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REGULAR RESEARCH ARTICLE

Polygenic Risk Scores Differentiating Schizophrenia From Bipolar Disorder Are Associated With Premorbid Intelligence in Schizophrenia Patients and Healthy Subjects

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Abstract

Background: Impairments in intelligence are more severe in patients with schizophrenia (SCZ) than in patients with bipolar disorder (BD) despite clinical and genetic similarities between the disorders. Genetic loci differentiating SCZ from BD, that is, SCZ-specific risk, have been identified. Polygenetic [risk] scores (PGSs) for SCZ-specific risk are higher in SCZ patients than in healthy controls (HCs). However, the influence of genetic risk on impaired intelligence is poorly understood. Here, we investigated whether SCZ-specific risk could predict impairments in intelligence in SCZ patients and HCs.

Methods: Large-scale genome-wide association study datasets related to SCZ vs BD, childhood intelligence (CHI), and adulthood intelligence ($n = 12\,441$–$282\,014$) were utilized to compute PGSs. PGSs derived from the genome-wide association studies were calculated for 130 patients with SCZ and 146 HCs. Premorbid and current intelligence and the decline were measured in SCZ patients and HCs. Correlations between PGSs and intelligence functions were investigated.

Results: High PGSs for SCZ-specific risk were correlated with low premorbid intelligence in SCZ patients and HCs ($\beta = -0.17$, $P = 4.12 \times 10^{-3}$). The correlation was still significant after adjusting for diagnostic status ($\beta = -0.13$, $P = .024$). There were no significant correlations between PGSs for SCZ-specific risk and current intelligence or intelligence decline ($P > .05$). PGSs for CHI were lower in SCZ patients than in HCs ($R2 = 0.025$, $P = .025$), while the PGSs for CHI were not significantly correlated with premorbid and current intelligence, the decline, or the PGSs for SCZ-specific risk ($P > .05$).

Conclusions: These findings suggest that genetic factors differentiating SCZ from BD might affect the pathogenesis of SCZ and/or pathological differences between SCZ and BD via the impairment of premorbid intelligence, that is, crystallized intelligence, while genetic factors for CHI might affect the pathogenesis of SCZ but not via impairments in intelligence.

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Significance Statement

- High polygenic risk scores differentiating schizophrenia from bipolar disorder were correlated with low premorbid intelligence in patients with schizophrenia and healthy controls.
- Polygenic scores for childhood intelligence were lower in schizophrenia patients than in healthy controls.
- Polygenic scores for childhood intelligence were not correlated with premorbid and current intelligence or the decline.
- Polygenic risk scores differentiating schizophrenia from bipolar disorder and polygenic scores for childhood intelligence were independently associated with the risk of schizophrenia.
- Genetic factors differentiating schizophrenia from bipolar disorder might affect the pathogenesis of schizophrenia and/or pathological differences between schizophrenia and bipolar disorder by impairing premorbid intelligence.

Key Words: Bipolar disorder, childhood intelligence, polygenic risk score, premorbid IQ, schizophrenia

Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are common psychiatric disorders with a lifetime prevalence of approximately 1%. SCZ and BD are the leading causes of years lived with disability worldwide (Whiteford et al., 2013), and these disorders impose substantial economic burdens on society (Cloutier et al., 2016; Bessonova et al., 2020). Cognitive impairments, including impaired intelligence, are a core feature of SCZ and BD (Schaefer et al., 2013; Trotta et al., 2015; Solé et al., 2016; Ohi et al., 2019). In addition, cognitive impairments are, to a lesser degree, found in unaffected first-degree relatives of SCZ and BD patients (Glahn et al., 2010; Ohi et al., 2019; de Zwarte et al., 2020; Kataoka et al., 2020). Cognitive impairments are relatively independent of psychotic (positive and negative) and manic symptoms, and cognitive impairments result in poor functional outcomes, such as social and occupational dysfunction (Green et al., 2000; Jaeger et al., 2007; Kahn and Keefe 2013). Patients with SCZ and BD display impairments in premorbid intelligence as well as in current intelligence, which involves a decline in intelligence from the premorbid level (Trotta et al., 2015; Ohi et al., 2019; Vaskinn et al., 2020). In particular, impairments in intelligence are more prominent in SCZ patients than in BD patients (de Zwarte et al., 2020).

SCZ and BD are highly heritable, with an estimated heritability of approximately 80% (Sullivan et al., 2003; Nöthen et al., 2010). Large-scale genome-wide association studies (GWASs) for SCZ and BD have been performed by the Psychiatric Genomics Consortium (PGC) to reveal genomic risk loci for these disorders (Ripke et al., 2014; Stahl et al., 2019). These GWASs successfully identified 108 and 30 independent loci for SCZ risk and BD risk, respectively. SCZ and BD show high degrees of polygenicity and have high genetic overlap (r_g=0.7–0.8) derived from common genetic variants [single nucleotide polymorphisms (SNPs)] (Stahl et al., 2019; Ohi et al., 2020c). Despite clinical and genetic similarities between disorders and a long argument about unitary psychosis, the current diagnostic criteria (DSM-5) adhere to the historical distinctions between SCZ and BD that have been used since the late 19th century. Therefore, we are beginning to untangle the common biology that links supposedly distinct psychiatric conditions (Marshall, 2020).

The SCZ and BD working groups of the PGC have identified 2 genome-wide significant loci differentiating SCZ from BD (SCZ vs BD), that is, disorder-specific genetic loci (Ruderfer et al., 2018). Because low intelligence is genetically correlated only with risk for SCZ (r_g=0.2) but not with risk for BD (Ohi et al., 2018; Toulopoulou et al., 2019), several researchers have investigated whether polygenetic susceptibility to SCZ or BD is associated with cognitive function (Nakahara et al., 2018; Shafee et al., 2018; Xavier et al., 2018; Comes et al., 2020; Engen et al., 2020; Kępińska et al., 2020; Richards et al., 2020). However, the findings were inconsistent among studies. Some studies have found that the polygenic [risk] scores (PGSs) for SCZ were associated with general cognitive deficits in healthy individuals (Shafee et al., 2018; Kępińska et al., 2020) and impairments in several cognitive domains in SCZ patients and healthy controls (HCs) (Nakahara et al., 2018), while other studies have reported that PGSs for SCZ or BD were not associated with any cognitive functions in SCZ patients, BD patients, or HCs (Xavier et al., 2018; Comes et al., 2020; Engen et al., 2020; Richards et al., 2020). We have demonstrated that PGSs differentiating SCZ from BD, that is, SCZ-specific genetic factors, are associated with case-control status in SCZ patients and HCs (Ohi et al., 2020b). In contrast, to the best of our knowledge, it is unknown whether the PGSs for SCZ-specific risk are associated with individual intelligence-related phenotypes. Further understanding the genetic factors differentiating SCZ from BD using intelligence-related phenotypes could be key to understanding the etiology of both disorders.

We hypothesized that genetic variants for SCZ-specific risk would be associated with impairments in intelligence. The present study investigated the associations of PGSs differentiating SCZ from BD based on GWASs with intelligence functions (premorbid intelligence, current intelligence, and intelligence decline) in SCZ patients and HCs. To further reveal the genetic relationship between the PGSs for SCZ-specific risk and intelligence, we explored whether PGSs for childhood and adulthood intelligence are associated with impairments in intelligence and PGSs for SCZ-specific risk in SCZ patients and HCs.

METHODS

Discovery Samples

To identify genetic variants related to SCZ-specific risk, childhood intelligence (CHI), and adulthood intelligence; *P* values; and effect sizes such as odds ratio (OR), beta, or z-score, we used publicly available GWAS datasets comparing SCZ and BD (Ruderfer et al., 2018) and datasets for CHI (Benyamin et al., 2014) and adulthood intelligence (Davies et al., 2018) as discovery samples. GWAS summary statistics on these phenotypes from the PGC, the Social Science Genetic Association Consortium, including the CHI Consortium, and the Center

for Cognitive Ageing and Cognitive Epidemiology at the University of Edinburgh, were available in public databases (PGC, https://www.med.unc.edu/pgc/results-and-downloads; Social Science Genetic Association Consortium, https://www.thessgac.org/data, and Center for Cognitive Ageing and Cognitive Epidemiology, http://www.ccace.ed.ac.uk/node/335).

The PGC performed a GWAS comparing SCZ and BD patients to find a disorder-specific risk in 23 585 independent SCZ patients and 15 270 BD patients of European ancestry (Ruderfer et al., 2018). The CHI Consortium performed a GWAS for CHI in 12 441 children of European ancestry (Benyamin et al., 2014). These children were aged between 6 and 18 years. CHI is assessed using the best available measure of general cognitive ability (*g*) or intelligence quotient (IQ) derived from diverse tests that assess both verbal and nonverbal ability. The Cohorts for Heart and Aging Research in Genomic Epidemiology, the Cognitive Genomics Consortium, and the UK Biobank performed a GWAS for adulthood intelligence in 282 014 population-based individuals of European ancestry (Davies et al., 2018). The population-based individuals were aged between 16 and 102 years. Patients with clinical stroke or prevalent dementia were excluded. Adulthood intelligence was measured as a *g* component constructed from multiple cognitive tasks in the cohorts of the Cohorts for Heart and Aging Research in Genomic Epidemiology and Cognitive Genomics Consortium consortia. Adulthood intelligence in the UK Biobank was assessed by verbal and numerical reasoning ("fluid" cognitive test) consisting of 13 multiple-choice questions. A detailed description of the sample information, genotyping, processing, quality control, and imputation procedures applied in each discovery GWAS sample was provided previously (Benyamin et al., 2014; Davies et al., 2018; Ruderfer et al., 2018).

Target Sample

One hundred-thirty patients with SCZ (mean age ± SD: 42.7 ± 13.1 years, 50 males/80 females) and 146 HCs (37.2 ± 14.1 years, 97 males/49 females) composed the target sample. The demographic information of these participants is summarized in Table 1. All these individuals participated in our previous studies (Ohi et al., 2020a, 2020b). The target sample was recruited from the Schizophrenia Non-Affected Relative Project (Ohi et al., 2019, 2020a, 2020b). All participants were of Japanese descent and had no biological first- or second-degree relatives. A detailed description of participant recruitment and diagnosis was provided previously (Ohi et al., 2019, 2020a, 2020b). Briefly, each patient was diagnosed based on unstructured clinical interviews, medical records, and clinical conferences according to the criteria in the DSM-5. HCs were evaluated using the Structured Clinical Interview for DSM-IV-Non-Patient version. Written informed consent was obtained from all participants after the procedures had been thoroughly explained. This study was performed in accordance with the World Medical Association's Declaration of Helsinki and was approved by the Research Ethics Committees of Gifu University and Kanazawa Medical University.

A detailed description of the genotyping, quality control, and imputation procedures applied in the target sample was provided previously (Ohi et al., 2020a, 2020b). Briefly, venous blood was collected from the target participants, and genomic DNA was extracted from whole blood samples. Genotyping was performed using the Infinium OmniExpressExome-8 v1.4 BeadChip (Illumina, San Diego, CA). Genotype imputation was performed using the 1000 Genomes Project Phase 3 dataset (https://mathgen.stats.ox.ac.uk/impute/1000GP_Phase3.html; Auton et al., 2015) as a reference panel. For the PGS analysis, SNPs with high imputation quality (>0.9) were retained. To remove SNPs that were in linkage disequilibrium, the SNPs in the target sample were pruned based on a pairwise r^2 threshold of 0.25 and a window size of 200 SNPs using PLINK v1.9 as described previously (Ohi et al., 2020a, 2020b). After pruning, 1 354 311 independent SNPs remained. As the PGSs for SCZ-specific risk at a liberal significance threshold ($P_{T\ cutoff} \leq .05$) were significantly higher in patients with SCZ than in HCs (Ohi et al., 2020b), PGSs constructed from SNPs showing a nominal association with SCZ-specific risk, CHI, and adulthood intelligence in the discovery GWASs were calculated according to $P_{T\ cutoff} \leq .05$ in the present study. For each individual included in the target sample, a PGS was calculated by weighting the scores for the "risk SNPs" by the logarithm of the OR or the OR converted from the beta or z-score (logOR) observed in each discovery dataset. The score, consisting of the number of risk alleles (0, 1, or 2) multiplied by the logOR, was summed over all the SNPs at $P_{T\ cutoff} \leq .05$ for each individual in the target sample.

Table 1. Demographic Information of the Target Sample

Variables	Schizophrenia (*n* = 130)	Healthy control (*n* = 146)	*P* values (*F*)
Age (y)	42.7 ± 13.1	37.2 ± 14.1	**8.37×10^{-4} (11.4)**
Sex (male/female)	50/80	97/49	**3.32×10^{-6} (21.6)**[a]
Education (y)	12.6 ± 2.2	16.1 ± 2.4	**1.38×10^{-28} (155.6)**
Estimated premorbid intelligence	99.1 ± 10.6	108.5 ± 7.6	**1.13×10^{-15} (72.5)**
Current intelligence	82.8 ± 18.5	107.8 ± 9.2	**3.40×10^{-27} (154.9)**
Intelligence decline	−16.4 ± 13.1	−0.8 ± 8.4	**8.95×10^{-21} (107.9)**
CPZ-eq. (mg/d)	509.6 ± 512.7	0	–
Age at onset (y)	26.9 ± 10.6	–	–
Duration of illness (y)	15.8 ± 11.3	–	–
PANSS positive symptoms	16.0 ± 6.2	–	–
PANSS negative symptoms	17.8 ± 6.8	–	–

Abbreviations: CPZ-eq., chlorpromazine equivalent of total antipsychotics; PANSS, Positive and Negative Syndrome Scale. The mean ± SD and *P* values are shown. The significant *P* values ($P < .05$) are shown in bold and underlined. Complete demographic information was not obtained from all participants (estimated premorbid intelligence in healthy controls, $n = 145$; current intelligence and intelligence decline in schizophrenia, $n = 115$; current intelligence and intelligence decline in healthy controls, $n = 104$). [a]$\chi 2$ test.

To estimate premorbid intelligence, the National Adult Reading Test (NART), in which participants have to read and pronounce 50 words, was developed because word-reading ability is relatively intact in SCZ patients (Dalby and Williams, 1986). The Japanese version of the NART (Matsuoka et al., 2006) has been widely used to estimate premorbid intelligence in Japanese-speaking SCZ patients (Ohi et al., 2015, 2017a, 2017b, 2019), and we administered the Japanese version of the NART to measure premorbid intelligence in the target sample. To measure current intelligence, we administered the full-scale Japanese version of the Wechsler Adult Intelligence Scale (WAIS)-III (Wechsler 1997; Sumiyoshi et al., 2016; Fujino et al., 2017; Ohi et al., 2017b, 2019). The full-scale WAIS-III was assessed by trained psychologists. Premorbid and current intelligence were corrected for the covariates of age and sex by applying linear regression to the overall group and taking the unstandardized residuals of the intelligence, although the current intelligence score had already been corrected for age. For each participant, the unstandardized residual was added to the intercept + $beta_i \times mean_i$, where $_i$ represents the different covariates. Therefore, we used age- and sex-corrected premorbid and current intelligence. Intelligence decline was estimated by subtracting the age- and sex-corrected estimated premorbid intelligence from the age- and sex-corrected current intelligence (Badcock et al., 2005; Hashimoto et al., 2013; Sumiyoshi et al., 2016; Fujino et al., 2017; Ohi et al., 2017b, 2019).

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM Japan, Tokyo, Japan) and R 3.6.1 (http://www.r-project.org/). Regarding demographic variables, continuous variables, such as age, were analyzed using parametric ANOVA, and the differences in categorical variable, such as sex, were analyzed using Pearson's χ^2 test. To examine whether PGSs for SCZ-specific risk could predict premorbid intelligence, current intelligence, and intelligence decline, we performed linear regression with intelligence as a dependent variable, PGSs for SCZ-specific risk as the independent variable, and diagnostic status (SCZ patient or HC) and years of education as covariates. Furthermore, linear or logistic regression models with intelligence or diagnostic status as a dependent variable and PGSs for CHI or adulthood intelligence as an independent variable were explored. As the intelligence decline was derived from the subtraction of premorbid from current intelligence, these phenotypes were correlated with each other and were not independent. Therefore, the significance level was set at a 2-tailed $P < .025$ ($\alpha = .05/2$; premorbid and current intelligence) to control for type I error.

RESULTS

Effects of PGSs for SCZ-Specific Risk on Impairments in Intelligence in Patients With SCZ and HCs

We investigated the associations of PGSs differentiating SCZ from BD (SCZ vs BD, i.e., SCZ-specific risk) with premorbid and current intelligence and intelligence decline in patients with SCZ and HCs. Of the intelligence-related phenotypes, the PGSs for SCZ-specific risk were significantly negatively correlated with premorbid intelligence in patients with SCZ and HCs (Figure 1). High PGSs for SCZ-specific risk were correlated with low premorbid intelligence in SCZ patients and HCs ($\beta = -0.17$, $P = 4.12 \times 10^{-3}$). As we previously demonstrated (Ohi et al., 2019, 2020b), patients with SCZ displayed lower premorbid intelligence than HCs ($\beta = -0.38$, $p = 5.57 \times 10^{-11}$), and PGSs for SCZ-specific risk were higher in SCZ patients than in HCs (Nagelkerke's $R^2 = 0.12$, $P = .046$) (Figure 1). Diagnostic status did not significantly impact the correlation between the PGSs and premorbid intelligence ($P > .05$). Certainly, the correlation was still significant even after correcting for diagnostic status ($\beta = -0.13$, $P = .024$) as well as years of education ($\beta = -0.13$, $P = .019$) as covariates. In contrast, there were no significant correlations between the PGSs

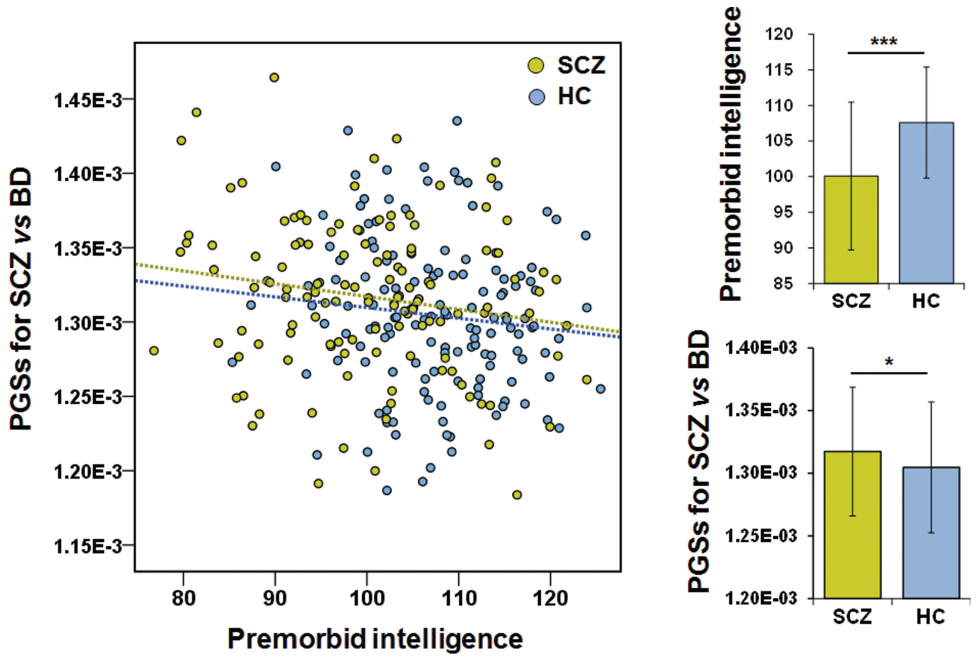

Figure 1. Correlation between polygenic scores (PGSs) differentiating schizophrenia (SCZ) from bipolar disorder (BD) (SCZ vs BD, i.e., SCZ-specific risk) and premorbid intelligence in patients with SCZ and healthy controls (HCs). $^{***}P < .001$, $^{**}P < .01$, $^{*}P < .05$.

for SCZ-specific risk and current intelligence or intelligence decline ($P > .05$).

Effects of PGSs for CHI and Adulthood Intelligence on the Risk of SCZ and Premorbid Intelligence in Patients With SCZ and HCs

As shown in Figure 2, the premorbid intelligence was not correlated with age in patients with SCZ or HCs ($P > .05$). The premorbid intelligence, that is, crystallized intelligence, was relatively stable during middle adulthood. In contrast, crystallized intelligence continues to develop from childhood to middle adulthood (Barbey, 2018).

To reveal the genetic factors underlying premorbid intelligence, we further investigated whether PGSs for CHI (aged between 6 and 18 years) and adulthood intelligence (in individuals aged between 16 and 102 years) would be associated with the levels of risk for SCZ as well as premorbid intelligence in patients with SCZ and HCs. PGSs obtained from GWAS for CHI were significantly lower in patients with SCZ than in HCs (Figure 3; Nagelkerke's $R^2 = 0.025$, $P = .025$), while the PGSs for CHI were not significantly correlated with premorbid intelligence or PGSs for SCZ-specific risk (Figure 3; $P > .05$). In addition, there were no significant correlations between the PGSs for adulthood intelligence and the risk of SCZ or intelligence ($P > .05$). The risk of SCZ was independently affected by PGSs for SCZ-specific risk ($P = .029$) and PGSs for CHI ($P = .016$) (Nagelkerke's $R^2 = 0.048$).

Discussion

The present study investigated for the first time, to our knowledge, whether PGSs differentiating SCZ from BD are correlated with individual intelligence-related phenotypes—premorbid intelligence, current intelligence, and intelligence decline—in patients with SCZ and HCs. Of the intelligence-related phenotypes, high PGSs differentiating SCZ from BD significantly predicted low premorbid intelligence in patients with SCZ and HCs. The finding was still significant even after adjusting for case-control status and years of education. There were no significant correlations between the PGSs differentiating SCZ from BD and current intelligence or intelligence decline. In contrast, the PGSs differentiating SCZ from BD were not correlated with the PGSs for CHI or the PGSs for adulthood intelligence. These findings suggest that genetic factors differentiating SCZ from BD might affect the pathogenesis of SCZ and/or pathological differences between SCZ and BD through their effects on impairment in premorbid intelligence.

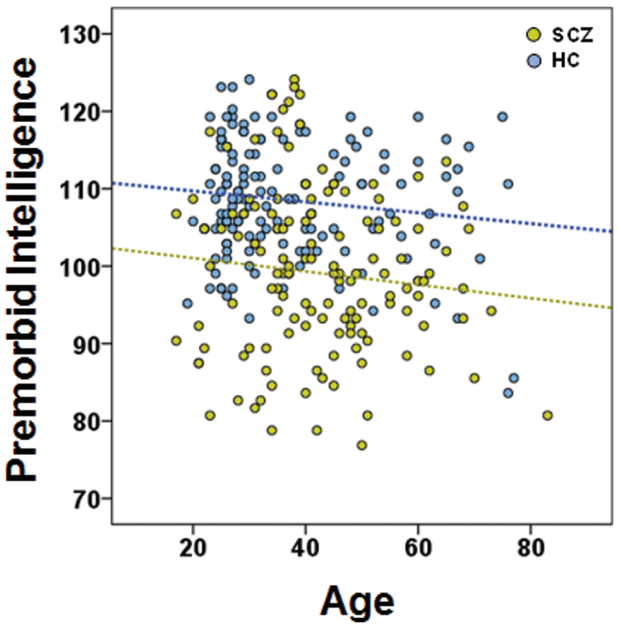

Figure 2. Relationship between premorbid intelligence and aging in patients with schizophrenia (SCZ) and healthy controls (HCs). Age- and sex-uncorrected premorbid intelligence is shown.

Although the results from neuropsychological tests are rarely available before the onset of SCZ, instruments for estimating the levels of premorbid intelligence have been established. Crystallized intelligence assessed by the NART and the Wechsler Test of Adult Reading compared with fluid intelligence assessed by full-scale intelligence on the WAIS remains intact even after the onset of SCZ (Dykiert and Deary 2013; Wells et al., 2015; Ohi et al., 2017b). Therefore, crystallized intelligence has been used to estimate premorbid intelligence. Crystallized intelligence tends to increase with age and is relatively stable during adulthood (Barbey, 2018), while fluid intelligence is affected by aging, peaks at approximately age 20 years, and then gradually declines (Lee et al., 2005). CHI is affected by developmental processes, whereas adulthood intelligence declines progressively with age. Premorbid intelligence in SCZ patients may be between CHI and adulthood intelligence. Therefore, we examined whether premorbid intelligence is affected by PGSs for CHI or PGSs for adulthood intelligence, which were mainly derived from fluid intelligence (Benyamin et al., 2014; Davies et al., 2018). However, there were no correlations between premorbid intelligence and PGSs for CHI or adulthood intelligence, suggesting that crystallized intelligence and fluid intelligence might be influenced by different genetic bases.

We demonstrated for the first time, to our knowledge, that PGSs for CHI were lower in SCZ patients than in HCs. Epidemiological studies have indicated that a lower CHI is associated with a higher risk of developing SCZ, while a higher CHI is associated with a higher risk of developing BD (Koenen et al., 2009; Agnew-Blais et al., 2015). On the other hand, patients with SCZ and BD show lower premorbid intelligence than HCs (Crawford et al., 1987; Ohi et al., 2019; Vaskinn et al., 2020). The discrepancy between higher CHI and lower premorbid intelligence in BD patients may be due to intelligence declines from CHI levels at premorbid and prodromal periods during adolescence and young adulthood. These findings attracted our interest in exploring whether PGSs for CHI are correlated with PGSs differentiating SCZ from BD. However, the PGSs for CHI were not correlated with PGSs for SCZ-specific risk. PGSs for SCZ-specific risk and PGSs for CHI were independently associated with case-control status in patients with SCZ and HCs. These findings suggest that genetic factors differentiating SCZ from BD might affect the risk for SCZ via impairments in premorbid intelligence but not CHI, while genetic factors for CHI might affect the pathogenesis of SCZ but not via impaired premorbid and current intelligence or intelligence decline.

Previous studies investigated associations between PGSs for SCZ and premorbid intelligence in patients with SCZ and HCs as well as a large population-based cohort (Shafee et al., 2018; Engen et al., 2020). These studies found that the PGSs for SCZ were not associated with premorbid intelligence in patients with SCZ or HCs. In contrast, several studies demonstrated that the PGSs for SCZ were associated with current cognitive abilities

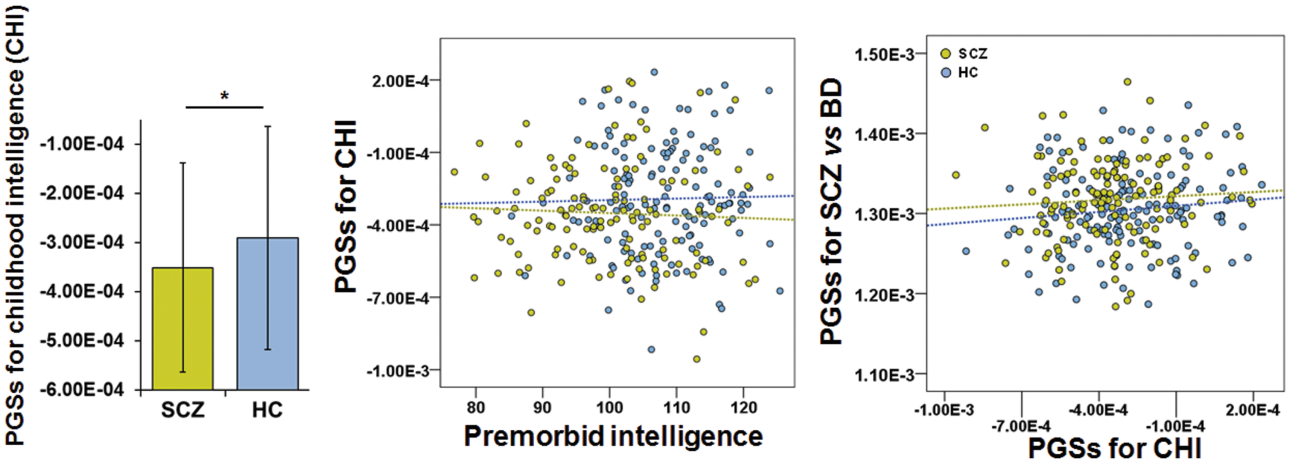

Figure 3. Associations of polygenetic (risk) scores (PGSs) for childhood intelligence (CHI) with the risk of schizophrenia (SCZ), premorbid intelligence, and PGSs for SCZ vs bipolar disorder (BD). *P < .05.

in SCZ patients and HCs (Nakahara et al., 2018; Shafee et al., 2018; Kępińska et al., 2020), although their findings were heterogeneous among studies. These findings indicate that current cognitive abilities may be more directly linked to the genetic risk factors for SCZ than premorbid intelligence.

We did not detect correlations between PGSs for SCZ-specific risk and current intelligence in 130 patients with SCZ or 146 HCs. The current intelligence reflects intelligence decline from the premorbid level in patients with SCZ. In addition, the current intelligence is affected by aging in both diagnostic groups, although our analyses were performed after including age as a covariate. These confounding factors might affect our lack of significant correlations. Further research using a larger sample size is required to verify our results.

There are some limitations to consider when interpreting our findings. The data provided by large-scale GWASs offer promising research opportunities for exploring the genetic architecture shared between the discovery GWAS and independent target traits. A critical factor in determining whether the PGSs based on discovery GWAS can predict the target trait depends on the sample size of the discovery GWAS (Dudbridge 2013; Ohi et al., 2016, 2021). Negative findings, especially related to CHI, should be interpreted with caution, as the sample size of the GWAS for CHI was relatively small. As there were no large-scale GWASs in individuals of non-European ancestry, our PGS analyses were based on large-scale discovery GWASs in individuals of European ancestry. Because any admixture of Europeans in Japan or Japanese in Europe could be highly confounding, we could not exclude the admixture effect. Furthermore, although our target sample size is comparable with that in a previous study reporting a significant association between PGSs for SCZ and cognitive domains in patients with SCZ and HCs (Nakahara et al., 2018), further study using a larger-scale discovery GWAS and/or a larger target sample is required to confirm our findings. As we did not have any data from Japanese BD patients at this time, we could not examine whether the PGSs for SCZ-specific risk are correlated with intelligence in BD patients. Further investigation using BD samples is warranted.

In conclusion, the polygenic factors differentiating SCZ from BD could partially explain low premorbid intelligence in patients with SCZ and HCs. Despite the clinical and genetic similarities between SCZ and BD, genetic components for SCZ-specific risk might contribute to the risk of SCZ through impairment in premorbid intelligence. Further identification of genetic factors contributing to disorder-specific risk will provide insight into the biology underlying both disorders. As cognitive impairments in SCZ and BD patients have considerable negative impacts on functional outcomes, further identification of the underlying mechanisms of the impairment of premorbid intelligence is necessary to develop efficient therapeutic drugs and treatment strategies for cognitive impairments.

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Interest Statement: None.

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