-mm full-width, half-maximum isotropic Gaussian kernel.

2.4. Statistical analyses

All statistical analyses, except for VBM analyses, were performed using IBM SPSS Statistics 24.0 software (IBM Japan, Tokyo, Japan). Demographic variables, such as age and age- and gender-corrected subscales of the BACS, were fitted to a normal distribution using the Kolmogorov-Smirnov test ($P > 0.05$), and continuous variables, such as age and the subscales of the BACS, were analyzed using the parametric analysis of variance (ANOVA). The difference in categorical variables, such as gender and ratios of the cluster, were analyzed using Pearson's χ^2 or Fisher's exact tests. To specify more homogeneous cognitive groups regardless of diagnostic status (SCZ, FR and HC), the clustering analysis was performed using a *k*-means clustering approach using the six age- and gender-corrected cognitive subscales of the BACS in all participants without using the diagnostic status. The *k*-means clustering aimed to partition n observations into *k* clusters in which each observation belongs to the cluster with the nearest mean. A three-cluster solution was considered based on our hypothesis. The effects of the diagnostic status or cognitive clusters on the BACS subscales were analyzed using ANOVA with age- and gender-corrected subscales of the BACS as dependent variables and diagnostic status (HC, FR and SCZ) or cognitive clusters (Clusters 1, 2 and 3) as independent variables. *Post hoc* tests with Fisher's Least Significant Difference (LSD) were used to evaluate significant differences among the diagnostic or cluster groups. Standardized effects were calculated using Cohen's *d* method (http://www.uccs.edu/faculty/lbecker). The significance level for the BACS analysis was set at a two-tailed $P < 8.33 \times 10^{-3}$ ($\alpha = 0.05/6$) to control for type I error.

For neuroimaging analyses, we performed whole-brain correlation analyses between GM voxels and the following parameters: diagnosis status (1, HC; 2, FR; 3, SCZ), cognitive clusters (1, Cluster 1; 2, Cluster 2; 3, Cluster 3) and their additive effects (1, Cluster 1 in HC; 2, Cluster 2 in HC; 3, Cluster 3 in HC; 4, Cluster 1 in FR; 5, Cluster 2 in FR; 6, Cluster 3 in FR; 7, Cluster 1 in SCZ; 8, Cluster 2 in SCZ; 9, Cluster 3 in SCZ). For these analyses, we employed a multiple regression model in SPM8. Age and gender were included as covariates in the analyses to control for confounding variables, and a non-sphericity estimation was used. After surveying the effects at a voxel-level threshold of $P_{uncorrected} < 0.001$, we applied a family-wise error (*FWE*) correction at the cluster level for multiple testing to avoid type I errors for the VBM analyses. The significance level for the VBM analyses was set at $FWE\text{-}_{corrected}$ $P < 0.05$.

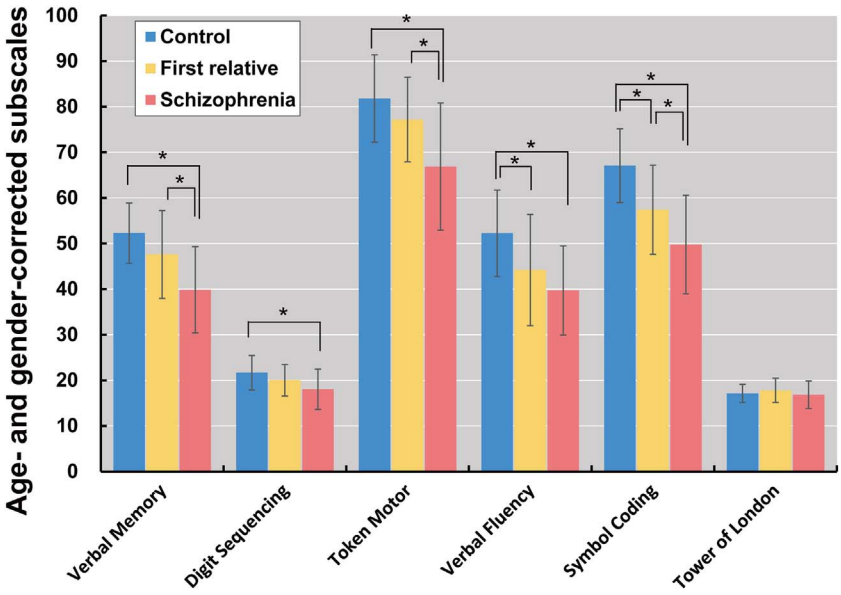

Fig. 1. Differences in the six subscales of the Brief Assessment of Cognition in Schizophrenia (BACS) among schizophrenia patients (SCZ), their unaffected first-degree relatives (FR) and healthy controls (HC). **Post hoc* $P < 0.05$.

3. Results

3.1. Differences in subscales of the BACS among SCZ, FR and HC

We first investigated diagnostic differences in the six subscales of the BACS among SCZ, FR and HC and found significant differences in five subscales of the BACS among the diagnostic groups (Fig. 1, verbal memory, $F_{2,123} = 20.6$, $P = 1.90 \times 10^{-8}$; digit sequencing, $F_{2,123} = 8.0$, $P = 5.65 \times 10^{-4}$; token motor, $F_{2,123} = 16.0$, $P = 6.92 \times 10^{-7}$; verbal fluency, $F_{2,123} = 14.8$, $P = 1.79 \times 10^{-6}$ and symbol coding, $F_{2,123} = 28.8$, $P = 5.64 \times 10^{-11}$) but not in the Tower of London task ($F_{2,123} = 1.0$, $P = 0.38$). *Post hoc* analyses showed that SCZ had impaired cognitive functions compared with those of HC (verbal memory, Cohen's $d = -1.52$, $P = 1.74 \times 10^{-8}$; digit sequencing, $d = -0.89$, $P = 2.00 \times 10^{-4}$; token motor, $d = -1.25$, $P = 8.31 \times 10^{-7}$; verbal fluency, $d = -1.30$, $P = 3.31 \times 10^{-7}$ and symbol coding, $d = -1.82$, $P = 1.47 \times 10^{-11}$). SCZ also had impaired cognitive functions compared with those of FR (verbal memory, $d = -0.81$, $P = 7.81 \times 10^{-4}$; token motor, $d = -0.87$, $P = 1.30 \times 10^{-3}$ and symbol coding, $d = -0.74$, $P = 3.05 \times 10^{-3}$), although there were no significant differences in digit sequencing ($d = -0.50$, $P = 0.06$) or verbal fluency ($d = -0.40$, $P = 0.08$) between SCZ and FR. Of the six subscales of the BACS, FR had significantly lower scores in the symbol coding subscale ($d = -1.07$, $P = 1.97 \times 10^{-3}$) and a marginally lower score in verbal fluency ($d = -0.74$, $P = 9.20 \times 10^{-3}$) than HC. Although the verbal memory ($d = -0.57$, $P = 0.085$), digit sequencing ($d = -0.46$, $P = 0.18$) and token motor scores ($d = -0.28$, $P = 0.22$) were not significantly different between FR and HC, all of the effect sizes were in the same direction. These findings indicate that SCZ had a wide range of impairments in cognitive function compared with those observed in the HC and FR, and FR had intermediately impaired cognitive function between SCZ and HC. Even after including years of education as a covariate in the analysis of covariance (ANCOVA), these findings did not change.

3.2. Cognitive clustering

Using a *k*-means clustering analysis approach with the six cognitive subscales of the BACS, participants were divided into three cognitive function groups (Clusters 1–3) regardless of diagnostic status (SCZ, FR and HC). The demographic information among the three cognitive clusters is summarized in Table 1B. The mean age, gender ratio, age at onset, duration of illness and PANSS scores in SCZ did not differ among the groups ($P > 0.05$); however, years of education, estimated premorbid IQ and chlorpromazine equivalents of total antipsychotics (CPZ-eq) in SCZ differed significantly among the groups ($P < 0.05$). As shown in Fig. 2, the neurocognitive profiles were clustered into a neuropsychologically normal cluster (Cluster 1, $N = 36$), a globally impaired cluster (Cluster 3, $N = 30$) and an intermediately impaired cluster (Cluster 2, $N = 60$). Interestingly, clinical diagnoses (SCZ, FR and HC) were significantly and not evenly distributed into the three cluster groups (Fig. 2 and Table 1B, $\chi^2 = 46.7$, $P = 5.33 \times 10^{-10}$). HC were mainly distributed to Cluster 1 (76.0%), followed by Cluster 2 (24.0%), but not Cluster 3 (0%). FR were mainly distributed to Clusters 1 (40.0%) and 2 (55.0%), while SCZ were mainly distributed to Clusters 2 (53.1%) and 3 (35.8%).

3.3. Differences in the BACS subscales among the cognitive clusters

We next investigated the differences in the six subscales of the BACS among the clusters. We found significant differences in all six subscales of the BACS among the cognitive cluster groups (Fig. 2, verbal memory, $F_{2,123} = 64.1$, $P = 8.49 \times 10^{-20}$; digit sequencing, $F_{2,123} = 35.7$, $P = 5.89 \times 10^{-13}$; token motor, $F_{2,123} = 71.7$, $P = 2.29 \times 10^{-21}$; verbal fluency, $F_{2,123} = 84.2$, $P = 9.05 \times 10^{-24}$; symbol coding, $F_{2,123} = 115.6$, $P = 5.70 \times 10^{-29}$ and Tower of London, $F_{2,123} = 6.9$, $P = 1.43 \times 10^{-3}$). *Post hoc* analyses indicated that Cluster 3 performed significantly worse on all subscales of the BACS than Cluster 1 (verbal memory, $d = -2.78$, $P = 8.78 \times 10^{-21}$; digit sequencing, $d = -2.10$, $P = 1.38 \times 10^{-13}$; token motor, $d = -2.97$, $P = 2.36 \times 10^{-22}$; verbal fluency, $d = -3.12$, $P = 1.29 \times 10^{-24}$; symbol coding, $d = -3.37$, $P = 5.97 \times 10^{-30}$ and Tower of London, $d = -0.85$, $P = 9.86 \times 10^{-4}$). Cluster 3 also performed significantly worse on the subscales than Cluster 2 (verbal memory, $d = -1.49$, $P = 7.45 \times 10^{-11}$; digit sequencing, $d = -0.84$, $P = 1.90 \times 10^{-4}$; token motor, $d = -1.57$, $P = 6.19 \times 10^{-12}$; verbal fluency, $d = -1.66$, $P = 7.86 \times 10^{-10}$; symbol coding, $d = -2.16$, $P = 2.02 \times 10^{-17}$ and Tower of London, $d = -0.67$, $P = 1.36 \times 10^{-3}$). Furthermore, Cluster 2 performed significantly worse on five of the subscales than Cluster 1 (verbal memory, $d = -1.28$, $P = 8.20 \times 10^{-8}$; digit sequencing, $d = -1.22$, $P = 9.27 \times 10^{-8}$; token motor, $d = -1.36$, $P = 2.50 \times 10^{-8}$; verbal fluency, $d = -1.58$, $P = 5.67 \times 10^{-13}$ and symbol coding, $d = -1.58$, $P = 3.88 \times 10^{-11}$) but not on the Tower of London subscale ($d = -0.11$, $P = 0.63$). Even after including duration of illness or

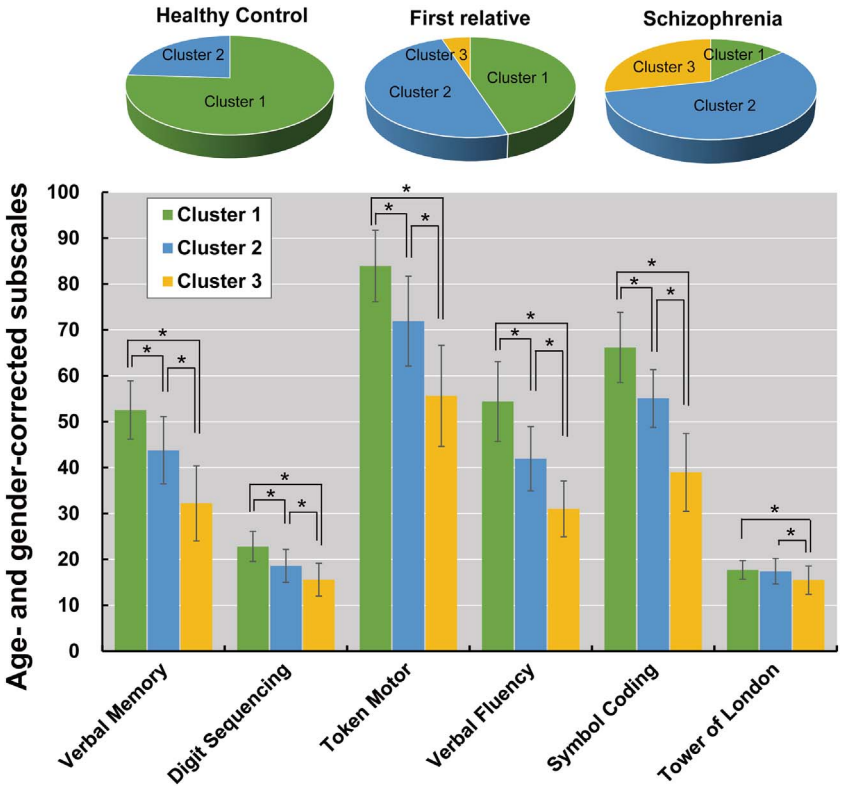

Fig. 2. Differences in the six subscales of the BACS among three cognitive cluster groups based on a *k*-means cluster analysis. Each pie is proportional to the frequencies of clusters in each diagnostic group. **Post hoc* $P < 0.05$.

antipsychotic medication as a covariate in the subgroup ANCOVA in SCZ, these differences in the BACS subscales among the clusters did not change. These findings suggest that cognitive clustering was successfully performed using the *k*-means approach.

3.4. Effects of the diagnosis and cognition on brain structure

We performed whole-brain analyses to examine the effects of the diagnosis and the cognitive clusters on brain volumes in SCZ, FR and HC. The schizophrenia diagnosis was nominally correlated with a wide range of decreased local GM volumes in frontal, temporal, and limbic areas (SCZ < FR < HC) ($P_{uncorrected} < 0.001$, blue areas in Fig. 3 and Supplementary Table 1), whereas it was not significantly correlated with any increased GM volumes (HC < FR < SCZ) ($P_{uncorrected} > 0.001$, Supplementary Table 1). By contrast, cognitive Cluster 3, with the worst cognitive performance, was also nominally correlated with decreased local GM volumes in frontal, temporal, and limbic areas (Clusters 3 < 2 < 1) ($P_{uncorrected} < 0.001$, red areas in Fig. 3 and Supplementary Table 2), whereas cognitive Cluster 1, with better cognitive performance, was not significantly correlated with any decreased GM volumes (Clusters 1 < 2 < 3) ($P_{uncorrected} > 0.001$, Supplementary Table 2). Of these nominally significant regions at the whole-brain level ($P_{uncorrected} < 0.001$), the effects of the diagnosis on the insula, anterior cingulate cortex (ACC; Fig. 4A, $x, y, z = 1.5, 40.5, 19.5$, $T = 5.19$), thalamus and frontal areas and the effects of cognition on the ACC (Fig. 4B, $T = 4.35$), insula, hippocampus, amygdala, superior temporal gyrus and frontal areas were still significant after applying the *FWE* correction ($FWE\text{-}_{corrected}$ $P < 0.05$, Supplementary Tables 1 and 2). Notably, the effects of the diagnosis and the cognitive clusters on the insula, ACC and frontal regions overlapped (Fig. 3). There was no interaction between the diagnosis and cognition on the brain volumes ($FWE\text{-}_{corrected}$ $P > 0.05$). When the cognitive clusters were included in the VBM analysis as covariates, the effect of the diagnosis on all brain volumes was diminished ($P_{uncorrected} < 0.001$, blue areas in Supplementary Fig. 1), although the effect of the diagnosis on the insula and frontal regions was still significant ($FWE\text{-}_{corrected}$ $P < 0.05$). Most importantly, the effect of the diagnosis on ACC volumes disappeared (Fig. 4C). By contrast, the effects of the cognitive clusters on all brain volumes disappeared after including diagnoses as covariates ($FWE\text{-}_{corrected}$ $P > 0.05$, red areas in Supplementary Fig. 1), suggesting that the effects of the diagnosis and the cognitive clusters on the volume of the overlapping brain regions were derived from the main effect of diagnostic status, except for the effects on the ACC volume. Indeed, the additive effects of both diagnosis and cognition were highlighted on the ACC volume ($FWE\text{-}_{corrected}$ $P < 0.05$, $T = 5.49$, Fig. 4D, Supplementary Figs. 2 and 3 and Supplementary Table 3).

4. Discussion

To the best of our knowledge, this study is the first to investigate the degree of the cognitive impairments across the BACS subscales among SCZ, FR and HC and perform cognitive clustering analysis based on the BACS neuropsychological battery regardless of clinical diagnosis (SCZ, FR and HC). Cognitive impairments, particularly in verbal fluency and symbol coding, were stronger in SCZ than in HC and were also observed in FR, although somewhat less pronounced than those in SCZ. Next, three meaningful cognitive clusters: neuropsychologically normal cognition (Cluster 1), intermediately impaired cognition (Cluster 2) and widespread impaired cognition (Cluster 3), were identified using a data-driven approach rather than pre-determined grouping criteria. HC were mainly distributed to Cluster 1 (76.0%), followed by Cluster 2 (24.0%), but not Cluster 3 (0%). FR were mainly distributed to Clusters 1 (40.0%) and 2 (55.0%), while SCZ were mainly distributed to Clusters 2 (53.1%) and 3 (35.8%), but not Cluster 1 (11.1%). These findings suggest that, while some SCZ suffer from widespread cognitive impairments, a subset of SCZ and FR exhibit mildly impaired cognition that is similar to that of a part of the general population (HC), indicative of a cognitive continuum among SCZ, FR and HC. Furthermore, the frontal and temporal volumes were affected by diagnosis (SCZ, FR and HC), whereas the ACC volumes were affected by the additive effects of diagnosis and cognition. Therefore, cognitive impairments and related changes in ACC volume would be useful intermediate phenotypes for

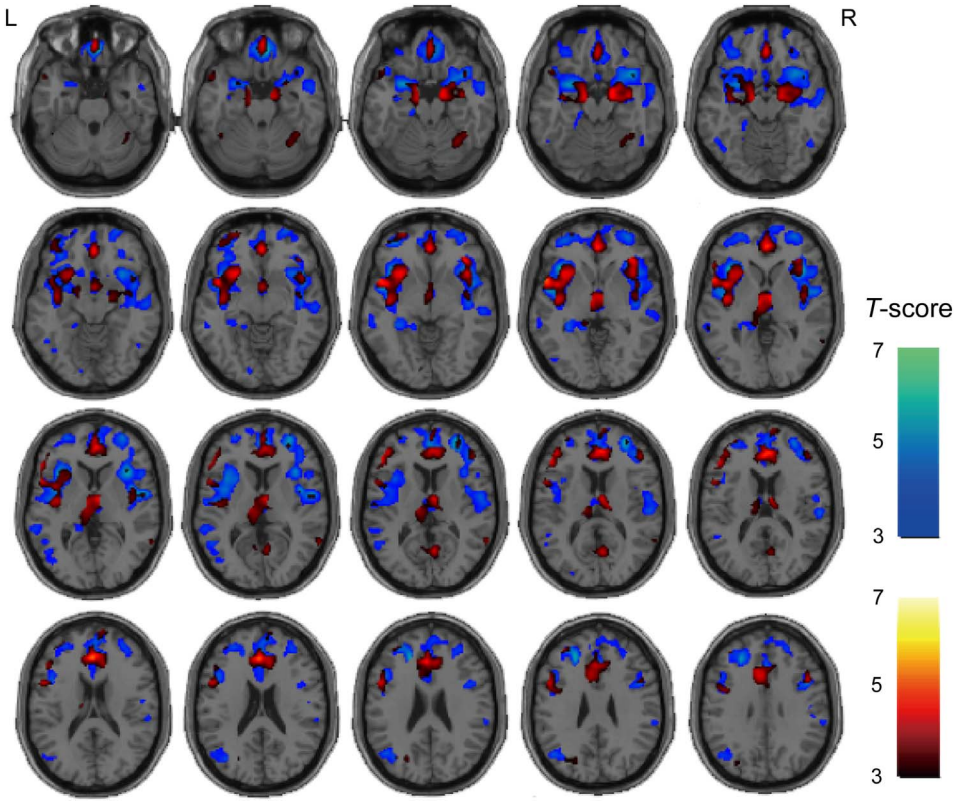

Fig. 3. Effects of diagnosis and cognitive clusters on GM volumes without cognitive clusters or diagnosis as covariates, respectively. There were diagnosis effects (SCZ < FR < HC) on decreased GM regions (blue areas shown on the winter color map). There were cognitive cluster effects (Clusters 3 < 2 < 1) on decreased GM regions (red areas shown on the hot color map). There were several regions where the effects of the diagnosis and cognition overlapped. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

schizophrenia to understand the pathophysiology implicated in schizophrenia.

We found cognitive differences among the diagnostic groups in five BACS subscales (SCZ, FR and HC) but not in the Tower of London subscale. Five SCZ (5/81, 6.2%), two FR (2/20, 10.0%), one HC (1/25, 4.0%) obtained the highest score of 22 in the Tower of London task. By contrast, no participants received the highest scores in the verbal memory, token motor or symbol coding tasks, and only two HC achieved the highest score on the digit sequencing task. Thus, we may have been unable to detect a significant difference in the Tower of

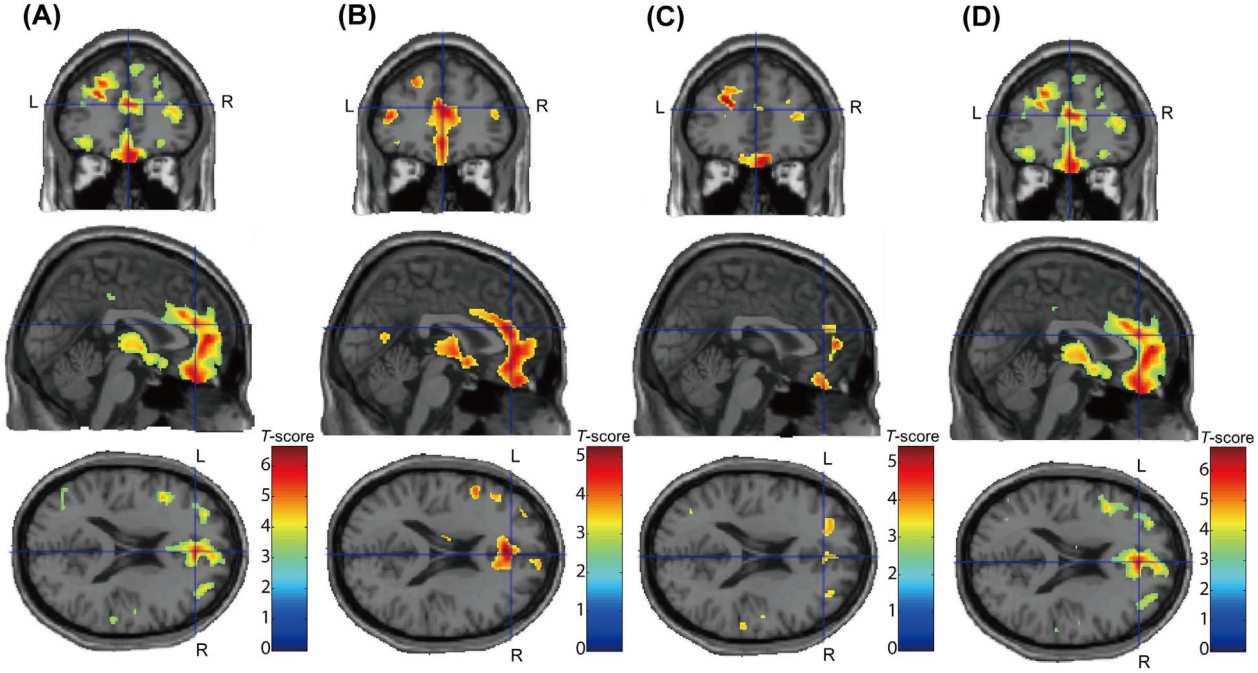

Fig. 4. Effects of the diagnosis and cognition on the anterior cingulate cortex (ACC) volume. Impacts of the diagnosis (A), cognition (B), diagnosis with cognitive clusters as covariates (C) and the additive effects of both diagnosis and cognition (D) on the ACC volume. Anatomical localizations are displayed on coronal, sagittal, and axial sections of a normal MRI spatially normalized into the Montreal Neurological Institute (MNI) template (cluster size > 100, $P_{\text{uncorrected}} < 0.001$). The overlapping ACC region ($x, y, z = 1.5, 40.5, 19.5$) is shown as a cross-hairline. The color bars show the T values corresponding to the color in the figures. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

London task among the groups owing to a ceiling effect.

Unaffected FR share half of the genetic risk for schizophrenia. The estimated heritability (h^2) on BACS subscales in schizophrenia pedigrees is 0.51 in verbal memory, 0.49 in digit sequencing, 0.32 in token motor, 0.33 in verbal fluency, 0.40 in symbol coding and 0.29 in Tower of London, suggesting that these cognitive deficits have modest heritability (Hill et al., 2013). Hill et al. (2013) have shown that SCZ have more impaired global neuropsychology scores ($z = -1.4$) on the BACS than HC, and FR have more impaired scores ($z = -0.5$) than HC but with a less prominent difference than SCZ (Hill et al., 2013). However, the previous study did not examine the degrees of cognitive performance in BACS subscales among SCZ, FR and HC. The current study indicates that robust cognitive deficits on BACS subscales were present in SCZ compared with those in FR and HC, and the cognitive deficits were also present in FR compared with those in HC. The effect sizes of the cognitive differences between FR and HC were half that of the differences between SCZ and HC. These findings suggest that the severity of cognitive impairments across SCZ, FR and HC was consistent with a continuum model.

While several studies have identified meaningful cognitive clusters within SCZ (Allen et al., 2003; Goldstein et al., 1998; Heinrichs and Awad, 1993; Hill et al., 2002; Seaton et al., 1999; Seaton et al., 2001) or in a cross-diagnostic sample of patients with psychotic disorders (Lewandowski et al., 2014; Van Rheenen et al., 2017), no study has examined cognitive performances in a genetic continuum of diagnostic groups (SCZ, FR and HC) using the clustering approach. According to evidence that cognitive function is one of the useful intermediate phenotypes for schizophrenia, we hypothesized that the clustering approach without using clinical information would produce cognitive cluster groups affected by the genetic continuum diagnostic groups (SCZ, FR and HC). We successfully identified three meaningful cognitive clusters, a neuropsychologically normal cluster and intermediate impaired and globally impaired clusters. Indeed, we revealed that the cognitive clusters were mainly affected by the diagnostic groups (SCZ, FR and HC). Interestingly, 11.1% (9/81) SCZ were distributed into Cluster 1 with a neuropsychologically normal cognition, consistent with previous studies that have reported that approximately 10–30% SCZ did not show cognitive impairments (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; Van Rheenen et al., 2017).

The effects of diagnosis and cognitive clusters on brain volumes overlapped in the frontal, temporal and limbic regions. SCZ and those in Cluster 3 with globally impaired cognition were associated with decreased GM volumes in these regions. Considering that Cluster 3 consisted primarily of SCZ, these regions would be mainly affected by a diagnosis effect. By contrast, ACC volumes were affected by clusters as well as diagnosis. The ACC is a functionally heterogeneous region involved in diverse cognitive processes, such as executive, attention, social cognitive, affective and motor functions (Fornito et al., 2009; Ohi et al., 2012b). A widespread GM reduction in the ACC has been found in FR as well as SCZ (Bhojraj et al., 2011; Fornito et al., 2009; Goghari et al., 2007). In addition, the GM reductions in the ACC precede the onset of psychosis in high-risk individuals (Chan et al., 2011; Fornito et al., 2009; Meredith et al., 2012). These reductions extend across the dorsal and rostral divisions of the limbic and paralimbic regions of the ACC and are accompanied by reductions in neuronal, synaptic, and dendritic density as well as increased afferent input in post-mortem brains (Fornito et al., 2009). Therefore, changes in ACC volume related to cognitive processes may be a useful intermediate phenotype for schizophrenia.

There are some limitations to the interpretations of our findings. Compared with the samples size of SCZ, those of the FR and HC were relatively small, potentially resulting in false positive findings. Future studies using larger sample sizes are needed to replicate our findings. The participants in the FR group had any familial relationship with the participants in the SCZ group. Shared genetics irrespective of risk of schizophrenia might also affect the cognitive function and brain morphology as well as the familial relationship between FR and SCZ. The parameter k in the k-means clustering approach is known to be hard to choose when not given by external constraints. Based on evidence for previous 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), we selected an arbitrary three-cluster solution. Therefore, we could not exclude possibility that other k-cluster solutions, such as two, four, five or six, might be suitable for the cognitive clustering. We performed *post hoc* analyses using other k-cluster solutions, such as two, four, five or six. Even after using other k-cluster solutions, clinical diagnoses (SCZ, FR and HC) were significantly and not evenly distributed into the k-cluster groups (two: $\chi^2 = 18.5$, $P = 3.47 \times 10^{-5}$, four: $\chi^2 = 60.0$, $P = 4.82 \times 10^{-11}$, five: $\chi^2 = 58.6$, $P = 2.80 \times 10^{-10}$, and six: $\chi^2 = 63.4$, $P = 1.53 \times 10^{-9}$). These findings support that at least three cluster solution could generate meaningful subgroups. Consistent with a previous study (Seaton et al., 1999), three clusters were differentiated on the basis of educational level and estimated premorbid IQ but not on the basis of symptom profile, medication or duration of illness. As expected, those in Cluster 1 with neuropsychologically normal cognition showed a higher educational level and premorbid estimated IQ than those in Clusters 2 and 3. Cognitive performance is generally highly correlated with educational level and estimated premorbid IQ. In our participants, some BACS subscales were correlated with educational level and estimated premorbid IQ ($P < 8.33 \times 10^{-3}$, Pearson's $r = 0.24$–0.48). However, our findings were still significant even after correcting for educational level or estimated premorbid IQ, suggesting that these cognitive differences among diagnoses or clusters were not due to these confounding factors. Most SCZ (75/81, 92.6%) took antipsychotics with a mean CPZ-eq ± SD of 495.6 ± 425.0. Although the CPZ-eq was not significantly correlated with any BACS subscales ($P > 8.33 \times 10^{-3}$), we could not completely exclude a medication effect on cognitive performance in SCZ.

In this study, we investigated the cognitive heterogeneity and cognitive continuum among SCZ, FR and HC. The cognitive clustering approach without using clinical diagnoses successfully produced more homogeneous cognitive clusters: a neuropsychologically normal, an intermediately impaired and a globally impaired cognitive cluster. Clinical diagnoses (HC, FR and SCZ) were not evenly distributed into the three clusters; *i.e.*, these clusters were mainly affected by clinical diagnoses. Both diagnoses and cognitive clusters were associated with decreased ACC volumes. Our findings demonstrate a cognitive continuum among SCZ, FR and HC and support the hypothesis that cognitive impairments and the related ACC volumes would be useful intermediate phenotypes in the pathophysiology of schizophrenia.

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