The relationship between polygenic risk scores and cognition in schizophrenia.

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Abstract

Background

Cognitive impairment is a clinically important feature of schizophrenia. Polygenic risk score (PRS) methods have demonstrated genetic overlap between schizophrenia, bipolar disorder (BD), major depressive disorder (MDD), educational attainment (EA) and IQ, but very few studies have examined associations between these PRS and cognitive phenotypes within schizophrenia cases.

Methods

We combined genetic and cognitive data in 3034 schizophrenia cases from 11 samples using the general intelligence factor *g* as the primary measure of cognition.

We used linear regression to examine the association between cognition and PRS for EA, IQ, schizophrenia, BD and MDD. The results were then meta-analysed across all samples. A GWAS of cognition was conducted in schizophrenia cases.

Results

PRS for both population IQ ($p=4.39x10^{-28}$) and EA ($p=1.27x10^{-26}$) were positively correlated with cognition in those with schizophrenia. In contrast there was no association between cognition in schizophrenia cases and PRS for schizophrenia (p=0.39), BD (p=0.51) or MDD (p=0.49). No individual variant approached genome-wide significance in the GWAS.

Conclusions

Cognition in schizophrenia cases is more strongly associated with PRS that index cognitive traits in the general population than PRS for neuropsychiatric disorders. This suggests the mechanisms of cognitive variation within schizophrenia are at least partly independent from those that predispose to schizophrenia diagnosis itself. Our findings indicate that this cognitive variation arises at least in part due to genetic factors shared with cognitive performance in populations and is not solely due to

illness or treatment related factors, although our findings are consistent with important contributions from these factors.

Keywords: Psychiatry, genomics, intelligence, bioinformatics

Introduction

Schizophrenia is an often debilitating, highly heritable mental disorder affecting around 1% of the population[1]. Individuals with schizophrenia show marked cognitive deficits, on average, compared to healthy controls[2]. Cognitive impairments are strongly associated with functional outcomes in schizophrenia, more so than positive symptoms[3]. Existing treatments focus on reducing positive symptoms principally through the use of antipsychotic medications, but neither these medications nor other treatments have major beneficial effects on cognition. Indeed it has been argued that antipsychotics, particularly at high doses, may exacerbate cognitive impairment[4]. Interventions, such as cognitive remediation therapy, have been shown to improve cognitive deficits to a limited extent but are not routinely available for most patients with schizophrenia[5].

The underlying causes of cognitive impairment in schizophrenia have been contested since first described by Kraepelin[6], but include factors secondary to illness-related behaviours (e.g. substance abuse, poor nutrition) and drugs used in treating the disorder for example high dose antipsychotics[7], anticholinergics[8] and benzodiazepines[9]. Nonetheless the demonstration in longitudinal population-based studies that cognitive impairment exists prior to schizophrenia onset[10] suggests a contribution from factors that are correlated with increased liability to the disorder, including those that are aetiological. Furthermore evidence that cognitive performance is impaired in the relatives of those with schizophrenia, and is heritable in these families[11], indicates a genetic contribution to cognitive impairment in schizophrenia, consistent with the neurodevelopmental hypothesis of the disorder.

Genome-wide association studies (GWAS) have proven to be an effective means of identifying risk alleles for schizophrenia[12, 13]. They have also identified common alleles that influence population variation in measures of cognitive ability, including IQ, as well as other proxy measures such as educational attainment. Furthermore, GWAS have provided evidence for shared genetic contributions to many of these traits (schizophrenia, bipolar disorder, major depressive disorder, IQ

and educational attainment)[14-20]. Common variant GWAS have previously been performed on cognition in schizophrenia cases at smaller sample sizes[21, 22].

The aggregated common variant genetic liability for disorders and traits can be estimated in individuals by a metric known as the polygenic risk score (PRS). The PRS for schizophrenia has been shown to be weakly associated with IQ and cognition in population samples[23-26] and appears to be associated with severity of negative, but not positive symptoms in those with schizophrenia[27]. IQ PRS has been shown to be significantly associated with schizophrenia diagnosis in a case/control sample[23].

To date few studies have examined the influence of PRS on cognition in those with schizophrenia, and those that have been performed have used a restricted range of polygenic risk scores, generally in small samples, and have found no convincing evidence for association between schizophrenia PRS and cognition[28-30]. Aiming to obtain insights into the origins of cognitive impairment in those with schizophrenia, we report analyses of what we believe is the largest schizophrenia sample to date for which both cognitive and genetic data are available. We derived *g*, the 'general intelligence factor', as a measure of general cognitive ability[31], since it has been used successfully in population-based genetic studies[15], it captures substantial variance in cognitive ability, particularly in schizophrenia[32], and can be derived from a diverse array of cognitive tests across different studies[33, 34].

We performed a GWAS of *g* within schizophrenia cases and systematically examined the relationship between *g* and polygenic risk scores for psychiatric disorders and cognitive traits in multiple schizophrenia case samples, using meta-analysis to combine the results. We had two primary hypotheses. First, under the hypothesis that variation in cognitive impairment in schizophrenia is essentially a consequence of liability to the disorder, with greater impairment indicating greater liability, we predicted that the measure of liability to schizophrenia (schizophrenia PRS) would be negatively associated with cognitive performance in those with the disorder (Hypothesis 1). Alternatively, under the hypothesis that variation in cognitive performance in schizophrenia is driven

by similar factors that influence cognition in the general population, albeit that variance occurs around a mean point that is lower as a consequence of the disorder, we predicted that cognition related PRS (for IQ and educational attainment) would be associated with cognition in those with schizophrenia (Hypothesis 2). We also investigated whether polygenic liability to bipolar disorder and major depressive disorder were associated with cognition, testing these as negative controls, since both are adult disorders that genetically overlap with schizophrenia but do not show genetic correlation with IQ[19].

Methods

We amalgamated genetic and cognitive data from those with schizophrenia and schizoaffective disorder from available datasets that were part of the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC), as well as additional samples from the European Union Gene Environment Interaction consortium (EUGEI) and from Ireland and Cardiff that have not yet been included in the published work of the PGC.

PGC Samples

Of the 11 datasets in this study, 8 were part of the 2014 PGC schizophrenia study (Table 1)[13]. Genetic data accessed from PGC servers with permission of the individual study principal investigators.

PGC genotype data

The PGC datasets included 2071 genotyped individuals of European ancestry, with research-verified diagnoses of schizophrenia or schizoaffective disorder for whom we also had sufficient cognitive data to calculate *g*, the general cognition factor. We used the quality control parameters reported by the PGC consortium[13], excluding individuals of non-European ancestry based on PCA. The datasets we analysed had been imputed using the 1000 Genomes phase 3 reference panel with the programs

SHAPEIT for haplotype phasing and IMPUTE2 for imputation. Full details of sample collection, genotyping, quality control and imputation are available in the associated paper[13]. After imputation, variants with an INFO score >0.1, MAF >0.5% and missingness <2% were retained for further analysis.

EUGEI and additional Irish samples

156 samples with schizophrenia and schizoaffective disorder collected and genotyped as part of Work Package 2 of the EUGEI study were included in the analysis (the European network of national schizophrenia networks studying gene environment interactions, see http://www.eu-gei.eu/)[35]. These samples were recruited as first episode psychosis cases with a schizophrenia or schizoaffective disorder diagnosis based on Operational Criteria (OPCRIT) ratings, following a research interview and case note review[35]. An additional 159 cases collected from centres across Ireland were included in the analysis; all had a DSM-IV diagnosis of schizophrenia/schizoaffective disorder. For details of genotyping, quality control and imputation, see Supplementary Information.

CardiffCOGS samples

We included 648 samples from the CardiffCOGS study with DSM-IV schizophrenia and schizoaffective disorder diagnoses, based on a SCAN interview[36] and clinical note review ratings[37]. For details of genotyping, quality control and imputation, see Supplementary Information.

Neuropsychological assessment

Participants in all studies underwent formal neuropsychological testing, administered by trained researchers. Protocols and results from each sample have been independently published[38-44] and we provide full details of testing procedures and batteries in Supplementary Information.

Calculation of g

The cognitive tests available differed for each study sample (Supplementary Table 1). For a dataset to be included we required tests from a minimum of two cognitive domains, having assigned cognitive tests to domains based on the approach taken by MATRICS[45, 46]. We then calculated *g* independently for each dataset using at most three tests from a particular cognitive domain. Subjects were excluded if they did not have valid scores for at least two cognitive tests. Outlier test scores were also excluded (see Supplementary Information).

g was calculated from the cognitive test scores using multidimensional scaling (MDS), as implemented in the R 'stats' package. Unlike principal component analysis (PCA), MDS can retain subjects with missing data while being mathematically analogous to PCA when data are complete. *g* was calculated as the first dimension produced by MDS analysis.

For five datasets, values of *g* were calculated using both MDS and PCA in samples with no missing data, and the results examined for correlation (see Supplementary Data and Supplementary Table 2 for more details). For PCA, the first principal component was taken to represent *g*. PCA- and MDS-derived estimates of *g* were highly correlated ($|r|>0.95$ in all datasets), endorsing our selection of MDS to derive *g*. A version of the primary analysis using values of g derived from PCA (thus excluding missing data) was also performed.

For the EUGEI sample, WAIS IQ estimates were available. Given their high correlation with *g*, and also because WAIS IQ had been standardised across the multiple countries present in the EUGEI

dataset, we used these scaled IQ scores for the EUGEI samples. This methodology follows the approach taken in equivalent research in non-clinical populations[23].

Genome-wide association analysis of g and meta-analysis

Mixed linear model association (MLMA) was performed genome-wide in each dataset using the program GCTA[47, 48], which calculates a genetic relationship matrix (GRM) for all samples that is then used to correct for sample relatedness and population stratification. To prevent overcorrection due to the inclusion of truly associated variants in the GRM, a leave-one-chromosome-out model was used where the GRM used for association testing for any variant on a given chromosome was derived after excluding all variants on that chromosome. The association results for the 11 datasets were combined using a standard error weighted, fixed effects meta-analysis in METAL[49]

Polygenic risk score (PRS) construction

Polygenic risk scores were constructed from GWAS of five disorders or traits as training sets (Supplementary Table 3); schizophrenia, major depression (MDD), bipolar disorder (BD), educational attainment (EA, measured in 'years in education'), and IQ[13, 18, 19, 50, 51]. The schizophrenia training set was based on the PGC2 meta-analysis, but excluded the cognitively informative samples used in this study for analysis of PRS and *g*. Clumping was performed in imputed best-guess genotypes for each dataset using PLINK (maximum r^2=0.2, window size=500kb, minimum MAF=10%, minimum INFO score=0.7), and variants within regions of long-range LD (including the MHC) excluded [52]. PRS were then constructed from best-guess genotypes using PLINK at 10 p-value thresholds (P_T=1, 0.5, 0.3, 0.2, 0.1, 0.05, 0.01, $1x10^{-4}$, $1x10^{-6}$, $5x10^{-8}$). We used P_T=0.05 for our primary analyses, except for MDD, where we used P_T=0.5 (see Supplementary Information).

Regression of g on PRS and meta-analysis

The relationships between *g* and PRS were analysed in each schizophrenia dataset using linear regression in R, with age, sex and population principal components as covariates (see Supplementary Table 4). PRS and *g* were normalised to have a mean of 0 and a standard deviation of 1, and so resulting effect size estimates give the number of standard deviations change in *g* for 1 standard deviation change in PRS. Results for each PRS were meta-analysed across all datasets with a fixed-effects model using the metagen function in the 'meta' package in R. I^2 values and random effects meta-analysis p-values were also calculated to examine the extent of heterogeneity in our sample.

To ensure that the results were not biased by samples with a small number of available cognitive tests, or by the use of WAIS IQ in place of *g* in the EUGEI sample, we also performed sensitivity analyses which excluded the EUGEI sample, and also individuals from two of the samples (Mannheim/Bonn and Ireland) for whom we had data for only two cognitive tests. Inclusion in the regression model of an age by sex interaction term and a non-linear effect of the age covariate produced consistent results.

Power calculations for the PRS analyses are presented in Supplementary Information. For all training sets except BD, our power to detect true effects was estimated to be over 99% (Supplementary Table 3).

Independent population samples

To examine whether the results for PRS predicting cognition in schizophrenia cases were comparable to results in a population-based sample, we tested the association between the IQ PRS (Savage *et al*[19]) and IQ in an independent dataset, the second wave of the Biobank sample (n=91468, P_T=0.05, IQ measure: fluid intelligence score, UK Biobank field ID: 20016). We also tested the association

between SZ PRS (Pardinas *et al*[12]) and IQ in the complete Biobank sample (n=133437, P_T=0.05, see Supplementary Information).

The analytic methods followed those of the main schizophrenia analysis and used population principal components, age at cognitive assessment and sex as covariates (see Supplementary Table 4). UK Biobank analyses were conducted under project number 13310.

Results

Consistent with other similarly sized GWAS of complex traits, no variants reached a genome-wide level of significance for association with *g*. (Supplementary Figure 1 – Manhattan plot, Supplementary Figure 2 – Q-Q plot (λ=1.027), Supplementary Table 5 – top hits; results available at ***https://walters.psycm.cf.ac.uk/***).

With respect to our primary hypotheses, we found no evidence to support the predictions of hypothesis 1, in that we observed no association between the schizophrenia PRS and *g* in schizophrenia cases (Table 2, Supplementary Figure 3). Thus, in our sample, common variant liability to schizophrenia was not associated with cognitive performance as measured by *g.* In contrast, a significant positive relationship was found between *g* and PRS derived from both IQ ($p=4.39x10^{-28}$, effect size=0.199) and educational attainment ($p=1.27x10^{-26}$, effect size=0.188), supporting hypothesis 2 (Table 2, Figure 1 and Supplementary Figure 4). These effect sizes were larger in magnitude than those observed for SZ, BD and MDD PRS, but somewhat smaller than those observed for the association of IQ PRS and fluid intelligence in non-psychotic individuals from the independent UK Biobank samples ($p<2.2x10^{-16}$, effect size=0.327). Similar results were obtained across differing p-value thresholds (Supplementary Table 6).

Sensitivity analysis following exclusion of the EUGEI samples (WAIS IQ was used instead of *g*) and samples with data on only two cognitive tests were consistent with the primary analyses

(Supplementary Table 7). Similar results were observed when random effects meta-analysis was used to minimise the effect of inter-sample heterogeneity (Supplementary Table 6). The magnitude and pattern of results remained unchanged when the calculation of *g* used a traditional PCA approach (thus excluding participants with any missing cognitive test data). SZ PRS significantly predicted fluid intelligence in non-psychotic individuals in the Biobank sample ($p<2.2x10^{-16}$, effect size=-0.137), though again with a smaller effect size than when using IQ PRS.

Secondary negative control analyses revealed no significant relationship between *g* and PRS for BD or MDD (Table 2; Supplementary Table 6).

Discussion

Here, we report a genome-wide investigation of what is, to date, the largest schizophrenia sample with both cognitive and genetic data. Given that much larger samples are generally required to yield robust association signals for complex phenotypes, and that this is true for general cognition in population samples[23], our aim was not to implicate loci associated with cognition within schizophrenia. Rather, our primary aim was to investigate the relationships between cognitive performance in people with schizophrenia and common variant genetic liability to both schizophrenia and to cognitive ability in the general population.

Specifically, we tested two primary hypotheses. First, under the hypothesis that variation in cognitive impairment in schizophrenia is a function of the degree of liability to the disorder, with greater impairment indicating greater liability, we predicted that the measure of liability to schizophrenia would be negatively associated with cognitive performance in those with the disorder. This hypothesis was not supported, as there was no significant relationship between schizophrenia PRS and *g*, although we cannot exclude the possibility that a significant relationship will emerge with further increases in sample size. The second hypothesis was that genetic variation in cognitive

performance in schizophrenia is essentially driven by factors that influence cognition in the general population, leading to the prediction that cognition related PRS based on the general population would be associated with cognition in those with schizophrenia. In contrast to hypothesis one, we found strong evidence to support the prediction from hypothesis two, PRS for IQ and for educational attainment (EA) being strongly associated with *g* in those with schizophrenia. As predicted we found no evidence of association between liability to MDD or BPD and *g*.

Overall, our results suggest that alleles associated with IQ and EA in the general population make a more important contribution to variance in cognition in those with schizophrenia than the alleles that confer liability to schizophrenia *per se*. This interpretation, however, only holds if we assume the schizophrenia PRS captures a similar, or greater, proportion of the liability to that disorder than IQ and EA do for their respective traits. Previous studies have shown this assumption to be valid, indeed the IQ PRS explains a smaller proportion of variance in IQ than the proportion of variance of schizophrenia case status explained by the schizophrenia PRS (liability scale R^2 = 0.052 for IQ, 0.07 for schizophrenia, 0.106 to 0.127 for educational attainment)[13]. Thus, the schizophrenia PRS is actually better powered to test the impact of schizophrenia liability than the IQ PRS, allowing us to conclude that differential power is unlikely to explain our finding. Furthermore the fact that the IQ and EA PRS predict cognition in cases indicates that the failure to detect a relationship between cognition and schizophrenia liability is not due to cognition measurement errors. Together, these considerations support the hypothesis that variance in cognition in schizophrenia and in the general population has common genetic causes.

We went on to examine whether the variance in cognition explained by the PRS for IQ was quantitatively as well as qualitatively similar in people with schizophrenia compared to those drawn from the wider population (Figure 1). This showed that the IQ PRS explained less of the variance in cognition in schizophrenia than in an independent population sample (UK Biobank - UKBB[53]). We consider this to be only an approximate comparison of variance; an accurate comparison would

require representative sampling at scale (population and case) and identical tests, neither condition being met in our schizophrenia sample. The IQ PRS was derived in large part from the UKBB (wave 1) which also provided our (non-overlapping) independent test dataset for the population IQ analysis (wave 2 of UKBB). Thus the observation that the variance explained in schizophrenia cases is modestly lower than in the UKBB population sample could be due, at least in part, to the more uniform cognitive assessment and similarity of sample characteristics (more restricted age range and demographics) in UKBB, which would serve to reduce unsystematic variation and increase power relative to the analysis in SZ cases. However our result is also consistent with important contributions to cognitive impairment in those with schizophrenia from factors that are illness-related; possible examples include delays in treatment, symptom severity and chronicity, pre- and post-natal complications, social isolation, as well as drug exposures (therapeutic or abused)[7-9, 54].

The fact that schizophrenia polygenic alleles *en masse* are not associated with variation in cognition in those with schizophrenia does not contradict previous findings that individual schizophrenia risk alleles or genes influence cognition or educational attainment[17], indeed we and others have reported consistent negative associations between schizophrenia PRS and performance on specific cognitive domains and educational attainment in population samples[23, 25], and show here that schizophrenia PRS shows a negative association with cognition in the UKBB. The fact that we did not detect a similar negative association in cases may be partly attributable to the schizophrenia samples effectively having been selected for high schizophrenia PRS and thus attenuating our power to examine whether variation in schizophrenia PRS is associated with cognition. In order to examine this as a potential explanation of our results we plotted the distributions and calculated metrics of normality for both the schizophrenia and IQ PRS (Supplementary figures 5 and 6). These distributions and metrics are very similar between the schizophrenia and IQ PRS and are not suggestive of a restricted distribution, hence, whilst a theoretical concern, the distribution of schizophrenia PRS seems unlikely to explain our findings.

Our findings thus argue against universal pleiotropy for schizophrenia alleles and cognition. Nonetheless our results do not suggest that schizophrenia risk alleles have no role in cognition; that seems unlikely given the highly significant relationship between schizophrenia PRS and case/control status and the similarly robust cognitive impairments in cases relative to controls. Robust associations between SZ PRS and cognition in the general population, as we confirm, are further evidence against this. Rather, our findings suggest that the effect of schizophrenia risk alleles on cognition is well captured by the schizophrenia diagnosis. In other words the schizophrenia PRS may contribute more to case control cognitive differences than it does to variance of cognition within cases which is the subject of this study. The impact of schizophrenia alleles on cognitive functioning within cases must be small or absent, and is certainly considerably less than the effect of alleles that contribute to IQ and EA PRS.

We acknowledge some limitations of our study design. Cross-sample cognitive analyses typically are hampered by differing test battery selection and administration. In the present study, we sought to mitigate this by using *g* as a cognitive metric, which allows the incorporation of samples that use a diverse set of cognitive tests and has the benefit of ease of interpretation and comparison within and between studies. Despite this, heterogeneous effects related to test administration and sample ascertainment present challenges to combining cognitive data cross-site although our findings suggest validity to our methods given the concordant results with equivalent population IQ studies. By conducting within sample PRS cognition analysis followed by meta-analysis we also avoided the need to directly combine cognitive test results across samples. It is further reassuring that the subsets of our data do not show large amounts of variation in terms of the relationship between PRS and *g* (see forest plots in Supplemental Figures 3-4), and that cognitive PRS was in fact associated with *g* in our sample. Our study does not address the contribution of rare high-penetrance variants, however, while rare CNVs and loss of function mutations clearly influence cognition and disorder liability, those that are currently known to do so are cumulatively so rare (2-3% of cases) that they cannot contribute substantially to cognitive variance in the population of cases[55, 56]. Finally, we note

our sample lacks matched healthy controls for whom similar cognitive data have been obtained, and therefore we cannot directly evaluate to what extent the cognitive PRS explains the average cognitive differences between those with and without the disorder. Despite the limitations of polygenic analysis with current sample sizes in explaining variance explained, it is unlikely that the major differences in cognition (1 to 2 standard deviations) seen between schizophrenia cases and healthy controls are explained by common genetic factors alone and that rare genetic variants and non-genetic exposures are likely to have important roles in aetiology.

In conclusion, the existence of a genetic contribution to cognition in schizophrenia that is not secondary to the disorder *per se* has previously been inferred from findings that at least some of the cognitive impairment in people with schizophrenia predates the onset of the condition [10], and by the fact that cognitive impairments are observed, albeit in a milder form, in relatives of those with schizophrenia[57]. We now extend these findings, showing for the first time that polygenic contribution to cognition overlaps in population and schizophrenia samples. We further show that in those with schizophrenia, variance in cognition is substantially independent of common variant liability to the disorder. This is important as it suggests the underlying biology of variation in cognition in schizophrenia will at least in part be elucidated through gaining insights into the genetic basis of cognition in population samples, and that such characterisation may provide insights to inform the development of therapeutics for cognitive deficits in schizophrenia.

Conflicts of interest

PF Sullivan reports the following potentially competing financial interests. Current: Lundbeck (advisory committee, grant recipient). Past three years: Pfizer (scientific advisory board), Element Genomics (consultation fee), and Roche (speaker reimbursement). CM Bulik (spouse) reports: Shire (grant recipient, Scientific Advisory Board member); Pearson and Walker (author, royalty recipient); OpenBiome (collaborator); uBiome (grant recipient/collaborator); Recovery Record (collaborator).

These interests are unrelated to this project. MJ Owen, MC O'Donovan, JTR Walters are supported by a collaborative research grant from Takeda. Takeda played no part in the conception, design, implementation, or interpretation of this study, which was completed prior to the funding award. No other conflicts of interest are reported.

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References

1. Gottesman, II, Shields J. A polygenic theory of schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America* Jul 1967;58(1):199-205.
2. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology* Jul 1998;12(3):426-445.

3. Bowie CR, Reichenberg A, Patterson TL, Heaton RK, Harvey PD. Determinants of real-world functional performance in schizophrenia subjects: correlations with cognition, functional capacity, and symptoms. *The American journal of psychiatry* Mar 2006;163(3):418-425.

4. Hill SK, Bishop JR, Palumbo D, Sweeney JA. Effect of second-generation antipsychotics on cognition: current issues and future challenges. *Expert review of neurotherapeutics* Jan 2010;10(1):43-57.

5. Bryce S, Sloan E, Lee S, Ponsford J, Rossell S. Cognitive remediation in schizophrenia: A methodological appraisal of systematic reviews and meta-analyses. *Journal of psychiatric research* Apr 2016;75:91-106.

6. Kraepelin E. *Dementia praecox and paraphrenia*. Huntington, N.Y.,: R. E. Krieger Pub. Co.; 1971.

7. Husa AP, Rannikko I, Moilanen J, et al. Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia - An observational 9-year follow-up study. *Schizophrenia research* Sep 2014;158(1-3):134-141.

8. Nishiyama K, Sugishita M, Kurisaki H, Sakuta M. Reversible memory disturbance and intelligence impairment induced by long-term anticholinergic therapy. *Internal medicine* Jun 1998;37(6):514-518.

9. Rammsayer TH, Rodewald S, Groh D. Dopamine-antagonistic, anticholinergic, and GABAergic effects on declarative and procedural memory functions. *Brain research Cognitive brain research* Jan 2000;9(1):61-71.

10. Khandaker GM, Barnett JH, White IR, Jones PB. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia research* Nov 2011;132(2-3):220-227.

11. Seidman LJ, Hellemann G, Nuechterlein KH, et al. Factor structure and heritability of endophenotypes in schizophrenia: findings from the Consortium on the Genetics of Schizophrenia (COGS-1). *Schizophrenia research* Apr 2015;163(1-3):73-79.

12. Pardinas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature genetics* Mar 2018;50(3):381-389.

13. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* Jul 24 2014;511(7510):421-427.

14. Allardyce J, Leonenko G, Hamshere M, et al. Association Between Schizophrenia-Related Polygenic Liability and the Occurrence and Level of Mood-Incongruent Psychotic Symptoms in Bipolar Disorder. *JAMA psychiatry* Jan 1 2018;75(1):28-35.

15. Davies G, Lam M, Harris SE, et al. Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function. *Nature communications* May 29 2018;9(1):2098.

16. Escott-Price V, Bracher-Smith M, Menzies G, Walters JTR, Kirov G, Owen MJ, O'Donovan MC. Genetic liability to schizophrenia is negatively associated with educational attainment in UK Biobank. *Molecular Psychiatry* 2018;In press.

17. Le Hellard S, Wang YP, Witoelar A, et al. Identification of Gene Loci That Overlap Between Schizophrenia and Educational Attainment. *Schizophrenia bulletin* May 1 2017;43(3):654-664.

18. Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature genetics* Aug 2018;50(8):1112-1121.

19. Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nature genetics* Jul 2018;50(7):912-919.

20. Smeland OB, Frei O, Kauppi K, et al. Identification of Genetic Loci Jointly Influencing Schizophrenia Risk and the Cognitive Traits of Verbal-Numerical Reasoning, Reaction Time, and General Cognitive Function. *JAMA psychiatry* Oct 1 2017;74(10):1065-1075.

21. Dickinson D, Straub RE, Trampush JW, et al. Differential effects of common variants in SCN2A on general cognitive ability, brain physiology, and messenger RNA expression in schizophrenia cases and control individuals. *JAMA psychiatry* Jun 2014;71(6):647-656.

22. Scult MA, Trampush JW, Zheng F, et al. A Common Polymorphism in SCN2A Predicts General Cognitive Ability through Effects on PFC Physiology. *Journal of cognitive neuroscience* Sep 2015;27(9):1766-1774.

23. Lencz T, Knowles E, Davies G, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). *Mol Psychiatry* Feb 2014;19(2):168-174.

24. Hagenaars SP, Harris SE, Davies G, et al. Shared genetic aetiology between cognitive functions and physical and mental health in UK Biobank (N=112 151) and 24 GWAS consortia. *Mol Psychiatry* Nov 2016;21(11):1624-1632.

25. Hubbard L, Tansey KE, Rai D, et al. Evidence of Common Genetic Overlap Between Schizophrenia and Cognition. *Schizophrenia bulletin* May 2016;42(3):832-842.

26. van Os J, van der Steen Y, Islam MA, Guloksuz S, Rutten BP, Simons CJ, Investigators G. Evidence that polygenic risk for psychotic disorder is expressed in the domain of neurodevelopment, emotion regulation and attribution of salience. *Psychological medicine* Oct 2017;47(14):2421-2437.

27. Fanous AH, Zhou B, Aggen SH, et al. Genome-wide association study of clinical dimensions of schizophrenia: polygenic effect on disorganized symptoms. *The American journal of psychiatry* Dec 2012;169(12):1309-1317.

28. van Scheltinga AF, Bakker SC, van Haren NE, et al. Schizophrenia genetic variants are not associated with intelligence. *Psychological medicine* Dec 2013;43(12):2563-2570.

29. Wang SH, Hsiao PC, Yeh LL, et al. Polygenic risk for schizophrenia and neurocognitive performance in patients with schizophrenia. *Genes, brain, and behavior* Jan 2018;17(1):49-55.

30. Shafee R, Nanda P, Padmanabhan JL, et al. Polygenic risk for schizophrenia and measured domains of cognition in individuals with psychosis and controls. *Translational psychiatry* Apr 12 2018;8(1):78.

31. Spearman C. "General intelligence " objectively determined and measured. *Am J Psychol* 1904;15:201-292.

32. Dickinson D, Goldberg TE, Gold JM, Elvevag B, Weinberger DR. Cognitive factor structure and invariance in people with schizophrenia, their unaffected siblings, and controls. *Schizophrenia bulletin* Nov 2011;37(6):1157-1167.

33. Johnson W, Bouchard TJ, Krueger RF, McGue M, Gottesman II. Just one g: consistent results from three test batteries. *Intelligence* 2004;32(1):95-107.

34. Johnson W, te Nijenhuis J, Bouchard TJ. Still just 1 g: Consistent results from five test batteries. *Intelligence* Jan-Feb 2008;36(1):81-95.

35. Quattrone D, Di Forti M, Gayer-Anderson C, et al. Transdiagnostic dimensions of psychopathology at first episode psychosis: findings from the multinational EU-GEI study. *Psychological medicine* 2018;in press.

36. Wing JK, Babor T, Brugha T, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Archives of general psychiatry* Jun 1990;47(6):589-593.

37. Lynham AJ, Hubbard L, Tansey KE, Hamshere ML, Legge SE, Owen MJ, Jones IR, Walters JTR. Examining cognition across the bipolar/schizophrenia diagnostic spectrum. *Journal of psychiatry & neuroscience : JPN* Jul 2018;43(4):245-253.

38. Ekerholm M, Firus Waltersson S, Fagerberg T, Soderman E, Terenius L, Agartz I, Jonsson EG, Nyman H. Neurocognitive function in long-term treated schizophrenia: a five-year follow-up study. *Psychiatry research* Dec 30 2012;200(2-3):144-152.

39. Athanasiu L, Mattingsdal M, Kahler AK, et al. Gene variants associated with schizophrenia in a Norwegian genome-wide study are replicated in a large European cohort. *Journal of psychiatric research* Sep 2010;44(12):748-753.

40. Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. *Nature* Aug 6 2009;460(7256):744-747.

41. Korver N, Quee PJ, Boos HB, Simons CJ, de Haan L, investigators G. Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *International journal of methods in psychiatric research* Sep 2012;21(3):205-221.

42. Manschreck TC, Boshes RA. The CATIE schizophrenia trial: results, impact, controversy. *Harvard review of psychiatry* Sep-Oct 2007;15(5):245-258.

43. International Schizophrenia C, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* Aug 6 2009;460(7256):748-752.

44. Ingason A, Giegling I, Hartmann AM, et al. Expression analysis in a rat psychosis model identifies novel candidate genes validated in a large case-control sample of schizophrenia. *Translational psychiatry* Oct 13 2015;5:e656.

45. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *The American journal of psychiatry* Feb 2008;165(2):203-213.

46. Kern RS, Nuechterlein KH, Green MF, et al. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. *The American journal of psychiatry* Feb 2008;165(2):214-220.

47. Yang J, Zaitlen NA, Goddard ME, Visscher PM, Price AL. Advantages and pitfalls in the application of mixed-model association methods. *Nature genetics* Feb 2014;46(2):100-106.

48. Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *American journal of human genetics* Jan 7 2011;88(1):76-82.

49. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* Sep 1 2010;26(17):2190-2191.

50. Stahl EA, Breen G, Forstner AJ, et al. Genomewide association study identifies 30 loci associated with bipolar disorder. *bioRxiv* 2018(doi: 10.1101/173062).

51. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature genetics* May 2018;50(5):668-681.

52. Price AL, Weale ME, Patterson N, et al. Long-range LD can confound genome scans in admixed populations. *American journal of human genetics* Jul 2008;83(1):132-135; author reply 135-139.

53. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS medicine* Mar 2015;12(3):e1001779.

54. Geddes JR, Lawrie SM. Obstetric complications and schizophrenia: a meta-analysis. *The British journal of psychiatry : the journal of mental science* Dec 1995;167(6):786-793.

55. Singh T, Walters JTR, Johnstone M, et al. The contribution of rare variants to risk of schizophrenia in individuals with and without intellectual disability. *Nature genetics* Aug 2017;49(8):1167-1173.

56. Rees E, Kendall K, Pardinas AF, et al. Analysis of Intellectual Disability Copy Number Variants for Association With Schizophrenia. *JAMA psychiatry* Sep 1 2016;73(9):963-969.

57. Light G, Greenwood TA, Swerdlow NR, et al. Comparison of the heritability of schizophrenia and endophenotypes in the COGS-1 family study. *Schizophrenia bulletin* Nov 2014;40(6):1404-1411.

Tables

Dataset name	In PGC2 SZ study?	Country / countries of origin	Number of study participants	Gender (% female)	Median age	Age range
Bonn/Mannheim	Yes	Germany	436	42	36	17-70
PAGES	Yes	Germany	148	37	39	19-70
CATIE	Yes	USA	350	23	43	18-65
Hubin	Yes	Sweden	77	30	45	25-70
TOP	Yes	Norway	286	43	29	17-62
GROUP sample 1	Yes	Netherlands	309	23	25	16-52
GROUP sample 2	Yes	Netherlands	119	24	25	15-45
Ireland (PGC samples)	Yes	Ireland	346	28	42	17-69
Ireland (additional samples)	No	Ireland	159	35	43	19-67
EU-GEI Work Package 2	No	France, Italy, Spain, Netherlands, UK	156	28	30	17-59
Cardiff Cognition	No	UK	648	38	43	17-74

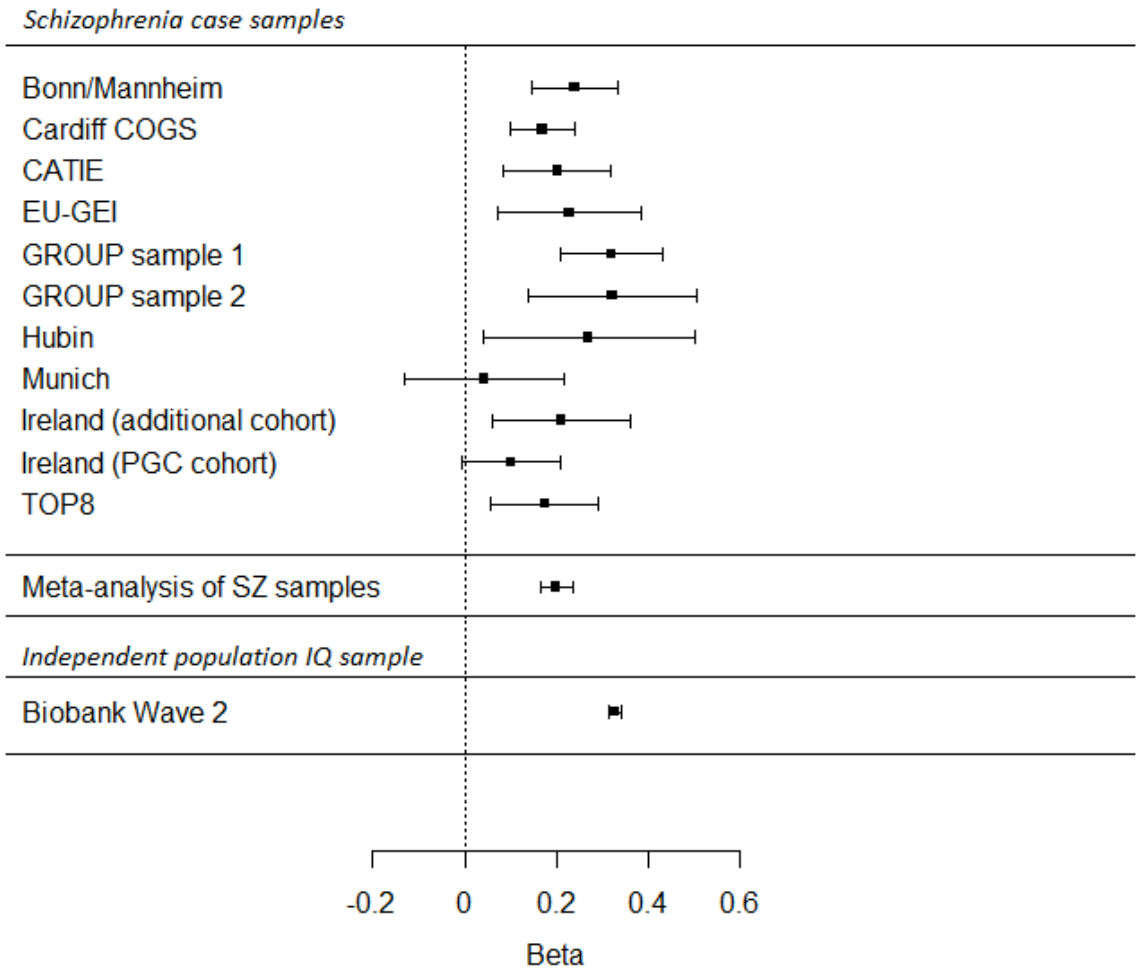
Table 1. Sample size and details of datasets included in study. PGC=Psychiatric Genomics Consortium, PAGES=Phenomics and Genomics Sample, CATIE=Clinical Antipsychotic Trials for Intervention Effectiveness, TOP=Tematisk omrade psykoser, GROUP=Genetic Risk and Outcome of Psychosis, EU-GEI=European Union Gene Environment Interaction. **Number of study participants refers to those with genomic, phenotypic and covariate data.**

Training set	P-value threshold	Effect size	Standard error	P-value
Schizophrenia	0.05	-0.017	0.019	0.386
Bipolar disorder	0.05	-0.012	0.018	0.509
Major depression	0.5	-0.013	0.018	0.488
IQ	0.05	0.199	0.018	4.39E-28
Educational attainment	0.05	0.188	0.018	1.27E-26

Table 2. Meta-analysis of regression of *g* on PRS

Figures

Figure 1. Forest plot showing effect sizes and confidence intervals for regression of *g* on IQ polygenic risk score (age, sex and population principal component covariates also included in model) in schizophrenia case samples and an independent IQ sample. Effect sizes based on standardised values of *g*/IQ and PRS (i.e. number of standard deviations change in *g*/IQ that occurs with 1 standard deviation change in PRS). Lower panel shows regression of IQ on IQ polygenic risk score in an independent population dataset, the second wave of the UK Biobank (n=91468).


Schizophrenia case samples
Bonn/Mannheim
Cardiff COGS
CATIE
EU-GEI
GROUP sample 1
GROUP sample 2
Hubin
Munich
Ireland (additional cohort)
Ireland (PGC cohort)
TOP8
Meta-analysis of SZ samples
Independent population IQ sample
Biobank Wave 2
-0.2
0
0.2
0.4
0.6
Beta

Supplementary Information

Neuropsychological assessment

Hubin Sample

Cognitive ability was assessed using the Cognitive Performance Indicator (CPI), a brief semi-computerized battery. Of CPI's six domains, five were included in the following study using the following tasks:

1. Speed of processing (Trail Making Test: Part A and B)
2. Working memory (Letter-Number Span)
3. Attention / vigilance (Continuous Performance Test: Identical Pairs)
4. Verbal learning (Rey Auditory Verbal Learning Test (total))
5. Executive functioning (Wisconsin Card Sorting Test (64 card version):

Cases were recruited from northwestern Stockholm County and ascertainment has been described previously[1-6]. Cases gave informed consent and the human subjects protocol was approved by the ethical committees of the Karolinska Hospital and the Stockholm Regional Ethical Committee. Controls were recruited either among subjects previously participating in biological research at the Karolinska Institute or drawn from a representative register of the population of Stockholm County[2]. All participants provided informed consent.

TOP sample

Cognitive ability was assessed with a 3 h test battery. Tests from multiple domains of cognition were used to calculate *g*, including:

1. Speed of processing (WAIS Digit-Symbol Coding)[7]
2. Working memory (WAIS - Digit Span Test)[7]
3. Verbal memory (CVLT-II, WASI Vocabulary)[8, 9]
4. Visual memory (WASI Block Design)[9]
5. Executive function (WASI Matrix Reasoning [9]

Participants were recruited as part of a large ongoing study on schizophrenia and bipolar disorder, the Thematic Organized Psychosis Research (TOP) Study, which is run from the University Hospitals in Oslo, Norway[10]. They were recruited from out-patient and in-patient psychiatric units at four University Hospitals in Oslo, Norway. The health care system is catchment area based, free of charge, and no other psychiatric health care provider exists. The patients were invited to participate in the study by the clinician responsible for their treatment. Healthy control participants were randomly selected from national statistical records from the same catchment area and contacted by letter inviting them to participate. Exclusion criteria for all groups were: IQ score below 70, hospitalized head injury, neurological disorder, unstable or uncontrolled medical condition that interferes with brain function (including hypothyroidism, uncontrolled hypertension and diabetes),

outside the age range 17-65 years. To assure valid neurocognitive test performance all participants had to have Norwegian as their first language or have received their compulsory schooling in Norway, and had to score ≥15 on the forced recognition trial in the California Verbal Learning Test (CVLT-II)[8]. Neurocognitive assessment was carried out by psychologists trained in standardized neuropsychological testing. The test battery was administered in a fixed order with two breaks with refreshments.

Bonn-Mannheim Sample

Patients from Bonn and Mannheim were collected within the MooDS Consortium and were ascertained as previously described[11]. The study was carried out according to the ethical standards from Declaration of Helsinki. All participants gave written informed consent and the local ethics committees approved the study. Subjects were also part of the PGC schizophrenia data set[12].

The applied instruments to assess cognitive ability differed between subsets of the sample. The present study used data from following domains and measures:

1. Speed of processing:

   Trail Making Test - Part A[13]

2. Executive function:

   Trail Making Test - Part B[13]

3. Working memory:

   Letter-Number Span[14]

4. Verbal learning:

   Verbal learning and memory test (VLMT)[15]

Scores from these tests were used to derive *g*.

GROUP cognitive dataset

Neuropsychological assessments were administered in a fixed order over a testing time of two hours[16-18]. These tests included:

1. Word learning task[18]
2. WAIS-III Digit Symbol Substitution test[17]
3. WAIS-III Information test[17]
4. WAIS-III Arithmetic test[17]
5. WAIS-III Block Design test[17]

These tests cover the majority of MATRICS domains, and the scores from them were used to derive *g*.

CATIE cognitive dataset

Cognitive ability was assessed using a selection of neurocognitive assessments chosen by an expert panel[19, 20]. Education level and the WRAT-III Reading subtest were administered. The following neurocognitive tests were administered.

1. Controlled Oral Word Association Test (Phonological Fluency)[21]

2. Semantic fluency (fruits, animals, vegetables categories)[21]

3. Wechsler Intelligence Scale for Children-third edition (WISC-m) Mazes[22]

4. Letter-Number Span Test[14]

5. Hopkins Verbal Learning Test[23]

6. WAIS-R Digit Symbol Test[24]

For each task, standardised z scores were derived by setting the mean of each measure to 0 and the standard deviation to 1 (across the whole patient sample)[20]. For selected measures, the performance of patients in this sample was compared to normative data derived from the general population. Scores from these six tests were then used to derive *g*.

Irish cognition dataset

Participants completed a full neuropsychological battery of measures to evaluate the cognitive deficits typically reported in schizophrenia (general cognitive function, episodic and working memory, attention, and social cognition). These tests included:

1. WAIS-III Vocabulary test[17]
2. WAIS-III Letter-Number sequencing test[17]
3. WMS-III Logical Memory test[17]

Scores from these tests were used to derive *g*.

Cardiff cognition dataset

Cognitive ability was assessed using the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB)[25, 26]. Excluding the social cognition domain, the MCCB measures seven domains of cognition using nine tasks:

1. Speed of processing (Brief Assessment of Cognition in Schizophrenia: Symbol Coding; Semantic Fluency: Animals; Trail Making Test: Part A)

2. Working memory (Wechsler Memory Scale III: Spatial Span; Letter-Number Span)

3. Attention / vigilance (Continuous Performance Test: Identical Pairs)

4. Verbal learning (Hopkins Verbal Learning Test-Revised)

5. Visual learning (Brief Visuospatial Memory Test-Revised)

6. Executive function (Neuropsychological Assessment Battery: Mazes)

For each task, z scores were derived using the mean and standard deviation of the control group (50% males, mean age = 41.7 years). These scores were then used to derive the g measure of generalised cognition as described below.

PAGES — Phenomics and Genomics Sample cognitive dataset

Within PAGES (Phenomics and Genomics Sample; combined samples from Munich and Halle, Germany)[27], unrelated outpatients or stable inpatients with a diagnosis of schizophrenia were ascertained from mental health services in the Munich. All participants were unrelated Caucasian middle Europeans. Detailed medical and psychiatric histories were collected, including the Structured Clinical Interview for DSM-IV (SCID), to evaluate lifetime Axis I and II diagnoses[28, 29]. Exclusion criteria included a history of head injury or neurological diseases. Participants were also rated for life time symptom severity using the PANSS[30]. Included patients were also part of the Psychiatric Genomics Consortium Schizophrenia Working Group dataset[12].

Written informed consent was obtained from all participants. The study was approved by the local ethics committee of the Ludwig-Maximilians-University, Munich, Germany and carried out according to the ethical standards from Declaration of Helsinki.

All patients completed an extensive neuropsychological battery including the following tests:

1. Speed of processing:

Semantic (categories: food, animals) and phonemic verbal fluency (number of words starting with the letter S (P) in 60s), German version of the fluency test[31]

2. Attention and vigilance

3-7 Continuous Performance Test (d-prime, hits, false alarms)[32]

3. Verbal learning and memory

German version of the California verbal learning test (CVLT/VLMT) (immediate, delayed recall: raw score across 5 trials)[33]

4. Executive functioning

Tower of London (total time across all trials)[34]

EU-GEI sample

An abbreviated version of the WAIS, adapted from the most recent version available in each country was used in cases and controls in order to estimate IQ scores[35]. All versions included Digit Symbol substitution, Arithmetic, Block Design and Information subtests from which raw and scaled scores were derived. An estimated sum of full IQ scaled scores was calculated from the sum of available scaled scores (11/4*sum of scaled scores) and then converted to IQ, by using appropriate tables, standardized for each country. WAIS full scale IQ was derived from four subtests that are also able to estimate cognitive domains, described as follows[36]:

1. Block Design: Visuo-spatial learning and memory

2. Arithmetic: Working memory
3. Digit Symbol Substitution: Processing speed
4. Information: Verbal learning and memory

Exclusion of outlier cognitive test scores

All outlier test scores (those outside three standard deviations of the mean) were manually checked and excluded if they appeared invalid based on the ranges of possible scores on a particular test or if the score was inconsistent with scores on other tests (i.e. scores outside two standard deviations of the mean from other tests).

Genotyping, genotype quality control and imputation of EUGEI and additional Irish samples

These were genotyped at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK) using a custom Illumina HumanCoreExome-24 BeadChip genotyping array covering 570,038 genetic variants[25]. SNP quality control exclusion parameters were: missingness >2%, Hardy Weinberg Equilibrium $p<10^{-6}$. Samples with >2% missingness, heterozygosity F_{het} >0.14 or <-0.11, who failed gender checks or who clustered with non-European samples in PCA analysis were excluded, as were one member of each pair with a relatedness coefficient above 0.2. Genotypes were imputed on the Michigan Imputation Server using the Haplotype Reference Consortium reference panel (version 1.1) and the programs Eagle for haplotype phasing and Minimac3 for imputation[37-39]. After imputation, variants with an imputation r2 > 0.6, MAF > 0.1% and missingness < 1% were retained for further analysis.

Genotyping, genotype quality control and imputation of CardiffCOGS samples

The CardiffCOGS samples were genotyped on Illumina HumanOmniExpress-12 and OmniExpressExome-8 arrays and then quality controlled as previously described[40]. SNP quality control exclusion parameters were: missingness >2% and Hardy Weinberg Equilibrium $p<10^{-6}$. Samples with >2% missingness, who failed gender checks or who appeared non-European in PCA analysis were excluded, as were one member of each pair with a relatedness coefficient above 0.2. The dataset was imputed using the 1000 Genomes phase 3 reference panel with the programs SHAPEIT for haplotype phasing and IMPUTE2 for imputation[41-43]. Variants with INFO >0.3 and MAF >0.1% were retained for further analysis.

Choice of P_T threshold for primary analysis

Schizophrenia PRS using P_T=0.05 is the median and modal threshold that maximally explains variance in schizophrenia case/control status in the leave-one-out analysis in the PGC2 SZ study[12]. Similarly, bipolar disorder PRS using P_T=0.05 explained the most variance in bipolar disorder case/control status in any leave-one-out analysis in the PGC BD study[44]. Hence, P_T=0.05 was used for the primary analysis in SZ and BD. In the PGC major depressive disorder GWAS, P_T=0.5 explained the most variance in all the replication analyses and so was used for the primary analysis[45].

In the IQ study, IQ PRS using P_T=0.058 explained the most variance in their largest replication analysis [46]. The closest threshold we examined was P_T=0.05, so we used this as our primary analysis. In the educational attainment study, only P_T=1, $5x10^{-8}$, $5x10^{-5}$ and $5x10^{-3}$ were used in replication analyses, with the most variance being explained by P_T=1 and P_T=$5x10^{-3}$ [47]. As P_T=0.05 fell between these two values and we wished to treat EA and IQ in a parallel manner given their phenotypic similarities, we used P_T=0.05 for the primary analysis of EA.

PRS power calculations

The R package AVENGEME was used to estimate the expected power of the PRS of the training sets to predict cognition in a dataset this size[48, 49], under the assumptions that cognitive variation in cases has similar heritability and cross-trait genetic correlations as IQ in the general population. These assumptions, which essentially correspond to power to test hypothesis 2, were required as little is known about the relevant parameters within cases. For all training sets except BD, our power to detect true effects was estimated to be over 99% (Supplementary Table 3). For BD, the lower genetic correlation with cognition meant our estimated power was 10.8%.

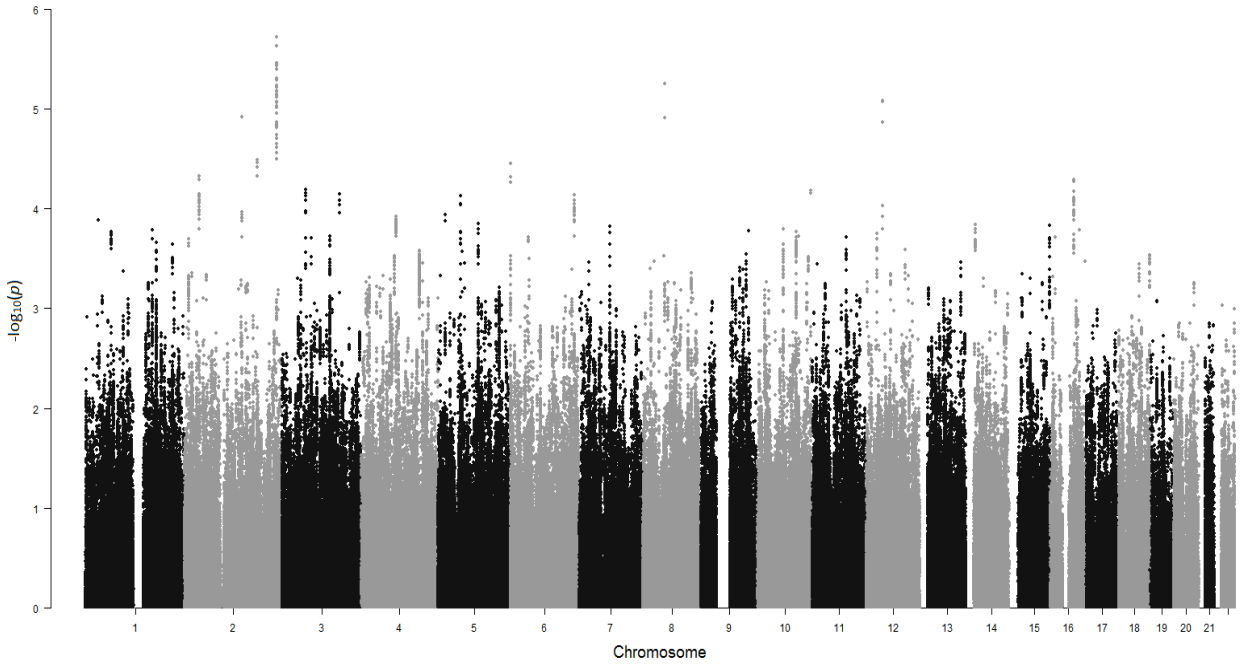
Defining schizophrenia, bipolar disorder and psychotic disorder in UK Biobank Wave 2 sample

Samples with a diagnosis of bipolar disorder, schizophrenia, or other psychosis were excluded from UK Biobank Wave 2 PRS analysis. We searched for evidence of a diagnosis of schizophrenia, bipolar affective disorder, and psychotic disorder from numerous sources within UK Biobank. Individuals were classed as having one of these disorders if there was any indication from any of the following sources (i) self-reported diagnosis at the assessment centre interview (UKBB field ID: 20002), (ii) an ICD-10 primary (UKBB field ID: 41202) or secondary (UKBB field ID: 41204) diagnosis from linked hospital records, (iii) an ICD-10 diagnosis from death records (UKBB field IDs: 40001 and 40002), or (iv) a self-reported diagnosis by a professional in the mental health questionnaire (MHQ) (UKBB field ID: 20544). The ICD-10 codes used for schizophrenia included F20 and F25, for bipolar affective disorder we included F30 and F31, and for psychotic disorder we included F21, F22, F23, F28 and F29.

Constructing IQ PRS in UK Biobank Wave 2 sample

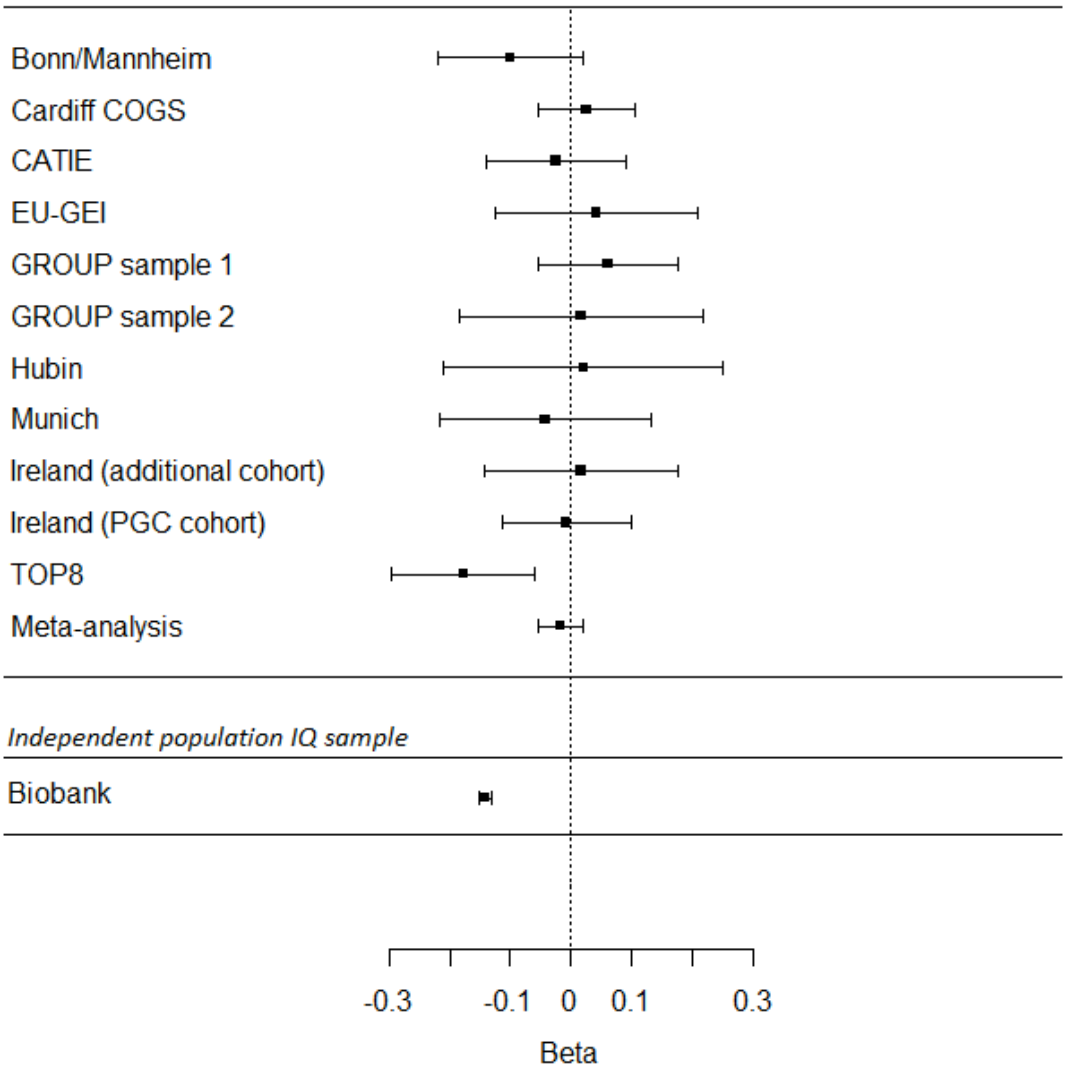
The training set for the IQ PRS in Biobank was a version of Savage *et al* with Biobank samples excluded[46]. The training set for the SZ PRS was taken from Pardinas *et al*[40]. The PRS was calculated in PRSice (v2) using imputation dosage data for each UK Biobank participant that passed QC measures[50]. One member from each related pair with a kinship coefficient > 0.15 was excluded at random and analyses were restricted to individuals with European genetic ancestry. We selected high quality SNPs to calculate the PRS: INFO > 0.9, MAF > 0.1, missingness < 0.05, Hardy-Weinberg equilibrium (HWE) < 1×10^{-6}, removed indels, and excluded the extended MHC region (25 MB – 35 MB). A reference panel of 1000 randomly selected UK Biobank participants was used to obtain relatively independent SNPs (r^2 < 0.2, window size < 500kb).

Supplementary Figures

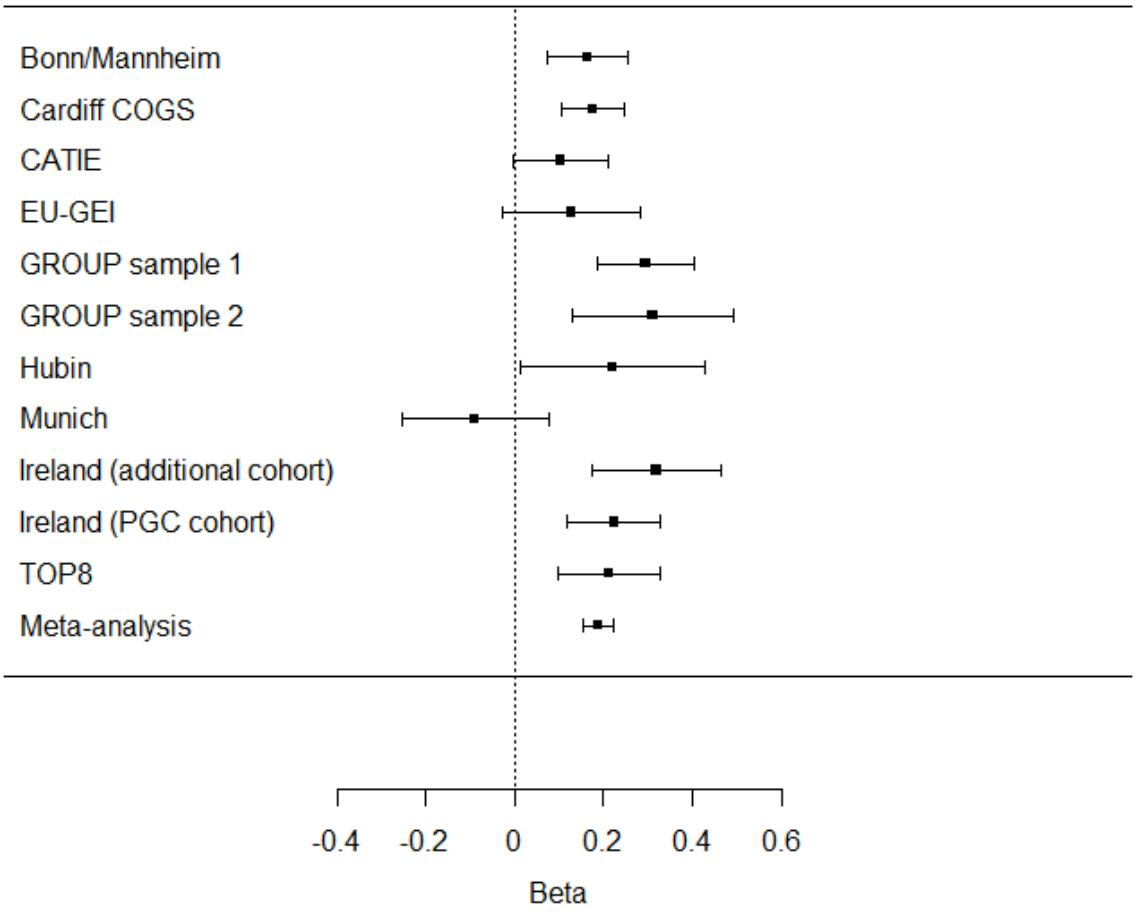


Supplementary Figure 1. Manhattan plot of GWAS of *g* meta-analysis

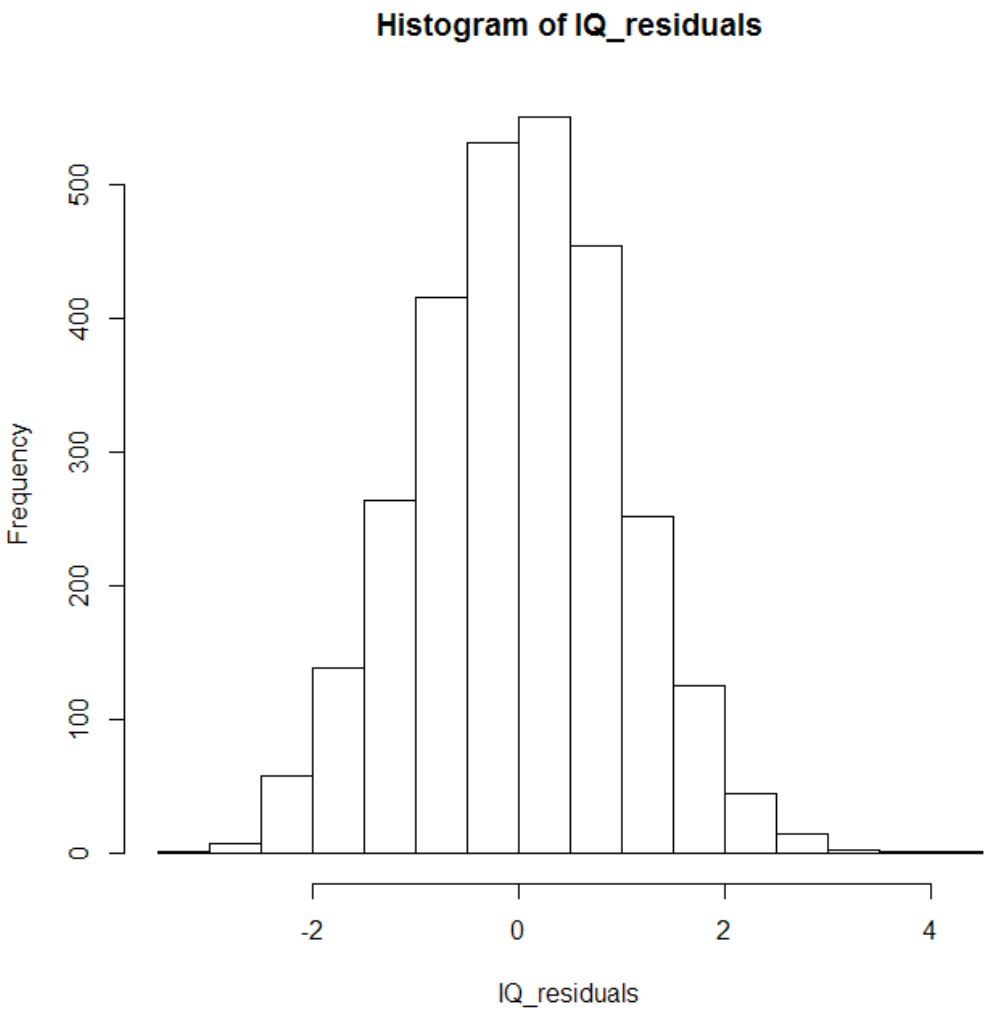
Supplementary Figure 2. Quantile-quantile plot of GWAS of *g* meta-analysis



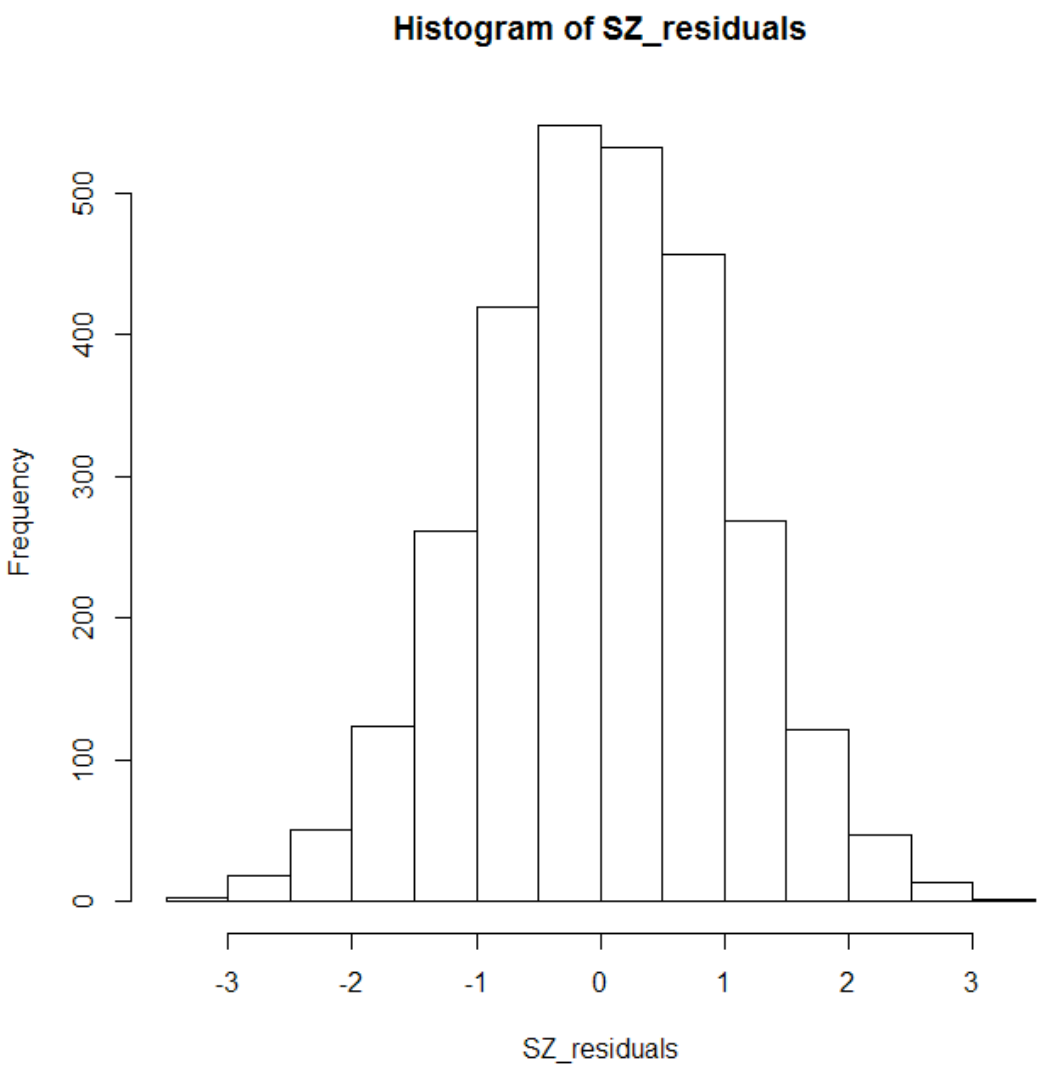
Supplementary Figure 3. Forest plot showing effect sizes and confidence intervals for regression of *g* on schizophrenia polygenic risk score (age, sex and population principal component covariates also included in model). Effect sizes based on standardised values of *g*/IQ and PRS (effect size is the number of standard deviations change in *g*/IQ that occurs when PRS changes by 1 standard deviation). WAIS IQ used instead of *g* for EU-GEI dataset. Lower panel shows regression of IQ on SZ polygenic risk score in an independent population dataset, the UK Biobank (n=133437).



Supplementary Figure 4. Forest plot showing effect sizes and confidence intervals for regression of *g* on educational attainment polygenic risk score (age, sex and population principal component covariates also included in model). Effect sizes based on standardised values of *g*/IQ and PRS (effect size is the number of standard deviations change in *g*/IQ that occurs when PRS changes by 1 standard deviation). WAIS IQ used instead of *g* for EU-GEI dataset.



Supplementary Figure 5. Histogram of scaled IQ PRS residual values (after effects of covariates removed with linear regression) across all subsets of data. Shapiro-Wilks normality test p-value=0.053, kurtosis=3.02.



Supplementary Figure 6. Histogram of scaled SZ PRS residual values (after effects of covariates removed with linear regression) across all subsets of data. Shapiro-Wilks normality test p-value=0.567, kurtosis=2.91.

Supplementary Tables

Dataset	Cognitive domain	Test	N
GROUP sample 1	Speed of processing	WAIS digit symbol substitution	309
	Verbal learning and memory	WAIS information	309
		Brand and Jolles word learning task	304
	Visuo-spatial learning and memory	WAIS block design	308
	Working memory	WAIS arithmetic	309
GROUP sample 2	Speed of processing	WAIS digit symbol substitution	119
	Verbal learning and memory	WAIS information	119
		Brand and Jolles word learning task	117
	Visuo-spatial learning and memory	WAIS block design	119
	Working memory	WAIS arithmetic	119
EU-GEI	Speed of processing	WAIS digit symbol substitution	156
	Verbal learning and memory	WAIS information	156
	Visuo-spatial learning and memory	WAIS block design	156
	Working memory	WAIS arithmetic	156
CATIE	Executive function	WISC-m mazes	342
	Speed of processing	WAIS digit symbol substitution	348
		Semantic fluency (fruits, animals, vegetables categories)	350
	Verbal learning and memory	Hopkins verbal learning test	348
		Controlled oral word association test	350
	Working memory	Letter number span	347
Cardiff cognition	Attention/Vigilance	Continuous Performance Test	601
	Executive function	Mazes (NAB)	647
	Speed of processing	Trail Making Test - part A	647
		Semantic fluency (animals category)	646
		Symbol Coding	640
	Verbal learning and memory	Hopkins verbal learning test	648
	Visuo-spatial learning and memory	Brief Visuospatial Memory Test Revised	644
	Working memory	Letter number span	642
		Spatial Span (WMS-III)	645
	Attention/Vigilance	Continuous Performance Test	77
	Executive function	Trail Making Test - part B	77
		Wisconsin card sorting test	77
	Speed of processing	Trail Making Test - part A	77

	Verbal learning and memory	Rey Auditory Verbal Learning Test	77
	Working memory	Letter number span	77
PAGES	Attention/Vigilance	Continuous Performance Test	144
	Executive function	Tower of London	145
	Speed of processing	Semantic fluency (food category)	146
		Phonemic Fluency (words starting with letter 'X')	146
	Verbal learning and memory	California Verbal Learning Test (immediate and delayed recall)	148
TOP	Executive function	WASI Matrix Reasoning	285
	Speed of processing	WAIS Digit-Symbol Substitution	285
	Verbal learning and memory	California Verbal Learning Test (delayed recall and total score)	283
		WASI Vocabulary	282
	Visuo-spatial learning and memory	WASI Block Design	279
	Working memory	WAIS Digit Span	286
Ireland (PGC samples)	Verbal learning and memory	WAIS-III Vocabulary	346
	Working memory	WMS-III Logical Memory	333
		WAIS-III Letter number span	326
Ireland (additional samples)	Verbal learning and memory	WAIS-III Vocabulary	162
	Working memory	WMS-III Logical Memory	160
		WAIS-III Letter number span	161
Bonn/ Mannheim	Executive function	Trail Making Test - part B	436
	Speed of processing	Trail Making Test - part A	437
	Verbal learning and memory	Verbal learning and memory test (VLMT)	196
	Working memory	Letter number span	212

Supplementary Table 1. Cognitive domains and tests available in each dataset. N indicates number of genotyped samples available for each test.

Dataset	**r**
Hubin	-0.99992
PAGES	-0.99924
TOP	0.999965
Ireland (PGC samples)	-0.99961
Bonn/Mannheim	-0.95418

Supplementary Table 2. Correlation between values of *g* derived from MDS and PCA.

Phenotype	Training set	Sample size	Power
Schizophrenia	PGC2 SZ (excluding cognitively informative samples)[12]	29958 cases, 39204 controls	0.998
Bipolar disorder	PGC Bipolar Disorder[44]	20352 cases, 31358 controls	0.108
Major depression	PGC MDD, Generation Scotland, GERA, deCODE, iPsych and UK Biobank meta-analysis[45]	51865 cases, 112200 controls	1.000
IQ	Savage *et al*[46]	269867 population samples	1.000
Educational attainment	Lee *et al*[47]	1131881 population samples	1.000

Supplementary Table 3. Training sets for PRS construction. Power is calculated using the R package AVENGEME.

Dataset	**Intelligence measure used**	**Predictor and covariates used**
PGC datasets	*g* (derived by MDS)	Normalised PRS, age, sex, 10 population principal components
Cardiff COGS dataset	*g* (derived by MDS)	Normalised PRS, age, sex, 10 population principal components
Additional Irish samples	*g* (derived by MDS)	Normalised PRS, age, sex, 10 population principal components
EU-GEI WP2 dataset	WAIS IQ	Normalised PRS, age, sex, country, 5 population principal components
Biobank population dataset	Fluid intelligence	Normalised PRS, age, sex, 14 population principal components

Supplementary Table 4. Parameters used in regression model. First 5 population principal components used for EU-GEI dataset. 10 population principal components used for PGC, COGS and additional Irish samples were those that showed association with SZ phenotype in PGC analysis[12]. 14 population principal components used for Biobank were those that showed association with fluid intelligence in Biobank.

SNP	CHR	BP	A1	A2	A1 Frequency	Effect size estimate	Standard error	P
rs911216	1	34375199	A	C	0.7963	0.1947	0.0509	0.0001317
rs1556742	1	95674341	A	C	0.3493	-0.1529	0.0433	0.0004215
rs10919140	1	169296744	A	T	0.1446	0.2258	0.06	0.0001656
rs16867210	2	10017166	A	G	0.241	-0.1843	0.0495	0.0001999
rs1396074	2	17339482	T	C	0.3233	0.1536	0.0437	0.0004424
rs34439217	2	36656809	A	T	0.1477	-0.2369	0.0582	4.72E-05
rs17045898	2	54660795	T	C	0.1687	0.1977	0.0565	0.0004644
rs2679441	2	142030276	A	T	0.2523	-0.2096	0.0479	1.20E-05
rs3106704	2	180486040	T	C	0.8929	-0.2813	0.0677	3.29E-05
rs60026510	2	228766207	A	G	0.5173	0.1974	0.0414	1.91E-06
rs73837372	3	59536718	T	G	0.8086	-0.2132	0.0534	6.49E-05
rs12632137	3	72285695	A	G	0.6117	0.1597	0.0429	0.0001974
rs6787458	3	119944395	T	C	0.0825	-0.2848	0.0763	0.0001912
rs6440154	3	142943025	A	G	0.3066	-0.18	0.0453	7.14E-05
rs114492241	4	19459837	C	G	0.0973	-0.2455	0.0705	0.0004945
rs2590820	4	54481514	T	C	0.5835	-0.1452	0.0415	0.0004722
rs116226341	4	82669798	T	C	0.1187	0.231	0.0639	0.0002986
rs11097084	4	86880701	T	C	0.7702	0.1899	0.0494	0.0001192
rs13134571	4	144659924	T	G	0.3277	-0.1564	0.0429	0.0002644
rs551305	4	152827837	A	G	0.5511	-0.1477	0.0414	0.0003566
rs181181726	5	6388840	A	C	0.0951	0.2479	0.0709	0.000474
rs35181898	5	19081083	T	C	0.7911	0.194	0.0503	0.0001156
rs96844	5	56196604	A	G	0.7454	-0.1874	0.0473	7.52E-05
rs7711530	5	61606610	T	C	0.6824	-0.1635	0.0449	0.0002678
rs190480	5	66133356	T	C	0.4811	0.1475	0.0413	0.0003498
rs6596210	5	101287088	T	C	0.3918	-0.163	0.0429	0.000142
rs1161903	6	946027	A	C	0.1897	0.2169	0.0525	3.57E-05
rs6902996	6	44475099	A	T	0.2499	-0.1786	0.0479	0.0001955
rs6914894	6	47695732	T	C	0.2162	0.1784	0.0496	0.0003196
rs1781624	6	154126171	A	G	0.3083	0.1578	0.0446	0.0004083
rs923198	6	159246717	T	C	0.4994	-0.1638	0.0413	7.32E-05
rs2938106	7	25580518	T	C	0.1123	-0.2407	0.0673	0.0003463
rs34236870	7	77547868	T	C	0.1164	-0.2437	0.0643	0.0001519
rs6997340	8	18286997	T	C	0.2768	-0.1601	0.0452	0.0004032
rs10095540	8	29355491	T	G	0.5466	-0.15	0.0419	0.0003419
rs7814396	8	55325204	A	G	0.9008	0.3207	0.0706	5.63E-06
rs1714656	8	122006764	A	G	0.5931	-0.1467	0.0417	0.0004406
rs10992382	9	95361063	A	C	0.7796	0.1747	0.0493	0.0003891
rs2786719	9	104598306	C	G	0.2675	0.1655	0.0468	0.0004048
rs12683723	9	117913870	A	G	0.922	0.2961	0.0787	0.000167
rs2136614	10	64701286	A	G	0.8601	0.2285	0.0606	0.0001615

rs61886339	10	96032866	T	C	0.6963	-0.1656	0.044	0.0001695
rs7091572	10	101327851	T	C	0.7254	0.1718	0.046	0.0001905
rs2459215	10	126089656	T	G	0.1825	0.194	0.0537	0.0003065
rs7894208	10	132757095	C	G	0.1595	-0.2297	0.0576	6.62E-05
rs10500797	11	13724572	T	C	0.2809	-0.1644	0.0461	0.0003618
rs475639	11	85689785	T	C	0.5314	-0.1545	0.0415	0.0001955
rs79565578	12	26601174	A	G	0.9111	0.2772	0.074	0.0001783
rs11177934	12	41099692	A	G	0.1357	-0.2696	0.0605	8.35E-06
rs10784131	12	61493136	A	T	0.612	-0.1493	0.0426	0.0004562
rs2032774	12	96651259	T	C	0.8863	0.2414	0.0661	0.0002593
rs12306148	12	106060589	T	G	0.9027	0.2427	0.0694	0.0004687
rs61966487	13	102662432	T	C	0.9274	-0.2894	0.0809	0.0003482
rs2331811	14	23199335	A	G	0.8564	-0.226	0.0595	0.0001448
rs11632769	15	33215074	T	C	0.3892	0.1484	0.0423	0.0004564
rs624613	15	53716187	A	G	0.6534	0.1512	0.0434	0.0004972
rs7180870	15	100621837	A	T	0.9405	-0.3319	0.0875	0.0001482
rs34864899	16	7986406	A	G	0.9054	-0.2459	0.0704	0.0004781
rs13339382	16	12269935	A	G	0.065	0.3168	0.085	0.0001935
rs9930096	16	60284392	A	G	0.2356	0.1949	0.0481	5.13E-05
rs12446726	16	74173688	C	G	0.1125	0.2496	0.0663	0.0001652
rs58407170	16	87753841	A	G	0.8321	-0.1953	0.0545	0.0003384
rs6508210	18	50747191	A	C	0.4514	0.148	0.0415	0.0003597
rs12961692	18	77508336	T	C	0.5154	0.1501	0.0415	0.0002946

Supplementary Table 5. Variants with association p<1e-4 in GWAS of *g.*

Training set	P-value threshold	Effect size (fixed effects)	SE (fixed effects)	P-value (fixed effects)	Meta-analysis I^2	P-value (random effects)
Bipolar disorder	1	-0.015	0.019	0.426	43.8	0.528
Bipolar disorder	0.5	-0.015	0.019	0.412	43.6	0.492
Bipolar disorder	0.3	-0.012	0.019	0.510	30.5	0.632
Bipolar disorder	0.2	-0.015	0.019	0.433	42.7	0.553
Bipolar disorder	0.1	-0.025	0.019	0.177	45.3	0.425
Bipolar disorder	0.05	-0.012	0.018	0.509	44.8	0.644
Bipolar disorder	0.01	-0.006	0.018	0.732	34.8	0.848
Bipolar disorder	1.00E-04	0.001	0.018	0.976	0	0.976
Bipolar disorder	1.00E-06	0.005	0.018	0.767	0	0.767
Bipolar disorder	5.00E-08	0.015	0.018	0.387	0	0.387
Major depression	1	-0.012	0.018	0.508	0	0.508
Major depression	0.5	-0.013	0.018	0.488	0	0.488
Major depression	0.3	-0.010	0.018	0.572	0	0.572
Major depression	0.2	-0.001	0.018	0.947	0	0.947
Major depression	0.1	0.008	0.018	0.646	0	0.646
Major depression	0.05	0.009	0.018	0.598	0	0.598
Major depression	0.01	0.013	0.018	0.472	29.6	0.488
Major depression	1.00E-04	-0.026	0.018	0.145	0	0.145
Major depression	1.00E-06	0.009	0.018	0.623	53.7	0.677
Major depression	5.00E-08	0.005	0.018	0.778	27	0.950
Schizophrenia	1	-0.019	0.020	0.338	28.9	0.819
Schizophrenia	0.5	-0.023	0.020	0.253	29.4	0.900
Schizophrenia	0.3	-0.026	0.020	0.187	28.7	0.927
Schizophrenia	0.2	-0.022	0.020	0.272	17.4	0.675
Schizophrenia	0.1	-0.018	0.020	0.354	2.7	0.499
Schizophrenia	0.05	-0.017	0.019	0.386	22.3	0.494

Schizophrenia	0.01	-0.031	0.019	0.097	26	0.575
Schizophrenia	1.00E-04	-0.026	0.018	0.149	29.1	0.660
Schizophrenia	1.00E-06	-0.040	0.018	0.024	55.6	0.660
Schizophrenia	5.00E-08	-0.019	0.018	0.275	34.3	0.853
IQ	1	0.198	0.018	3.36E-27	20.5	1.31E-20
IQ	0.5	0.198	0.018	2.81E-27	13.6	1.16E-22
IQ	0.3	0.202	0.018	2.45E-28	27.7	2.69E-19
IQ	0.2	0.202	0.018	2.17E-28	21.6	4.66E-21
IQ	0.1	0.201	0.018	1.64E-28	31.5	1.92E-18
IQ	0.05	0.199	0.018	4.39E-28	31.6	2.13E-18
IQ	0.01	0.177	0.018	4.20E-23	39	7.16E-14
IQ	1.00E-04	0.132	0.018	1.15E-13	44	4.46E-08
IQ	1.00E-06	0.098	0.018	4.04E-08	16.4	1.08E-06
IQ	5.00E-08	0.089	0.018	7.43E-07	0	7.43E-07
Educational attainment	1	0.183	0.018	3.28E-25	52.7	2.21E-11
Educational attainment	0.5	0.182	0.018	7.43E-25	54.5	8.07E-11
Educational attainment	0.3	0.185	0.018	7.13E-26	54.1	2.57E-11
Educational attainment	0.2	0.182	0.018	5.06E-25	54	4.81E-11
Educational attainment	0.1	0.187	0.018	2.34E-26	59.7	2.94E-10
Educational attainment	0.05	0.188	0.018	1.27E-26	57.9	5.02E-11
Educational attainment	0.01	0.178	0.018	5.37E-24	61.2	1.79E-09
Educational attainment	1.00E-04	0.15	0.018	2.22E-17	47.9	8.11E-09
Educational attainment	1.00E-06	0.145	0.018	2.43E-16	47.7	8.32E-08
Educational attainment	5.00E-08	0.132	0.018	1.18E-13	40.3	2.83E-07

Supplementary Table 6. Meta-analysis of regression of *g* on PRS across multiple p-value thresholds.

Training set	P-value threshold	Effect size	SE	P-value
Bipolar disorder	0.05	-0.012	0.02	0.54
Major depression	0.05	0.010	0.02	0.62
Schizophrenia	0.05	-0.011	0.02	0.61
IQ	0.05	0.202	0.02	1.53E-25
Educational attainment	0.05	0.201	0.02	8.46E-27

Supplementary Table 7. Meta-analysis of regression of *g* on PRS at P_T=0.05, sensitivity analysis excluding the EU-GEI dataset and samples with two or fewer cognitive tests available

References

1. Ekerholm M, Firus Waltersson S, Fagerberg T, Soderman E, Terenius L, Agartz I, Jonsson EG, Nyman H. Neurocognitive function in long-term treated schizophrenia: a five-year follow-up study. *Psychiatry research* Dec 30 2012;200(2-3):144-152.

2. Jonsson EG, Edman-Ahlbom B, Sillen A, et al. Brain-derived neurotrophic factor gene (BDNF) variants and schizophrenia: an association study. *Progress in neuro-psychopharmacology & biological psychiatry* Jul 2006;30(5):924-933.

3. Lawyer G, Nyman H, Agartz I, Arnborg S, Jonsson EG, Sedvall GC, Hall H. Morphological correlates to cognitive dysfunction in schizophrenia as studied with Bayesian regression. *Bmc Psychiatry* 2006;6.

4. Nesvag R, Frigessi A, Jonsson EG, Agartz I. Effects of alcohol consumption and antipsychotic medication on brain morphology in schizophrenia. *Schizophrenia research* Feb 2007;90(1-3):52-61.

5. Vares M, Ekholm A, Sedvall GC, Hall H, Jonsson EG. Characterization of patients with schizophrenia and related psychoses: Evaluation of different diagnostic procedures. *Psychopathology* 2006;39(6):286-295.

6. Ekholm B, Ekholm A, Adolfsson R, Vares M, Osby U, Sedvall GC, Jonsson EG. Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. *Nordic journal of psychiatry* 2005;59(6):457-464.

7. Wechsler D. *Wechsler Adult Intelligence Scale - Third Edition (WAIS-III). Norwegian manual.* Stockholm: Pearson Assessment; 2003.

8. Delis DC, Kramer JH, Kaplan E, Ober BA. *California Verbal Learning Test - Second Edition (CVLT-II). Norwegian Manual supplement.* Stockholm: Pearson Assessment; 2004.

9. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI). Norwegian manual supplement.* Stockholm: Pearson Assessment; 2007.

10. Athanasiu L, Mattingsdal M, Kahler AK, et al. Gene variants associated with schizophrenia in a Norwegian genome-wide study are replicated in a large European cohort. *Journal of psychiatric research* Sep 2010;44(12):748-753.

11. Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. *Nature* Aug 6 2009;460(7256):744-747.

12. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* Jul 24 2014;511(7510):421-427.

13. Arnett JA, Labovitz SS. Effect of Physical Layout in Performance of the Trail Making Test. *Psychol Assessment* Jun 1995;7(2):220-221.

14. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Archives of general psychiatry* Feb 1997;54(2):159-165.

15. Helmstaedter C, Durwen HF. [The Verbal Learning and Retention Test. A useful and differentiated tool in evaluating verbal memory performance]. *Schweizer Archiv fur Neurologie und Psychiatrie* 1990;141(1):21-30.

16. Korver N, Quee PJ, Boos HB, Simons CJ, de Haan L, investigators G. Genetic Risk and Outcome of Psychosis (GROUP), a multi-site longitudinal cohort study focused on gene-environment interaction: objectives, sample characteristics, recruitment and assessment methods. *International journal of methods in psychiatric research* Sep 2012;21(3):205-221.

17. Wechsler D. *WAIS-III: Wechsler Adult Intelligence Scale (3rd edition) Administration and Scoring Manual*. San Antonio, TX: Psychological Corporation; 1997.

18. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. *The Journal of general psychology* Apr 1985;112(2):201-210.

19. Keefe RS, Mohs RC, Bilder RM, Harvey PD, Green MF, Meltzer HY, Gold JM, Sano M. Neurocognitive assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project schizophrenia trial: development, methodology, and rationale. *Schizophrenia bulletin* 2003;29(1):45-55.

20. Keefe RS, Bilder RM, Harvey PD, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* Sep 2006;31(9):2033-2046.

21. Benton AL, Hamscher K. *Multilingual Aphasia Examination Manual (revised)*. Iowa City, LA: University of Iowa; 1978.

22. Wechsler D. *Wechsler Intelligence Scale for Children*. San Antonio, TX: Psychological Corporation; 1991.

23. Brandt J. The hopkins verbal learning test: Development of a new memory test with six equivalent forms. *Clinical Neuropsychologist* 1991;5(2):125-142.

24. Wechsler D. *Wechsler Adult Intelligence Scale-Revised*. San Antonio, TX: Psychological Corporation; 1974.

25. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *The American journal of psychiatry* Feb 2008;165(2):203-213.

26. Kern RS, Nuechterlein KH, Green MF, et al. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. *The American journal of psychiatry* Feb 2008;165(2):214-220.

27. Ingason A, Giegling I, Hartmann AM, et al. Expression analysis in a rat psychosis model identifies novel candidate genes validated in a large case-control sample of schizophrenia. *Translational psychiatry* Oct 13 2015;5:e656.

28. First M, Gibbon M, Spitzer R, Williams J, Benjamin L. *Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II)*. Washington, D.C.: American Psychiatric Press, Inc.; 1997.

29. First MB, Spitzer RL, Gibbon M, Williams JB. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington D.C.: American Psychiatric Press, Inc.; 1996.

30. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin* 1987;13(2):261-276.

31. Aschenbrenner S, Tucha O, Lange KW. *Regensburger verbal fluency test*: Hogsrefe; 2000.

32. Nuechterlein K, Arsanow R. *3-7 Continuous Performance Test*. Los Angeles: University of California; 2004.

33. Helmstaedter C, Lendt M, Lux S. *Verbaler Lern- und Merkfähigkeitstest (VLMT*. Goettingen: Beltz; 2001.

34. Tucha O, Lange KW. *TL- D Turm von London - Deutsche Version*. Goettingen: Hogrefe; 2004.

35. Ryan JJ, Lopez SJ, Werth TR. Administration time estimates for WAIS-III subtests, scales, and short forms in a clinical sample. *J Psychoeduc Assess* Dec 1998;16(4):315-323.

36. Taub GE, Benson N. Matters of Consequence: An Empirical Investigation of the WAIS-III and WAIS-IV and Implications for Addressing the Atkins Intelligence Criterion. *J Forensic Psychol P* Jan 1 2013;13(1):27-48.

37. Das S, Forer L, Schonherr S, et al. Next-generation genotype imputation service and methods. *Nature genetics* Oct 2016;48(10):1284-1287.

38. McCarthy S, Das S, Kretzschmar W, et al. A reference panel of 64,976 haplotypes for genotype imputation. *Nature genetics* Oct 2016;48(10):1279-1283.

39. Loh PR, Danecek P, Palamara PF, et al. Reference-based phasing using the Haplotype Reference Consortium panel. *Nature genetics* Nov 2016;48(11):1443-1448.

40. Pardinas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nature genetics* Mar 2018;50(3):381-389.
41. Genomes Project C, Auton A, Brooks LD, et al. A global reference for human genetic variation. *Nature* Oct 1 2015;526(7571):68-74.
42. Delaneau O, Marchini J, Zagury JF. A linear complexity phasing method for thousands of genomes. *Nature methods* Dec 4 2011;9(2):179-181.
43. Howie BN, Donnelly P, Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS genetics* Jun 2009;5(6):e1000529.
44. Stahl EA, Breen G, Forstner AJ, et al. Genomewide association study identifies 30 loci associated with bipolar disorder. *bioRxiv* 2018(doi: 10.1101/173062).
45. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature genetics* May 2018;50(5):668-681.
46. Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. *Nature genetics* Jul 2018;50(7):912-919.
47. Lee JJ, Wedow R, Okbay A, et al. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature genetics* Aug 2018;50(8):1112-1121.
48. Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS genetics* Mar 2013;9(3):e1003348.
49. Palla L, Dudbridge F. A Fast Method that Uses Polygenic Scores to Estimate the Variance Explained by Genome-wide Marker Panels and the Proportion of Variants Affecting a Trait. *American journal of human genetics* Aug 6 2015;97(2):250-259.
50. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics* May 1 2015;31(9):1466-1468.