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Intra-individual variability in neurocognitive function in schizophrenia: relationships with the corpus callosum

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ABSTRACT

Patients with schizophrenia not only have impairments in neurological function, but also have instability and variability in neurocognitive function. However, previous researchers have not fully studied the relationships between dispersion across multiple neurocognitive domains and white matter (WM) structures of the brain. This study focuses on intra-individual variability (IIV) in patients with schizophrenia and its relationship with WM integrity of the corpus callosum (CC). Thirty-eight patients with schizophrenia were enrolled in the study. All subjects underwent assessments of neurocognitive function using the Korean-Wechsler Adult Intelligence Scale-Revised (K-WAIS-R) and the severity of clinical symptoms using the Positive and Negative Syndrome Scale (PANSS). IIV across subtests of the K-WAIS-R was calculated using the Holtzer's equation. Tract-based spatial statistics were used to analyze diffusion tensor images. In subjects with schizophrenia, a negative correlation was found between IIV in performance intelligence quotient (PIQ) and fractional anisotropy (FA) values in the genu of the CC. In addition, FA values of the same region were negatively correlated with the total and subscale scores of positive symptoms and general psychopathology from the PANSS. Our findings suggest that the genu of the CC may play an important role in IIV in PIQ and symptomatology in patients with schizophrenia.

1. Introduction

Patients with schizophrenia have neurocognitive deficits across a wide range of neurocognitive domains (Bang et al., 2015; Lencz et al., 2006; Marder and Fenton, 2004). A large body of literature has suggested that cognitive abnormalities are independent core features of schizophrenia (Bowie et al., 2008; Gold, 2004; Green et al., 2004). Compared to healthy individuals, patients with schizophrenia have lower scores on tests of attention, memory, processing speed, executive function, and social cognition, as well as impaired performance on the Wechsler Adult Intelligence Scale (Michel et al., 2013). These deficits lead to maladaptation in aspects of everyday life, including self-care, interpersonal relationships, and occupational functioning (Aleman et al., 1999; Hughes et al., 2003).

Most neurological and cognitive studies have focused on mean differences between groups. However, such studies might overlook random errors due to intra-individual variance (IIV) and oversimplify individual characteristics (Bunce et al., 2004; Hultsch et al., 2008). Recent findings have suggested that IIV in cognitive function is not coincidental, but is associated with normal aging and pathological neurocognitive dysfunction (Hultsch et al., 2002; Hultsch et al., 2000). IIV is assessed in two ways: by measuring multiple tasks at the same time (Hale et al., 1988), and by measuring a single task repeatedly at intervals (Hultsch et al., 1992; Shammi et al., 1998). The former reflects dispersion among different neurocognitive domains, while the latter demonstrates persistence of cognitive functioning over time. IIV in neurocognitive function could be used to identify neurological deficits, as many studies have shown that the elderly and patients with neurocognitive disorders, traumatic brain injury, attention-deficit hyperactivity disorder, and schizophrenia tend to have higher IIV than normal individuals (Castellanos and Tannock, 2002; Mazerolle et al., 2013; Stuss et al., 2003). Previous studies have shown that

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neuropsychological deficits in schizophrenia are observed not only in single neurocognitive domain but also in the context of general intellectual impairments (Reichenberg and Harvey, 2007). Instability of information processing was reported in patients with schizophrenia, even in those with high functioning (Rentrop et al., 2010), and teenagers with higher IIV of intelligence quotient (IQ) were found to have more risk to manifest schizophrenia later on (Reichenberg et al., 2006). Furthermore, unaffected siblings of patients with schizophrenia showed higher IIV across multiple neurocognitive domains than healthy individuals did (Cole et al., 2011).

Prior research has suggested that IIV is closely related to structural and functional alterations of the brain, especially with degeneration and deformation of white matter (WM) regions (MacDonald et al., 2009; Strauss et al., 2002; Williams et al., 2005; Winterer and Weinberger, 2004). In particular, the corpus callosum (CC), the largest WM tract in the brain, has been suggested as one of the neural correlates of IIV (Anstey et al., 2007; MacDonald et al., 2009). The CC plays a crucial role in the exchange of information between the two cerebral hemispheres and functional integration among various cognitive functions including learning, memory, attention, visuospatial ability and executive function (Gazzaniga, 2000). Therefore, it would be plausible that dispersion across multiple neurocognitive domains is associated with abnormalities in the CC. In patients with schizophrenia, a dysconnection syndrome with impairments in integrated information processing (Friston et al., 2016), previous neuroimaging studies have consistently reported a reduction in the size and integrity of the CC, which is implicated in clinical manifestations of schizophrenia (Arnone et al., 2008; David, 1994; Downhill et al., 2000; Innocenti et al., 2003; Mitelman et al., 2009). However, a relationship between abnormalities of the CC and IIV has been relatively less investigated in patients with schizophrenia. Furthermore, given that neurocognitive impairments are a core feature of schizophrenia (Green et al., 2004), it would be noteworthy to explore whether abnormalities of the CC related to IIV are associated with clinical symptoms.

Here, we aimed to investigate WM microstructures of the CC using diffusion tensor imaging (DTI) to elucidate its relationships with the dispersion in IQ and clinical symptoms in patients with schizophrenia. We hypothesized that IIV across IQ domains would be related to WM integrity of the CC in patients with schizophrenia. In addition, WM integrity of the CC regions associated with IIV in IQ was expected to be associated with the severity of clinical symptoms.

2. Methods

2.1. Subjects and clinical assessment

Thirty-eight subjects with schizophrenia (16 men and 22 women) were recruited from patients who were treated at the Department of Psychiatry of CHA Bundang Medical Center (Seongnam, Republic of Korea) between January 2011 and June 2015. All subjects were right-handed Koreans between the ages of 18 and 60 years and met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV. Subjects were excluded if they had a lifetime history of a comorbid mood or anxiety disorders, mental retardation, neurocognitive disorders, traumatic brain injury, or serious medical disorders.

All subjects were taking atypical antipsychotic drugs, and the mean total duration of antipsychotic treatment before brain magnetic resonance imaging (MRI) scan was 136.21 (*SD* = 507.86) days. The severity of clinical symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a semi-structured interview designed to measure the severity of positive and negative symptoms, as well as that of general psychopathology. Positive symptoms consist of 7 items: delusions, conceptual disorganization, hallucinatory behaviors, excitement, grandiosity, suspiciousness/persecution, and hostility. Negative symptoms include blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. The severity of each symptom is rated from 1 (none) to 7 (severe) based on the interview or reports from family members or primary caregivers. Table 1 summarizes the sociodemographic and clinical characteristics of all subjects with schizophrenia.

Table 1
Sociodemographic and clinical characteristics of study subjects (n = 38).

Variable	
Sex	
Male (%)	16 (42.11)
Female (%)	22 (57.89)
Age at scan (years, mean ± *SD*)	32.97 ± 11.12
Intracranial volume (ml, mean ± *SD*)	1484.00 ± 124.74
Years of education (years, mean ± *SD*)	13.74 ± 2.27
Duration of illness (years, mean ± *SD*)	5.18 ± 7.32
Family history of schizophrenia spectrum, yes (%)	6 (15.79)
Total duration of antipsychotic treatment before MRI scan (days, mean ± *SD*)	136.21 ± 507.86
Baseline PANSS score	
Total score (mean ± *SD*)	115.64 ± 25.56
Positive symptom (mean ± *SD*)	28.91 ± 5.60
Negative symptom (mean ± *SD*)	27.70 ± 8.70
General psychopathology (mean ± *SD*)	58.12 ± 13.74
Kinds of antipsychotics and daily dosage	
Paliperidone (%)	27 (71.05)
Chlorpromazine equivalence (mg, mean ± *SD*)[a]	585.47 ± 199.53
Risperidone (%)	2 (5.26)
Chlorpromazine equivalence (mg, mean ± *SD*)[b]	500.00 ± 141.42
Amisulpride (%)	6 (15.79)
Chlorpromazine equivalence (mg, mean ± *SD*)[c]	573.33 ± 140.44
Aripiprazole (%)	2 (5.26)
Chlorpromazine equivalence (mg, mean ± *SD*)[d]	450.00 ± 212.13
Clozapine (%)	1 (2.63)
Chlorpromazine equivalence (mg, mean ± *SD*)[e]	600.00 ± 0.00

Abbreviation: PANSS, Positive and Negative Syndrome Scale; MRI, magnetic resonance imaging; SD, standard deviation.
[a] The approximate equivalent oral doses to 1.5 mg paliperidone are given.
[b] The approximate equivalent oral doses to 1 mg risperidone are given.
[c] The approximate equivalent oral doses to 116.3mg amisulpride are given.
[d] The approximate equivalent oral doses to 66.7 mg aripiprazole are given.
[e] The approximate equivalent oral doses to 50 mg aripiprazole are given.

All study procedures complied with the Institutional Review Board regulations of the CHA Bundang Medical Center, the Declaration of Helsinki, and the principles of Good Clinical Practice. In addition, all subjects were provided with a complete description of the study and provided full written informed consent before participation.

2.2. Neurocognitive tests

Neurocognitive function was assessed using the Korean-Wechsler Adult Intelligence Scale-Revised (K-WAIS-R). This widely-used instrument is one of the most reliable measures for assessing general intellectual abilities across multiple facets including memory, processing speed, verbal comprehension, and perceptual organization in adults (Reichenberg, 2010; Tulsky et al., 2003). The K-WAIS-R includes 11 subtests: information, comprehension, arithmetic, digit span, similarities, vocabulary, picture arrangement, picture completion, block design, object assembly, and digit symbol. The test results are reported as two sub-indices of verbal IQ (VIQ) and performance IQ (PIQ), as well as full-scale IQ (FSIQ). In this study, trained clinical psychologists carried out the full test using standard administration and scoring procedures. The scaled scores of all 11 subtests were z-transformed to calculate IIV, as an index of disproportionate neurocognitive functioning within individuals. IIV values were estimated using the Holtzer's equation (Holtzer et al., 2008) as shown below.

$$A_i = \sum_{1}^{k} \frac{Z_K}{k},\ IIV = \sqrt{\sum_{k=1}^{k} \frac{(Z_{ik} - A_i)^2}{(k-1)}}$$

2.3. Neuroimaging data acquisition

DTI data were acquired on a 3.0 Tesla GE Signa HDxt scanner (GE Healthcare; Milwaukee, WI, USA). Diffusion-weighted images were acquired using an echo planar imaging (EPI) sequence, with the following parameters: repetition time of 17,000 ms, echo time of 108 ms, field of view 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 option was used to reduce eddy current-related distortions. An 8-channel coil and an array of spatial sensitivity encoding techniques (GE Healthcare) with a sensitivity encoding speed-up factor of two were used to reduce the impact of EPI spatial distortions. Seventy axial slices parallel to the anterior commissure-posterior commissure line covering the whole brain were acquired in 51 directions with a b-value of 900 s/mm^2. Eight baseline scans with b = 0 s/mm^2 were also acquired. DTIs were estimated from the diffusion-weighted images using the least-squares method (approximate scan time = 17 min).

2.4. Neuroimaging analysis

Voxel-wise statistical analysis of the fractional anisotropy (FA) data was performed using Tract-Based Spatial Statistics (TBSS version 1.2), implemented in the FMRIB Software Library (FSL version 4.1; Oxford, UK; http://www.fmrib.ox.ac.jk/fsl) according to the standard procedure published elsewhere (Smith et al., 2006). First, DTI preprocessing, including skull stripping using the Brain Extraction Tool, and eddy current correction were performed using the FSL. Subsequently, FA images were created by fitting a tensor model to the raw diffusion data (Smith, 2002). All subjects' FA data were aligned in the standard space (Montreal Neurologic Institute 152 standard) using the FMRIB's nonlinear image registration tool. All transformed FA images were combined and applied to the original FA map, resulting in a standard-space version of the FA map. A mean FA image was calculated and skeletonized to create a mean FA skeleton, including only the centers of the WM tracts. The skeleton was thresholded using an FA value > 0.2 (the TBSS default) to include only major fiber bundles.

To estimate axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD), we used the FA images to achieve nonlinear registration and skeletonization stages, and to estimate the projection vectors from each individual subject onto the mean FA skeleton. The nonlinear warps and skeleton projection were also applied to other images.

Mean FA skeletons were multiplied using the Johns Hopkins University DTI-based probabilistic tractography atlas, which contains CC tracts/regions of the genu, body, and splenium (Mori and Aggarwal, 2014). The above-mentioned CC regions of interest were extracted using 3D Slicer version 3.6 (Pieper et al., 2004) to create a mask (Fig. 1A). The created mask of the CC regions was applied in subsequent voxel-wise statistical analysis.

2.5. Statistical analysis

Voxel-wise correlation analysis of the DTI data were conducted within the CC regions using TBSS general linear model regression analysis with IIV in VIQ and PIQ as factors. To determine statistical significance, nonparametric permutation tests corrected for multiple comparisons were performed using the FSL randomize program (Nichols and Holmes, 2002). The statistical significance level was set to $p < 0.05$ and corrected for the family-wise error rate (FWE). Statistical results were corrected for multiple comparisons with the threshold-free cluster enhancement (TFCE) method (Smith and Nichols, 2009) to avoid an arbitrary choice of the cluster-forming threshold while preserving the sensitivity benefits of cluster-wise correction. Next, we extracted FA, AD, RD, and MD values from the WM clusters which were found to be significantly associated with IIV in VIQ and PIQ. These values were assessed for possible correlations with PANSS scores using Pearson's correlation analysis in the SPSS 23.0 software (IBM Corp., Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

3. Results

3.1. IIV in IQ

The IQ values of subjects with schizophrenia are presented in Table 2. IQ was not associated with age, sex, intracranial volume, duration of illness, or symptom severity. Years of education had positive correlations with FSIQ ($r = 0.357$, $p = 0.028$) and VIQ ($r = 0.426$, $p = 0.008$), but not with PIQ. The mean IIV values for VIQ and PIQ were 0.67 ($SD = 0.26$) and 0.69 ($SD = 0.39$), respectively. There were no significant differences between men and women (IIV in VIQ, $t = 0.238$, $p = 0.813$; IIV in PIQ, $t = -0.309$, $p = 0.759$). Besides, no significant relationships were found between IIV and age, duration of illness, total and subscale scores of the PANSS, or type and dosage of antipsychotic drugs.

3.2. Relationships between WM integrity of the CC and IIV

Voxel-wise correlation analysis using TBSS revealed a significant association between IIV in PIQ and FA values of the CC, particularly the genu region (Fig. 1B, FWE-corrected $p = 0.04$), while no significant correlation was found with IIV in VIQ. For other DTI measures, AD, RD, and MD values of the CC did not show any significant correlation with IIV in VIQ and PIQ. When the effects of age, duration of illness, and dosage of antipsychotic drugs were controlled for, the results remained unchanged.

3.3. Relationships between IIV-associated WM integrity and the severity of clinical symptoms

The PANSS total and subscale scores had significant correlations with the extracted FA values of the genu region (Fig. 2). Specifically, the scores of the positive symptom and general psychopathology subscales and total scores were negatively correlated with FA of the genu. No significant correlation was found with the severity of negative symptoms.

4. Discussion

To our knowledge, this is the first study to show the association between WM integrity in the genu region of the CC and IIV in PIQ in patients with schizophrenia. Furthermore, and the severity of clinical symptoms, particularly positive symptoms, was negatively correlated with FA values of the genu of the CC. Our findings are grossly in line with previous studies which have showed that IIV across multiple neurocognitive domains is one of the important feature of neurocognition in patient with schizophrenia (Cole et al., 2011; Reichenberg et al., 2006).

Previous studies have investigated IIV in neurocognitive function and its relationships with different brain areas in samples of individuals with normal aging and dementia. Bunce et al. (2007) suggested frontal WM hyperintensity in individuals with normal aging was associated with greater IIV, while Walhovd and Fjell (2007) showed a negative relationship between IIV and WM volume. In studies of subjects with neurocognitive disorders, IIV in response time was associated with the area of the CC in patients with mild cognitive disorders, but not in subjects with normal aging (Anstey et al., 2007). Although the results of many studies have been inconsistent, they all indicate that IIV is

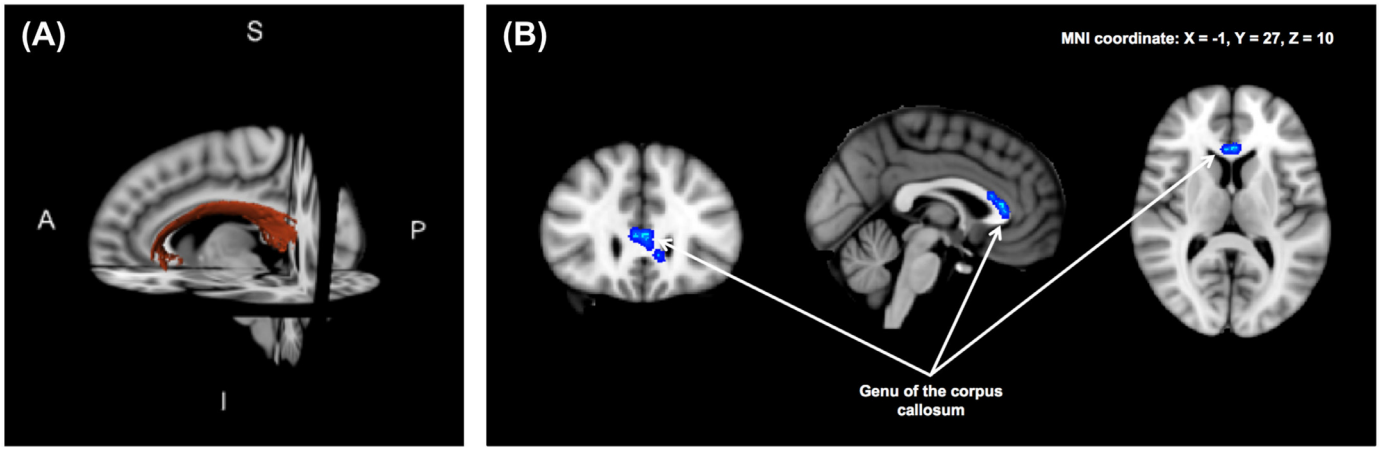

Fig. 1. (A) The region-of-interest mask of the corpus callosum. (B) FA values of the genu region of the corpus callosum showed a significant negative correlation with IIV in performance IQ in patients with schizophrenia (n = 38, FWE-corrected $p < 0.04$). Abbreviations: FA, fractional anisotropy; IIV, intra-individual variability; IQ, intelligence quotient, FWE, family-wise error.

Table 2
Scores on neurocognitive tests and intra-individual variability of study participants (n = 38).

	Mean ± *SD*
K-WAIS-R score	
Full-scale IQ	100.29 ± 11.22
Verbal IQ	100.92 ± 12.88
Information	10.71 ± 2.93
Digit span	10.21 ± 2.64
Vocabulary	10.68 ± 2.36
Arithmetic	8.92 ± 3.15
Comprehension	10.68 ± 2.06
Similarities	10.37 ± 2.67
Performance IQ	96.37 ± 16.53
Picture completion	9.08 ± 2.47
Picture arrangement	9.08 ± 2.73
Block design	10.39 ± 3.28
Object assembly	9.97 ± 3.05
Digit symbol	10.08 ± 2.76
Intra-individual variability in verbal IQ	0.67 ± 0.26
Intra-individual variability in performance IQ	0.69 ± 0.39

Abbreviation: K-WAIS-R, Korean-Wechsler Adult Intelligence Scale-Revised; IQ, intelligence quotient; SD, standard deviation.

associated with neuroanatomical integrity (Hultsch et al., 2008). There is growing evidence that patients with schizophrenia have deficits in neurocognitive domains, and especially problems with integration and connectivity of brain function (Fervaha et al., 2014; Rüsch et al., 2007). Therefore, it would be assumed that patients with schizophrenia may share similar neurocognitive deficits with those with neurocognitive spectrum disorders.

The CC is the largest WM structure in the brain and connects the bilateral cerebral hemispheres. It has been implicated as an anatomical mediator of interhemispheric transfer (David, 1994). The CC are divided into three areas: the genu, body, and splenium (Witelson, 1989). Fibers from the frontal lobes traverse the genu, which comprises the anterior part of CC (Seltzer and Pandya, 1986). It is possible that the WM abnormalities in the genu of the CC disrupt functional connectivity among different cortical regions (Chung et al., 2004). Previous research has demonstrated a clear association between the genu and prefrontal regions. As such, deficits in the genu may result in worse functioning in neurocognitive domains associated with the prefrontal cortex.

We found a negative correlation between IIV in PIQ and FA values in the genu of the CC. This result might imply that poor connectivity in the genu interferes with communication and integration of information, and eventually increases the variance between and instability in PIQ values. The PIQ value of the WAIS-R is not only a measure of processing speed, but also a measure of executive functioning, including visuoperceptual function and planning ability (Carroll, 1993). It would be inferred that patients with schizophrenia with lower FA values in the genu of the CC may have deficient performance in executive function tasks. Our findings are consistent with those of prior studies indicating that increased IIV was closely related to neuronal deficiencies (Balevich et al., 2015; Castellanos and Tannock, 2002), and that patients with schizophrenia are more likely to have significant reductions in size and FA value in the anterior genu (Amminger et al., 2000).

In our study, negative correlations were observed between positive symptoms and the FA values of the genu, which were significantly correlated with IIV in PIQ. The relationship between the anisotropy of the CC and symptom severity in schizophrenia remains controversial. Some studies have shown that positive symptoms in patients with schizophrenia may result from hyperconnectivity, i.e., higher FA values in the genu (Whitford et al., 2010). It has been hypothesized that aberrant connections and disconnections might result in increased neural noise and decreased segregation, which can lead to auditory hallucination (Crow, 1998; Rotarska-Jagiela et al., 2008). In contrast, consistent with the findings of our study, Brambilla et al. (2005) and Rotarska-Jagiela et al. (2008) have reported that positive symptoms of schizophrenia are associated with lower FA values throughout the CC. Positive symptoms of schizophrenia have also been shown to be associated with reduced callosal size (Lee et al., 2013; Tibbo et al., 1998; Woodruff et al., 1997). Other studies have found no relationship between symptoms and the CC (Foong et al., 2000; Goghari et al., 2005). In summary, our findings indicate that the genu region of the CC, which is associated with IIV, may be closely related to positive symptoms and general psychopathology. Further investigation is needed to determine the nature of this association.

Several limitations in this study are worth mentioning. First, it would be possible that the use of antipsychotic medication influenced WM integrity in study participants. Although the total duration of antipsychotic treatment was relatively short, future studies with drug-naïve patients would be necessary. Second, our study did not include comparison groups such as healthy controls. Therefore, additional research on patients with other mental disorders or healthy subjects is recommended. Third, we were unable to draw conclusions regarding causality for the relationships among decreased WM integrity of the CC, neurocognitive function, and disease etiology. A prospective longitudinal study would be needed to elucidate a temporal correlation between the different factors. Lastly, there are reports of crossing fibers in the CC (Hofer and Frahm, 2006). Therefore, we cannot completely rule out the possibility of crossing fiber problems in patients with

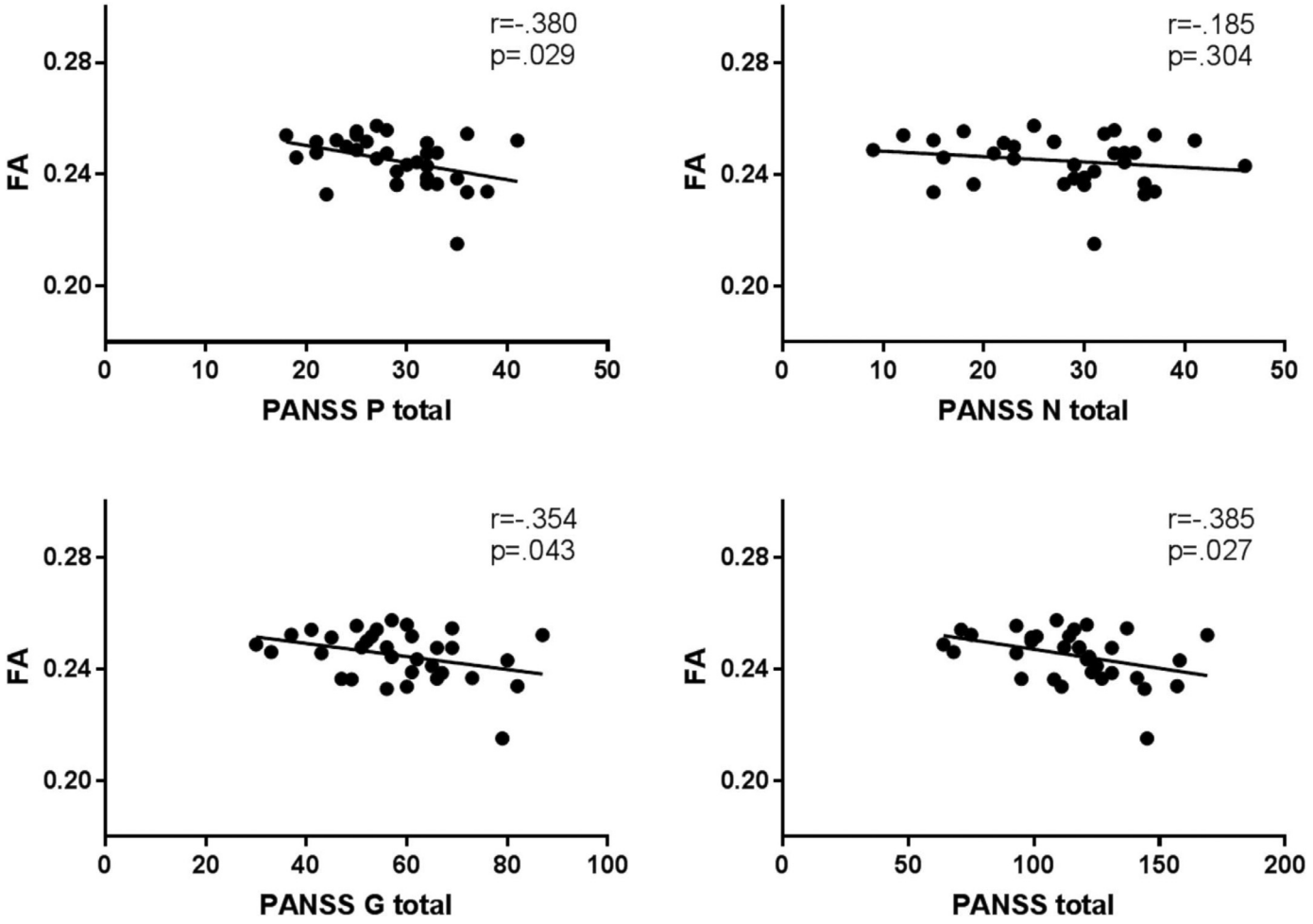

Fig. 2. Correlations between the total and subscale scores of the PANSS and the mean FA values of the genu region showing a significant negative correlation with IIV in performance IQ. Abbreviations: PANSS, Positive and Negative Syndrome Scale; P, positive symptom scale; N, negative symptom scale; G, general psychopathology scale; FA, fractional anisotropy; IIV, intra-individual variability; IQ, intelligence quotient.

schizophrenia. Future studies are needed to elucidate this issue.

In conclusion, we showed that lower WM integrity in the genu of the CC were associated with IIV in PIQ in patients with schizophrenia, and that symptoms of schizophrenia were negatively correlated with the FA values of the genu of the CC. These findings suggest that the genu of the CC may play an important role in the development of IIV across multiple neurocognitive domains and may be a biomarker for symptomatology in patients with schizophrenia.

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Contributors

Ji-In Ahn: literature search, data acquisition, statistical analysis, drafting of the manuscript, and revision of manuscript.

Seung-Taek Yu: data acquisition and statistical analysis

Gyhye Sung: statistical analysis, manuscript editing, and critical revision

Tai-Kiu Choi: data acquisition and critical revision.

Kang-Soo Lee: data acquisition and critical revision.

Minji Bang: literature search, interpretation of the results, manuscript editing, and critical revision.

Sang-Hyuk Lee: data acquisition, statistical analysis, manuscript editing, and critical revision.

Conflict of interest

All authors declare that they have no conflicts of interest.

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