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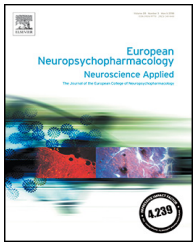

Intelligence decline between present and premorbid IQ in schizophrenia: Schizophrenia Non-Affected Relative Project (SNARP)

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Abstract
Schizophrenia patients (SCZ) display widespread cognitive deficits that are strongly associated with functional outcomes. Cognitive impairments occur along a genetic continuum among SCZ, their unaffected first-degree relatives (FRs) and healthy controls (HCs). Although SCZ impairs the premorbid intelligence quotient (IQ) and causes a subsequent intelligence decline (ID), a decrease in present IQ from the premorbid level, it remains unclear when during the illness course these impairments develop. Differences in premorbid and present IQ and ID were investigated among 125 SCZ, 61 FRs and 107 HCs, using analysis of covariance and a paired *t*-test. Furthermore, these subjects were classified into preserved and deteriorated IQ groups based on the degree of ID, and we investigated which factors contribute to this classification. We found significant differences in premorbid and present IQ among the diagnostic groups. Compared with HCs, SCZ and FRs displayed lower premorbid and present IQ. There was no significant difference in premorbid IQ between SCZ and FRs, but SCZ had a significantly lower present IQ than FRs. Only SCZ showed a significant ID. As most FRs and HCs did not display an ID, there were fewer subjects with deteriorated IQ among FRs

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and HCs than among SCZ. Subjects with preserved IQ showed higher educational attainment than those with deteriorated IQ among SCZ and FRs. These findings suggest that the impairment of premorbid IQ and the ID in SCZ become evident before and around the time of onset, respectively, and different pathophysiological mechanisms might be related to these impairments.

1. Introduction

Cognitive impairment, i.e., a decrease of 1 to 2 standard deviations (SDs) in cognitive function on a neuropsychological test compared to the results of healthy individuals, is a core feature of schizophrenia (SCZ) (Keefe and Fenton, 2007; Schaefer et al., 2013) and contributes to social and/or occupational dysfunction and poor life outcomes (Green, 1996; Green et al., 2000; Kahn and Keefe, 2013). Although the diagnosis of SCZ is currently based on positive and negative symptoms, such as delusions, hallucinations, blunted affect and withdrawal, cognitive impairments and these psychotic symptoms are relatively independent dimensions of SCZ (Badcock et al., 2005). The focus on psychotic symptoms as the primary target for research and treatment of the disorder has obscured an obvious issue: SCZ is not primarily a psychotic disorder; it is a cognitive illness (Kahn and Keefe, 2013). Cognitive impairments in patients with SCZ are poorly addressed by current antipsychotic medications.

A lower intelligence quotient (IQ) in childhood is associated with a high risk of SCZ spectrum psychoses (Agnew-Blais et al., 2015). In addition to impairments in childhood IQ, impairments in premorbid IQ during adolescence and young adulthood, with a decrease of approximately half an SD compared to that of control subjects, are associated with subsequent development of SCZ (Woodberry et al., 2008). These impairments in premorbid IQ in patients with SCZ may be caused by early neurodevelopmental abnormalities (Weinberger, 1987; Sommer et al., 2016).

SCZ patients exhibit relatively intact levels of crystallized intelligence on the National Adult Reading Test (NART) and the Wechsler Test of Adult Reading (WTAR) and general knowledge (Vocabulary) on the Wechsler Adult Intelligence Scale (WAIS) (Mathias et al., 2007; Dykiert and Deary, 2013; Mullen and Fouty, 2014); in addition, the crystallized intelligence of SCZ patients is stable over time (Morrison et al., 2000). Therefore, crystallized intelligence, as measured by these tests, is used to estimate the premorbid IQ in SCZ patients. On the other hand, many SCZ patients display impairments in fluid intelligence, i.e., present IQ, assessed by full-scale IQ or subscales, such as Similarity and Arithmetic, on the WAIS (Wells et al., 2015; Ohi et al., 2017c).

Intelligence decline (ID) represents intraindividual differences in intelligence function at different time points. The ID in SCZ patients is defined as a decrease in present IQ (after the onset of schizophrenia) from the premorbid level (before onset) (Badcock et al., 2005; Hashimoto et al., 2013; Fujino et al., 2017; Ohi et al., 2017c). A meta-analysis of pre- and postonset testing within the same sample demonstrated that ID in SCZ patients was related to the onset of psychosis (Woodberry et al., 2008). Based on premorbid and present IQ estimates, SCZ patients can be classified into preserved, deteriorated and compromised IQ groups (Weickert et al., 2000; Badcock et al., 2005; Kremen et al., 2008; Potter and Nestor, 2010; Leeson et al., 2011; Mercado et al., 2011; Ammari et al., 2014; Wells et al., 2015; Weinberg et al., 2016; Ohi et al., 2017c). Approximately 30% of SCZ patients have a decline of less than 10 points. In contrast, approximately 70% of SCZ show a deterioration of IQ (Ohi et al., 2017c). The distinct subtypes of ID in patients with SCZ may reflect different courses of neurodevelopmental abnormalities and may be associated with different prognoses.

Cognitive impairments are prominent around or after the onset of schizophrenia, while in a substantial proportion of cases, these impairments exist even before disorder onset (Sheitman et al., 2000; Kremen et al., 2010; Benyamin et al., 2014). First, we hypothesize that cognitive impairments in SCZ patients precede the onset of psychosis by several years, i.e., premorbid IQ is impaired, and the IQ impairment progresses around or after disease onset, i.e., ID. Therefore, diverse molecular mechanisms may underlie the pathophysiology of impaired premorbid IQ and ID. Unaffected first-degree relatives of SCZ patients (FRs) exhibit slight cognitive impairments (Green, 2006; Toulopoulou et al., 2010; Hill et al., 2013), indicating that cognitive impairments occur in a genetic continuum among SCZ patients, FRs and healthy controls (HCs) (Ohi et al., 2017b). These cognitive impairments could be useful intermediate phenotypes for understanding the genetic mechanisms implicated in the pathophysiology of SCZ (Ohi et al., 2017b). However, it is unknown whether the cognitive impairments in FRs are comparable to the impairment in premorbid IQ, the ID, or both, and it remains unclear whether not only SCZ patients but also FRs display both impairments in premorbid IQ and an ID. Second, we hypothesize that HCs and FRs would not display a significant ID between premorbid and present IQ because HCs and FRs do not develop the illness. On the other hand, not all SCZ patients display an ID, as evidenced by the preserved IQ group. Furthermore, it remains unclear which factor contributes to the classification of preserved and deteriorated IQ. To resolve these clinical questions, we utilized cognitive data for SCZ patients and HCs, as well as FRs. In this study, we first investigated diagnostic differences in premorbid and present IQ among SCZ patients, FRs and HCs. We next investigated whether SCZ patients, FRs and HCs display an ID, a decrease in present IQ from the premorbid level. Then, we investigated differences in demographic variables between IQ groups based on the degree of ID.

Table 1. Demographic variables among patients with schizophrenia, their unaffected first-degree relatives and healthy subjects.

Variables	HC ($n=107$)	FR ($n=61$)	SCZ ($n=125$)	p values (F or χ^2)	*post hoc*
Age (years)	39.3 ± 16.5	59.0 ± 14.3	43.0 ± 13.4	**7.94 x 10−15 (36.4)**	HC<FR, FR>SCZ
Gender (male/female)	69/38	22/39	54/71	**3.35 x 10−4 (16.0)**[a]	-
Education (years)	15.7 ± 2.7	12.8 ± 2.2	12.5 ± 2.1	**2.11 x 10−24 (66.2)**	HC>FR, SCZ
CPZ-eq (mg/day)	0	0	488.2 ± 491.4	-	-
Age at onset (years)	-	-	27.9 ± 11.4	-	-
Duration of illness (years)	-	-	15.1 ± 11.7	-	-
PANSS positive symptoms	-	-	15.9 ± 6.2	-	-
PANSS negative symptoms	-	-	17.9 ± 6.9	-	-

HC, healthy controls; FR, unaffected first-degree relatives of patients with schizophrenia; SCZ, patients with schizophrenia; and CPZ-eq; chlorpromazine equivalents of total antipsychotics. The mean ± SD is shown.
[a] χ^2 test. P values<0.05 are shown in boldface and underlined, and *post hoc* analysis was performed.

2. Experimental procedures

2.1. Subjects

The subjects consisted of 125 SCZ patients (54 males/71 females, mean age±SD: 43.0 ± 13.4 years), 61 unaffected FRs (43 parents/14 siblings/4 offspring, 22 males/39 females, 59.0 ± 14.3 years) and 107 HCs (69 males/38 females, 39.3 ± 16.5 years). The study sample was recruited from the Schizophrenia Non-Affected Relative Project (SNARP) at Kanazawa Medical University. All subjects were of Japanese descent. Patients and their unaffected FRs were recruited from both the outpatient and inpatient populations at Kanazawa Medical University Hospital. Each patient was diagnosed by at least two trained psychiatrists based on unstructured clinical interviews, medical records and clinical conferences (Ohi et al., 2016b, 2017a, 2018a, 2018b; Yasuyama et al., 2016). The SCZ patients were diagnosed according to the criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5). Their unaffected FRs were evaluated using the nonpatient version of the Structured Clinical Interview for DSM-IV (SCID) to exclude individuals who had current or past contact with psychiatric services or who had received psychiatric medication. HCs were recruited through local advertisements and from among hospital staff at Kanazawa Medical University and were also evaluated using the nonpatient version of the SCID to exclude individuals who had current or past contact with psychiatric services, who had received psychiatric medication or who had a family history of any neuropsychiatric diseases among 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 intellectual disability. The demographic information of the three diagnostic groups is summarized in Table 1. The mean age, gender ratio and years of education differed significantly among the groups ($p<0.05$). Current clinical symptoms in SCZ patients were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Written informed consent was obtained from all participants after the procedures had been thoroughly explained. This study was performed in accordance with the Declaration of Helsinki from the World Medical Association and was approved by the Research Ethical Committee of Kanazawa Medical University.

2.2. Premorbid and present IQ

The NART is a test that was developed to estimate premorbid IQ because reading ability is relatively intact in SCZ patients (Dalby and Williams, 1986), and its validity has been confirmed in English-speaking SCZ patients (Amminger et al., 2002; Badcock et al., 2005; Schretlen et al., 2007). The Japanese version of the NART (JART, Matsuoka et al., 2006) is widely used to estimate premorbid IQ in Japanese-speaking patients, as an equivalent to the NART (Ohi et al., 2013a, 2013b, 2014, 2015, 2016a, 2016c, 2017a). To measure the premorbid IQ, we administered the JART. In contrast, to measure the present IQ, we measured the full-scale IQ with the Japanese version of the WAIS-III (Wechsler 1997; Sumiyoshi et al., 2016; Fujino et al., 2017; Ohi et al., 2017c). The subjects were assessed by trained psychologists to obtain a full-scale IQ on the WAIS-III.

2.3. ID

ID can be estimated by subtracting the estimated premorbid IQ from the present IQ using the Adult Reading Test and the WAIS, respectively (Badcock et al., 2005; Hashimoto et al., 2013; Sumiyoshi et al., 2016; Fujino et al., 2017; Ohi et al., 2017c). According to the degree of ID, the participants were typically classified into three distinct subgroups based on intellectual level: the deteriorated, preserved and compromised IQ groups (Weickert et al., 2000; Badcock et al., 2005; Kremen et al., 2008; Potter and Nestor, 2010; Leeson et al., 2011; Mercado et al., 2011; Ammari et al., 2014; Wells et al., 2015; Weinberg et al., 2016; Fujino et al., 2017; Ohi et al., 2017c). Subjects who showed a deteriorated IQ elicited $a \geq 10$-point difference between present and premorbid IQ, while subjects who showed a preserved or compromised IQ did not show such a decline (<10-point difference). Furthermore, the latter subjects were divided into subjects with preserved and compromised IQ based on an estimated premorbid IQ score >90 or below 90, respectively.

(a) Deteriorated IQ: Subjects with a difference of 10 points or more between estimated premorbid and present IQ.
(b) Preserved IQ: Subjects with a less than 10-point difference between estimated premorbid and present IQ and with an estimated premorbid IQ score >90.
(c) Compromised IQ: Subjects with a less than 10-point difference between estimated premorbid and present IQ and with an estimated premorbid IQ below 90.

As the compromised IQ subgroup generally includes SCZ patients who have intellectual disability, and subjects who have intellectual disability were excluded from the present study during recruitment, we compared the deteriorated and preserved IQ groups without including the compromised IQ group in further analysis.

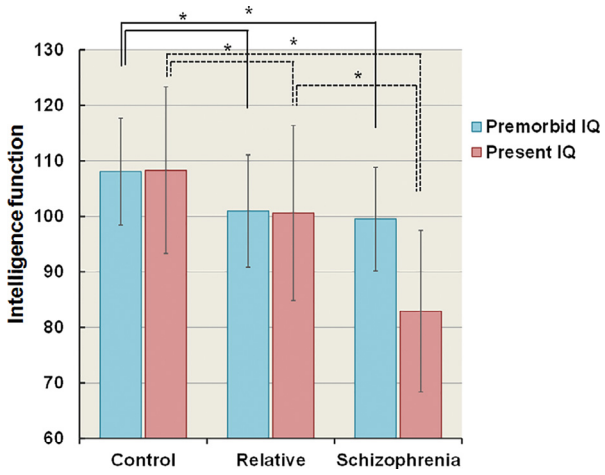

Fig. 1 Estimated premorbid and present IQ among patients with schizophrenia, their unaffected first-degree relatives and healthy subjects. Estimated premorbid and present IQ scores were corrected by age and gender. Error bars represent the standard deviation. *post hoc $p<0.05$.

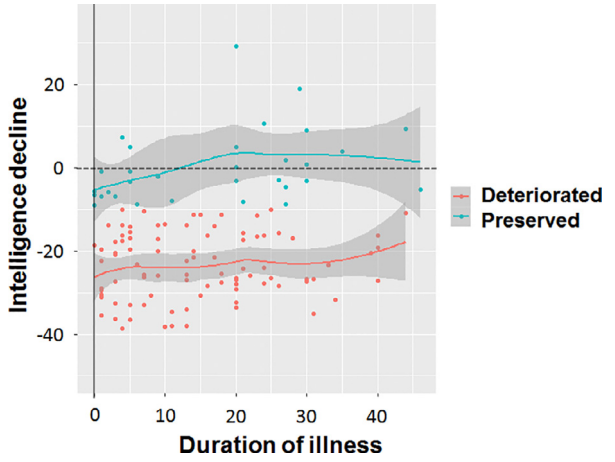

Fig. 2 Relationship between intelligence decline and duration of illness in schizophrenia patients with preserved and deteriorated IQ. The intelligence decline of each patient is shown as a dot. A colored line represents a locally estimated scatterplot smoothing (LOESS) fit across the duration of illness. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4. Statistical analyses

All statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM Japan, Tokyo, Japan). Differences in continuous variables, such as age and years of education, among diagnostic groups were analyzed using analysis of variance (ANOVA). Differences in categorical variables, such as gender, were analyzed using Pearson's χ^2 test. The effects of diagnostic status on premorbid or present IQ were analyzed using analysis of covariance (ANCOVA) with premorbid and present IQ as dependent variables and diagnostic status (SCZ, FR or HC) as an independent variable. The effect of ID classification on years of education was analyzed using ANCOVA, with years of education as a dependent variable and ID classification (preserved and deteriorated IQ groups) as an independent variable. Age and gender were included as covariates in both analyses, although the present IQ score had already been corrected for age. *Post hoc* tests with Fisher's Least Significant Difference (LSD) test were used to evaluate significant differences among groups. The ID between premorbid and present IQ in each diagnostic group was assessed using a paired *t*-test. Standardized effects were calculated using Cohen's *d* method (http://www.uccs.edu/faculty/lbecker). The significance level was set at a two-tailed $p<0.025$ ($\alpha=0.05/2$; premorbid and present IQ) to control for type I error.

3. Results

3.1. Differences in premorbid and present IQ among SCZ patients, FRs and HCs

We investigated diagnostic differences in premorbid and present IQ among SCZ patients, FRs and HCs. There was a significant difference in premorbid IQ among the diagnostic groups (Fig. 1, $F_{2,288}=24.3$, $p=1.77\times10^{-10}$). *Post hoc* analyses showed that SCZ patients and FRs had lower premorbid IQ than HCs (SCZ, Cohen's $d=-0.90$, $p=4.21\times10^{-11}$, FR, $d=-0.72$, $p=2.83\times10^{-5}$). There was no significant difference in premorbid IQ between SCZ patients and FRs ($d=-0.15$, $p=0.36$). Premorbid IQ is highly and positively correlated with years of education (Pearson's $r=0.49$, $p=6.25\times10^{-19}$); however, even after including years of education as a covariate in the ANCOVA, these findings did not change. We also found significant differences in present IQ among the diagnostic groups (Fig. 1, $F_{2,288}=91.2$, $p=2.13\times10^{-31}$). *Post hoc* analyses showed that SCZ patients and FRs had lower present IQ than HCs (SCZ, $d=-1.72$, $p=6.24\times10^{-31}$, FR, $d=-0.50$, $p=3.41\times10^{-3}$). In addition, SCZ patients had significantly impaired present IQ compared to that of FRs ($d=-1.17$, $p=3.35\times10^{-12}$). Present IQ in FRs showed an intermediate impairment, with scores between those of SCZ patients and HCs.

3.2. ID in SCZ patients, FRs and HCs

We next investigated ID, a decrease in present IQ from the premorbid level, in SCZ patients, FRs and HCs. Premorbid IQ was significantly and positively correlated with present IQ in each group (SCZ, $r=0.69$, $p=3.61\times10^{-19}$, FR, $r=0.69$, $p=1.12\times10^{-9}$, HC, $r=0.57$, $p=1.65\times10^{-10}$). We found that SCZ patients showed a significant ID between premorbid and present IQ (Fig. 1, $t=14.4$, $p=2.48\times10^{-28}$). In contrast, there was no significant ID between premorbid and present IQ in FRs or HCs ($p>0.05$).

3.3. Subjects with preserved and deteriorated IQ

Based on the degree of ID, patients were classified into two groups: patients with preserved ($n=31$, mean ID±SD: 0.01±8.72) and deteriorated IQ ($n=90$, −23.58±7.98). Patients with compromised IQ ($n=4$) were excluded from further analysis, as mentioned in the Materials and Methods section. As shown in Fig. 2, the ID was not correlated with the duration of illness in patients with preserved or deteriorated IQ. The ID in each IQ group was relatively stable over time. We investigated differences in demographic

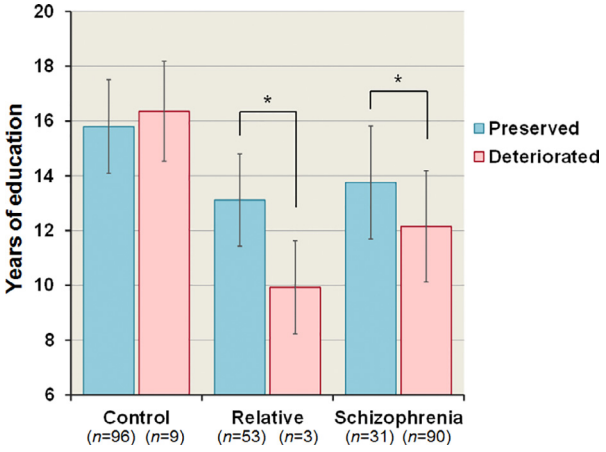

Fig. 3 Years of education in the preserved and deteriorated IQ groups among patients with schizophrenia, their unaffected first-degree relatives and healthy subjects. The years of education were corrected by age and gender. Error bars represent the standard deviation. $^{*}p<0.05$.

variables between SCZ patients with preserved and deteriorated IQ (Table 2). Patients with preserved IQ were significantly older, with more years of education and fewer chlorpromazine equivalents of total antipsychotics (CPZ-eq) than patients with deteriorated IQ ($p<0.05$). There were no differences in age at onset, duration of illness or psychiatric symptoms ($p>0.05$). Even after including age, gender and CPZ-eq as covariates, the ID classification was significantly associated with years of education (Fig. 3, $F_{1,116}=13.4$, $p=3.73\times10^{-4}$). Patients with preserved IQ had more years of education than those with deteriorated IQ.

We also classified FRs and HCs into two ID groups: FR: preserved ($n=53$, mean ID±SD: 3.38±8.72) and deteriorated ($n=3$, −23.20±8.58); HC: preserved ($n=96$, 0.68±6.27) and deteriorated ($n=9$, −17.00±6.89). As most FRs and HCs did not display ID, the number of subjects with deteriorated IQ in the FR and HC groups was obviously smaller than that in the SCZ group. However, consistent with the results obtained for SCZ patients, FRs with preserved IQ had more years of education than FRs with deteriorated IQ (Fig. 3, $F_{1,52}=8.6$, $p=4.91\times10^{-3}$). In contrast, there was no difference in years of education between HCs with preserved and deteriorated IQ ($F_{1,101}=0.9$, $p=0.35$).

4. Discussion

To our knowledge, this is the first study to comprehensively investigate premorbid and present intelligence levels and the decline in those levels among SCZ patients, FRs and HCs. Both premorbid and present IQ were lower in SCZ patients and FRs than in HCs. There was no significant difference in premorbid IQ between SCZ patients and FRs, while present IQ was lower in SCZ patients than in FRs. The different findings related to premorbid and present IQ in SCZ and FR were derived from the ID. Our findings suggest that the impaired premorbid IQ in SCZ patients decreases further around or after the onset of schizophrenia.

We demonstrated that there is an IQ deterioration beyond the premorbid deficit in SCZ patients, and unaffected FRs did not exhibit an ID because they had no onset of illness. Individuals who develop schizophrenia in adulthood exhibit IQ deficits in childhood relative to HCs (Agnew-Blais et al., 2015). These premorbid IQ impairments are evident by age 13 years, many years prior to psychosis onset (Dickson et al., 2012). Although poor intellectual function is a robust risk factor for SCZ, it remains unclear whether the IQ impairment is present at birth, whether a relative developmental decline occurs at some point prior to the onset of illness and when during the illness course the ID in SCZ patients occurs. Meta-analytic studies have indicated no evidence of ID with age during the premorbid period (Woodberry et al., 2008; Khandaker et al., 2011). In contrast, some studies found a significant ID from the premorbid to postonset stages in SCZ samples compared to comparison subjects (Caspi et al., 2003; Seidman et al., 2006; Woodberry et al., 2008). Based on our finding that FRs displayed an impairment in premorbid IQ but did not exhibit an ID, we suggest that the ID might be related to the onset of illness and occur around the time of onset.

We found a moderate effect size for impairment in premorbid IQ (Cohen's $d=-0.90$) and a large effect size for impairment in present IQ ($d=-1.72$) in SCZ patients compared to HCs. The effect size for the present IQ was approximately double the effect size for the premorbid IQ. Compared with the effect sizes for premorbid IQ in previous meta-analyses

Table 2. Demographic variables in schizophrenia patients with preserved and deteriorated IQ.

Variables	Preserved ($n=31$)	Deteriorated ($n=90$)	p values (F or χ^2)
Age (years)	46.7 ± 12.3	41.1 ± 12.8	**0.034 (4.6)**
Gender (male/female)	17/14	37/53	0.19 (1.8)[a]
Education (years)	13.5 ± 2.0	12.2 ± 2.1	**5.30 × 10−3 (8.1)**
CPZ-eq (mg/day)	331.9 ± 302.7	543.1 ± 540.1	**0.041 (4.3)**
Age at onset (years)	29.4 ± 11.9	26.5 ± 10.2	0.19 (1.7)
Duration of illness (years)	17.0 ± 13.7	14.6 ± 11.1	0.32 (1.0)
PANSS positive symptoms	14.6 ± 6.6	16.1 ± 6.0	0.23 (1.4)
PANSS negative symptoms	15.8 ± 6.3	18.4 ± 7.0	0.067 (3.4)

CPZ-eq; chlorpromazine equivalents of total antipsychotics. The mean ± SD is shown.
[a] χ^2 test. P values<0.05 are shown in boldface and underlined.

(d=−0.43 to −0.54) (Woodberry et al., 2008; Khandaker et al., 2011), the effect size for premorbid IQ in this study was large (d=−0.90). The present study recruited only SCZ patients, while the previous meta-analyses included not only SCZ but also related disorders, such as schizophreniform, schizoaffective, schizotypal and other psychotic disorders. In addition, we estimated premorbid IQ after the onset of SCZ, while these previous studies measured IQ during the premorbid period before onset. These differences in subjects and methods for measuring premorbid IQ might have caused the differences in effect size for premorbid IQ among studies. Considering our finding that FRs also showed impairments in premorbid IQ, i.e., intellectual underperformance, the degree of premorbid IQ may be, at least in part, related to the genetic risk for developing SCZ.

Although intellectual underperformance precedes the onset of illness, and the ID occurs around the time of onset, it is unclear whether the ID continues and develops even after psychosis onset. Based on the degree of ID, our subjects were classified into two groups: (i) preserved IQ with a less than 10-point difference between premorbid and present IQ and premorbid IQ score >90, and (ii) deteriorated IQ with $a \geq$ 10-point difference between present and premorbid IQ. As most FRs and HCs did not display a significant ID, the number of subjects with a deteriorated IQ in the FR (4.9%) and HC (8.4%) groups was obviously smaller than that in the SCZ (72.0%) group. Consistent with previous studies (Keefe and Fenton, 2007; Ohi et al., 2017c), approximately 30% of SCZ patients were cognitively intact (preserved IQ group). A meta-analysis of studies with at least two intelligence assessments once the diagnosis was established indicated that SCZ is characterized by a lack of increases in cognitive abilities over time, possibly due to the absence of a practice effect (Hedman et al., 2013). We showed that the degree of ID was not correlated with the duration of illness in SCZ patients with deteriorated or preserved IQ, suggesting that the ID is stable over time after the onset of illness, although this correlation was not assessed within the same subjects. To identify the key period for the ID, further studies with more frequent assessment of IQ through the premorbid, prodromal, early and chronic phases of illness are required.

Consistent with previous studies (Leeson et al., 2011; Wells et al., 2015), the ID classification (preserved and deteriorated IQ groups) in SCZ patients was differentiated mainly based on education level but not based on symptom profile, medication age at onset or duration of illness. SCZ patients with preserved IQ showed a higher education level than SCZ patients with deteriorated IQ. Additionally, FRs with preserved IQ also had higher educational attainment than FRs with deteriorated IQ. Poor school achievement and poor school performance at age 16 are associated with an increased risk for developing SCZ (MacCabe et al., 2008). Children with the lowest grades have a 4-fold risk for SCZ, and repeating a grade carries the highest risk for SCZ (MacCabe et al., 2008; Kahn and Keefe, 2013; Kendler et al., 2016). Given that educational attainment is associated with present IQ, premorbid IQ and ID, educational attainment is a meaningful indicator for functional outcome in patients with SCZ. We suggest that higher educational attainment may be protective in SCZ, probably by increasing active cognitive reserve.

There are some limitations to the interpretations of our findings. The participants in the FR group had familial relationships with the participants in the SCZ group. Shared genetics, irrespective of the risk for SCZ, might also affect intelligence function and the familial relationship between FRs and SCZ patients. The mean scores in both premorbid and present IQ among HCs were above the standard mean score for IQ (100). The mean scores in both premorbid and present IQ among FRs were almost exactly 100. The higher IQ of HCs may be reflected by higher educational attainment among our hospital staff. FRs and SCZ patients with higher educational attainment usually visit university hospitals to receive advanced medical treatments. Therefore, most of our participants might have higher educational attainment than the general population. Initially, we did not control for educational level, as it strongly affected premorbid and present IQ; however, our findings were still significant even after correcting for educational level. Intellectual underperformance prior to psychosis has not been definitively shown to be specific to SCZ. Several psychiatric disorders other than SCZ also exhibit impairments in premorbid IQ (Koenen et al., 2009; Urfer-Parnas et al., 2010). However, the premorbid IQ level could distinguish individuals who later develop SCZ from individuals who later develop other major psychotic disorders, such as bipolar disorder.

In this study, using unaffected FRs, we demonstrated that intellectual underperformance in SCZ patients and FRs precedes the onset of schizophrenia, and ID occurs around the time of onset in SCZ patients but not FRs. These impairments in premorbid and present IQ and ID would be expected on the basis of the level of education. Educational attainment related to these intelligence functions is an important predictor of general functional outcomes in patients with SCZ. Current treatment strategies, including cognitive remediation and psychopharmacology, largely fail to ameliorate intelligence impairments in SCZ patients (Keefe et al., 2013). A better understanding of the pathogenesis underlying intelligence impairments is required to develop more efficient treatment strategies for SCZ.

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Contributors

K. Ohi supervised the entire project, collected the data, wrote the manuscript and was critically involved in the design, analysis and interpretation of the data. K. Ohi and T. Shimada were responsible for performing the literature review. T. Shimada, Y. Kataoka, Y. Koide, K. Yasuyama, T. Uehara, H. Okubo, and Y. Kawasaki were heavily involved in

the collection of the majority of the data and intellectually contributed to data interpretation. All authors contributed to and approved the final manuscript.

Conflicts of interest

None.

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