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

Kazutaka Ohi, Daisuke Nishizawa, Shunsuke Sugiyama, Kentaro Takai, Ayumi Kuramitsu, Junko Hasegawa, Midori Soda, Kiyoyuki Kitaichi, Ryota Hashimoto, Kazutaka Ikeda, Toshiki Shioiri

Department of Psychiatry and Psychotherapy, Gifu University Graduate School of Medicine, Gifu, Japan (Drs Ohi, Sugiyama, Takai, Kuramitsu, and Shioiri); Department of General Internal Medicine, Kanazawa Medical University, Ishikawa, Japan (Dr Ohi); Addictive Substance Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan (Dr Nishizawa, Ms Hasegawa, and Dr Ikeda); Department of Biomedical Pharmaceutics, Gifu Pharmaceutical University, Gifu, Japan (Drs Soda and Kitaichi); Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan (Dr Hashimoto).

Correspondence: K. Ohi, MD, PhD, Department of Psychiatry and Psychotherapy, Gifu University Graduate School of Medicine, Gifu, 1-1 Yanagido, Gifu, Gifu, 501–1194, Japan (k_ohi@gifu-u.ac.jp).

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 \( (n=12441–282014) \) 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 \( (R^2=0.025, P=.025) \), 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.
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; Bessono 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 Genetics 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 ($r^2 = 0.7–0.8$) 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 ($r = 0.2$) but not with risk for BD (Ohi et al., 2018; Toulopoulou et al., 2019), several researchers have investigated whether polygenic 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; Kępńska 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; Kępńska 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 was assessed using the best available measure of general cognitive ability (IQ) 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 28,204 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-S v1.4 BeadChip (Ilumina, 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 PCS 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 r2 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 PGs for SCZ-specific risk at a liberal significance threshold (P_{\text{PGS}} ≤ .05) were significantly higher in patients with SCZ than in HCs (Ohi et al., 2020b), PGs constructed from SNPs showing a nominal association with SCZ-specific risk, CHI, and adulthood intelligence in the discovery GWASs were calculated according to P_{\text{PGS}} ≤ .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_{\text{PGS}} ≤ .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 (%) |
|----------------------|-------------------------|---------------------------|--------------|
| 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^{-4} (21.6)* |
| Education (y)        | 12.6 ± 2.2              | 16.1 ± 2.4                | 1.38 × 10^{-24} (155.6) |
| Estimated premorbid intelligence | 99.1 ± 10.6           | 108.5 ± 7.6               | 1.13 × 10^{-13} (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  | 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). χ2 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 × mean, where 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 χ² 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 (α = .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 (β = −0.17, P = 4.12 × 10⁻³). As we previously demonstrated (Ohi et al., 2019, 2020b), patients with SCZ displayed lower premorbid intelligence than HCs (β = −0.38, p = 5.57 × 10⁻¹¹), and PGSs for SCZ-specific risk were higher in SCZ patients than in HCs (Nagelkerke’s R² = 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 (β = −0.13, P = .024) as well as years of education (β = −0.13, P = .019) as covariates. In contrast, there were no significant correlations between the PGSs...
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.

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 (Dykert 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.
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.

Acknowledgments

We thank all individuals who participated in this study. This work was supported by Grants-in-Aid for Scientific Research (C) (19K08081), Young Scientists (B) (16K19784), Young Scientists (20K16624) and KAKENHI Advanced Animal Model Support (AdAMS) (16H06276) from the Japan Society for the Promotion of Science (JSPS); a grant from the SENGHIN Medical Research Foundation; a grant from the Uehara Memorial Foundation; a grant from the Takeda Science Foundation; a grant from the YOKOYAMA Foundation for Clinical Pharmacology (YRY-1807); and a grant from the Smoking Research Foundation.

Interest Statement: None.

References

Agnew-Blais JC, Buka SL, Fitzmaurice GM, Smoller JW, Goldstein JM, Seidman LJ (2015) Early childhood IQ trajectories in individuals later developing schizophrenia and affective psychoses in the New England family studies. Schizophr Bull 41:817–823.

Auton A, Brooks LD, Durbin RM, Garrison EP, Kang HM, Korbel JO, Marchini JL, McCarthy S, McVean GA, Abecasis GR (2015). A global reference for human genetic variation. Nature 526:68-74.

Badcock JC, Dragović M, Waters FA, Jablensky A (2005) Dimensions of intelligence in schizophrenia: evidence from patients with preserved, deteriorated and compromised intellect. J Psychiatr Res 39:11–19.

Barbey AK (2018) Network neuroscience theory of human intelligence. Trends Cogn Sci 22:8–20.

Benyamin B, et al.; Wellcome Trust Case Control Consortium 2 (WTCCC2) (2014) Childhood intelligence is heritable, highly polygenic and associated with FBNP1L. Mol Psychiatry 19:253–258.
The economic burden of bipolar disorder in the United States: a systematic literature review. Clinicoecon Outcomes Res 12:481–497.

Cloutier M, Aigbogun MS, Guerin A, Nitulescu R, Ramanakumar AV, Kamat S, Delucia M, Duffy R, Legacy SN, Henderson C, Francois C, Wu E (2016) The economic burden of schizophrenia in the United States in 2013. J Clin Psychiatry 77:764–771.

Comes AL, et al. (2020) The genetic relationship between educational attainment and cognitive performance in major psychiatric disorders. Transl Psychiatry 9:210.

Crawford JR, Besson JA, Parker DM, Sutherland KM, Keen PL (1987) Estimation of premorbid intellectual status in depression. Br J Clin Psychol 26:313–314.

Dalby JT, Williams R (1986) Preserved reading and spelling ability in psychotic disorders. Psychol Med 16:171–175.

Davies G, et al. (2018) Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. Nat Commun 9:2998.

de Zwarte SMC, et al. (2020) Intelligence, educational attainment, and brain structure in those at familial high-risk for schizophrenia or bipolar disorder. Hum Brain Mapp doi: 10.1002/hbm.25206. Online ahead of print.

Dudbridge F (2013) Power and predictive accuracy of polygenic risk scores. Plos Genet 9:e1003348.

Dykert D, Deary IJ (2013) Retrospective validation of WTAR and NART scores as estimators of prior cognitive ability using the Lothian Birth Cohort 1936. Psychol Assess 25:1361–1366.

Engen MJ, Lyngstad SH, Ueland T, Simonsen CE, Vaskinn A, Smeland O, Bettella F, Lagerberg TV, Djurovic S, Andreassen OA, Melle I (2020) Polygenic scores for schizophrenia and general cognitive ability: associations with six cognitive domains, premorbid intelligence, and cognitive composite score in individuals with a psychotic disorder and in healthy controls. Transl Psychiatry 10:416.

Fujino H, et al.; for COCORO (2017) Estimated cognitive decline in patients with schizophrenia: a multicenter study. Psychiatry Clin Neurosci 71:294–300.

Glahn DC, Almasy L, Barguil M, Hare E, Peralta JM, Kent JW Jr, Dassori A, Contreras J, Pacheco A, Lanzagorta N, Nicolini H, Raventós H, Escamilla MA (2010) Neurocognitive endophenotypes for bipolar disorder identified in multiplex multigenerational families. Arch Gen Psychiatry 67:168–177.

Green MF, Kern RS, Braff DL, Mintz J (2000) Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? Schizophren Bull 26:119–136.

Hashimoto R, Ikeda M, Ohi K, Yasuda Y, Yamamori H, Fujimoto M, Umeda-Yano S, Fukunaga M, Fujino H, Watanabe Y, Iwase M, Kazui H, Iwata N, Weinberger DR, Takeda M (2015) Glutamate networks implicate cognitive impairments in schizophrenia: genome-wide association studies of 52 cognitive phenotypes. Schizophren Bull 41:909–918.

Ohi K, Kikuchi M, Ikeda M, Yamamori H, Yasuda Y, Fujimoto M, Fujino H, Miura K, Fukunaga M, Nakaya A, Iwata N, Hashimoto R (2016) Polygenetic components for schizophrenia, bipolar disorder and rheumatoid arthritis predict risk of schizophrenia. Schizophr Res 175:226–229.

Ohi K, Shimada T, Nemoto K, Kataoka Y, Yasuyama T, Kimura K, Okubo H, Uehara T, Kawasaki Y (2017a) Cognitive clustering in schizophrenia patients, their first-degree relatives and healthy subjects is associated with anterior cingulate cortex volume. Neuroimage Clin 16:248–256.

Ohi K, Sumiyoshi C, Fujino H, Yasuda Y, Yamamori H, Fujimoto M, Sumiyoshi T, Hashimoto R (2017b) A brief assessment of intelligence decline in schizophrenia as represented by the difference between current and premorbid intellectual quotient. Front Psychiatry 8:293.

Ohi K, Shimada T, Kataoka Y, Koide Y, Yasuyama T, Uehara T, Okubo H, Kawasaki Y (2019) Intelligence decline between current and premorbid IQ in schizophrenia: Schizophrenia Non-Related Affected Relative Project (SNARP). Eur Neuropsychopharmacol 29:653–661.

Ohi K, Nishizawa D, Muto Y, Sugiya S, Hasegawa J, Soda M, Kitaichi K, Hashimoto R, Shioiri T, Ikeda K (2020a) Polygenic risk scores for late smoking initiation associated with the risk of schizophrenia. NPJ Schizoph 6:36.

Ohi K, Nishizawa D, Shimada T, Kataoka Y, Hasegawa J, Shioiri T, Kawasaki Y, Hashimoto R, Ikeda K (2020b) Polygenetic risk scores for major psychiatric disorders among schizophrenia
patients, their first-degree relatives, and healthy participants. Int J Neuropsychopharmacol 23:157–164.

Ohi K, Shimada T, Kataoka Y, Yasuyama T, Kawasaki Y, Shioiri T, Thompson FM (2020c) Genetic correlations between subcortical brain volumes and psychiatric disorders. Br J Psychiatry 216:280–283.

Ohi K, Otowa T, Shimada M, Sugiyama S, Muto Y, Tanahashi S, Kiiya H, Nishimura F, Sasaki T, Tanii H, Shioiri T (2021) Shared transethnic genetic basis of panic disorder and psychiatric and related intermediate phenotypes. Eur Neuropsychopharmacol 42:87–96.

Richards AL, et al.; GROUP Investigators; EUGEI WP2 Group; Schizophrenia Working Group of the Psychiatric Genomics Consortium (2020) The relationship between polygenic risk scores and cognition in schizophrenia. Schizophr Bull 46:335–344.

Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans PA, Lee P, Bulik-Sullivan B, Collier DA, Huang H (2014). Biological insights from 108 schizophrenia-associated genetic loci. Nature 511:421–427.

Ruderfer D, et al. (2018) Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. Cell 173:1705–1715, e1716.

Schaefer J, Giangrande E, Weinberger DR, Dickinson D (2013) The global cognitive impairment in schizophrenia: consistent over decades and around the world. Schizophr Res 150:42–50.

Sha fee R, Nanda P, Padmanabhan JL, Tandon N, Aliley-Rodriguez N, Kalaparakkel S, Weiner D, Kur RE, Keefe RSE, Hill SK, Bishop JR, Clementz BA, Tamminga CA, Gershon ES, Pearson GD, Keshavan MS, Sweeney JA, McCarron SA, Robinson EB (2018) Polygenic risk for schizophrenia and measured domains of cognition in individuals with psychosis and controls. Transl Psychiatry 8:78.

Solé B, Jiménez E, Torrent C, Del Mar Bonnin C, Torres I, Reinares M, Priego Á, Salamero M, Colom F, Vare C, Vieta E, Martínez-Arán A (2016) Cognitive variability in bipolar II disorder: who is cognitively impaired and who is preserved. Bipolar Disord 18:288–299.

Stahl EA, et al.; eQTLGen Consortium; BIOS Consortium; Bipolar Disorder Working Group of the Psychiatric Genomics Con sor- tum (2019) Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 51:793–803.

Sullivan PF, Kendler KS, Neale MC (2003) Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. Arch Gen Psychiatry 60:1187–1192.

Sumiyoshi C, Fujino H, Sumiyoshi T, Yasuda Y, Yamamori H, Ohi K, Fujimoto M, Takeda M, Hashimoto R (2016) Usefulness of the Wechsler Intelligence Scale short form for assessing functional outcomes in patients with schizophrenia. Psychiatry Res 245:371–378.

Toulopoulou T, Zhang X, Cherny S, Dickinson D, Berman KF, Straub RE, Sham P, Weinberger DR (2019) Polygenic risk score increases schizophrenia liability through cognition-relevant pathways. Brain 142:471–485.

Trotta A, Murray RM, MacCabe JH (2015) Do premorbid and post-onset cognitive functioning differ between schizophrenia and bipolar disorder? A systematic review and meta-analysis. Psychol Med 45:381–394.

Vaskinn A, Haatveit B, Melle I, Andreassen OA, Ueland T, Sundet K (2020) Cognitive heterogeneity across schizophrenia and bipolar disorder: a cluster analysis of intellectual trajectories. J Int Neuropsychol Soc 26:860–872.

Wechsler D (1997) Wechsler adult intelligence scale. 3rd ed. San Antonio, TX: The Psychological Corporation.

Wells R, Swaminathan Y, Sundram S, Weinberg D, Bruggemann J, Jacomb I, Cropy V, Lenroot R, Pereira AM, Zalesky A, Bousman C, Pantelis C, Weickert CS, Weickert TW (2015) The impact of premorbid and current intellect in schizophrenia: cognitive, symptomatic, and functional outcomes. NPJ Schizophr 1:15043.

Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T (2013) Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382:1575–1586.

Xavier RM, Dungan JR, Keefe RSE, Vorderstrasse A (2018) Polygenic signal for symptom dimensions and cognitive performance in patients with chronic schizophrenia. Schizophr Res Cogn 12:11–19.