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Polygenic risk score increases schizophrenia liability through cognition-relevant pathways

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Cognitive deficit is thought to represent, at least in part, genetic mechanisms of risk for schizophrenia, with recent evidence from statistical modelling of twin data suggesting direct causality from the former to the latter. However, earlier evidence was based on inferences from twin not molecular genetic data and it is unclear how much genetic influence 'passes through' cognition on the way to diagnosis. Thus, we included direct measurements of genetic risk (e.g. schizophrenia polygenic risk scores) in causation models to assess the extent to which cognitive deficit mediates some of the effect of polygenic risk scores on the disorder. Causal models of family data tested relationships among key variables and allowed parsing of genetic variance components. Polygenic risk scores were calculated from summary statistics from the current largest genome-wide association study of schizophrenia and were represented as a latent trait. Cognition was also modelled as a latent trait. Participants were 1313 members of 1078 families: 416 patients with schizophrenia, 290 unaffected siblings, and 607 controls. Modelling supported earlier findings that cognitive deficit has a putatively causal role in schizophrenia. In total, polygenic risk score explained 8.07% [confidence interval (CI) 5.45–10.74%] of schizophrenia risk in our sample. Of this, more than a third (2.71%, CI 2.41–3.85%) of the polygenic risk score influence was mediated through cognition paths, exceeding the direct influence of polygenic risk score on schizophrenia risk (1.43%, CI 0.46–3.08%). The remainder of the polygenic risk score influence (3.93%, CI 2.37–4.48%) reflected reciprocal causation between schizophrenia liability and cognition (e.g. mutual influences in a cyclical manner). Analysis of genetic variance components of schizophrenia liability indicated that 26.87% (CI 21.45–32.57%) was associated with cognition-related pathways not captured by polygenic risk score. The remaining variance in schizophrenia was through pathways other than cognition-related and polygenic risk score. Although our results are based on inference through statistical modelling and do not provide an absolute proof of causality, we find that cognition pathways mediate a significant part of the influence of cumulative genetic risk on schizophrenia. We estimate from our model that 33.51% (CI 27.34–43.82%) of overall genetic risk is mediated through influences on cognition, but this requires further studies and analyses as the genetics of schizophrenia becomes better characterized.

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Abbreviations: L-COG = cognition, latent; L-PRS = polygenic risk scores, latent; L-SZ = schizophrenia liability; PGC = Psychiatric Genomics Consortium; PRS = polygenic risk score; SNP = single nucleotide polymorphism

Introduction

A wealth of evidence from adoption, family, and twin studies as well as from linkage and association studies confirms genetics contribute significantly to risk for schizophrenia (Sullivan *et al.*, 2003*b*; Lichtenstein *et al.*, 2009; Purcell *et al.*, 2009; Ripke *et al.*, 2013). While earlier association studies resulted in few replicated findings, recent large-scale genome-wide association studies (GWAS), which allow for testing of millions of single nucleotide polymorphisms (SNPs) in the genome, have produced statistically robust results implicating over 100 independent risk loci across the genome (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Gandal *et al.*, 2016). Common SNPs appear to contribute the majority of interindividual variation in schizophrenia risk (Purcell *et al.*, 2009; Bergen and Petryshen, 2012; Ripke *et al.*, 2013), while copy number variants (CNVs), including rare *de novo* and inherited CNVs, contribute small increments in population risk variation despite larger effect sizes (Manolio *et al.*, 2009; Malhotra and Sebat, 2012; Kotlar *et al.*, 2015; Genovese *et al.*, 2016). The cumulative sum of risk associated alleles at common variants across the genome derived from the recent Psychiatric Genomic Consortium (PGC) genome-wide association study, a so-called polygenic risk score (PRS), has been shown to account for ~7% of the variance in disease risk (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

One strategy that has been used to understand how risk-associated SNPs might affect brain function is to examine their relationship with measures of brain structure and function that are consistently altered in schizophrenia, and which may represent inherited biological mechanisms of risk (e.g. endophenotypes or intermediate phenotypes) (Flint *et al.*, 2014; Glahn *et al.*, 2014; Blokland *et al.*, 2018). In this regard, numerous patient, family, twin, prospective, and high-risk studies have shown that schizophrenia is associated with deviations in cognition, in brain neurophysiology, and to a less consistent degree, structure (Friston and Frith, 1995; Callicott *et al.*, 2000; Pantelis *et al.*, 2003; Bramon *et al.*, 2004; Ragland *et al.*, 2009; Olincy *et al.*, 2010; van den Heuvel *et al.*, 2013; Crossley *et al.*, 2016). To the extent that these deviations are found in unaffected relatives, they have been considered as representing inherited neurobiological risk rather than effects of the disease state (Goldberg *et al.*, 1995; Gur *et al.*, 2007*a*, *b*; Wood *et al.*, 2008; Waters-Metenier and Toulopoulou, 2010, 2011*a*, *b*; Owens *et al.*, 2012; Millard *et al.*, 2016).

One of the most consistently and robustly implicated intermediate phenotypes in schizophrenia is cognitive deficit (Schaefer *et al.*, 2013; Mark and Toulopoulou, 2016). Cognitive deficits associated with schizophrenia have been shown to be: (i) heritable and aggregate amongst unaffected family members of individuals with schizophrenia including parents and healthy siblings (Egan *et al.*, 2001*a*; Toulopoulou *et al.*, 2003*a*, *b*; Gur *et al.*, 2007*b*; Calkins *et al.*, 2013; Zhang *et al.*, 2016); (ii) are more concordant among identical than non-identical schizophrenia twins who are discordant for the clinical disorder (Cannon *et al.*, 2000*b*; Toulopoulou *et al.*, 2007); and (iii) are observed in children and adults who later develop schizophrenia (Cannon *et al.*, 2000*a*; Reichenberg *et al.*, 2010; Seidman *et al.*, 2013; Meier *et al.*, 2014; Agnew-Blais *et al.*, 2015). Statistical modelling of twin and family data have further suggested a shared genetic link between cognition and schizophrenia risk, which has been extended by recent genetic association studies of schizophrenia PRSs and cognitive performance (Toulopoulou *et al.*, 2007, 2010*b*, 2015; Owens *et al.*, 2011*a*, *b*; Fowler *et al.*, 2012; McIntosh *et al.*, 2013; Walters *et al.*, 2013; Lencz *et al.*, 2014; Hatzimanolis *et al.*, 2015; Kauppi *et al.*, 2015; Germine *et al.*, 2016; Hagenaars *et al.*, 2016; Hubbard *et al.*, 2016; Liebers *et al.*, 2016; Alloza *et al.*, 2017; Cosgrove *et al.*, 2017; Rampino *et al.*, 2017; Ranlund *et al.*, 2018). In summary, this extensive literature suggests that cognitive deficit is reliably linked with inherited risk for schizophrenia and that it often predates the diagnosis.

Studies of genetic associations between schizophrenia and cognition, either based on molecular data or statistical modeming of twin and family samples, provide evidence of shared genetic influences but typically do not address causation. However, in a recent paper in a pan-European sample of twins with schizophrenia, Toulopoulou *et al.* (2015) sought to identify through statistical inference the direction of causation between the liability to schizophrenia and several candidate intermediate phenotypes. Using novel reciprocal causation models, we reported that cognitive deficits lay upstream of schizophrenia liability, with about

a quarter of the genetic variation in schizophrenia risk mediated through genetic variation in cognition (Toulopoulou *et al.*, 2015). This finding was directionally specific for cognition, suggesting that cognitive deficit contributed causally to schizophrenia, but not vice versa.

While the aforementioned study examined the potentially causal relationship between cognitive deficit and schizophrenia liability, the models were based on inferences from twin rather than molecular genetic data. Here we extended the earlier causal modelling to the molecular genetic level, seeking to quantify the extent to which cognitive deficit may mediate some of the effect of cumulative genetic risk as measured by the PRS for schizophrenia. Specifically, we used trivariate causal modelling to test our hypothesis that cognition mediated the effect of PRSs on schizophrenia risk against alternative hypothetical models (e.g. that schizophrenia mediated the polygenic score effect on cognition). We report support for our hypothesis that cognitive deficit mediates some of the effects of PRS on schizophrenia, adding substantial evidence that cognitive deficit is an intermediate phenotype on the causal path to diagnosis with possible implications for diagnosis, prediction, and intervention.

Materials and methods

Participants

Participants were 1313 Caucasian individuals with European ancestry from 1078 families including 416 schizophrenia patients, 290 unaffected siblings, and 607 unrelated controls. All participants were assessed as part of the Clinical Brain Disorders Branch (CBDB) Sibling Study, one of the largest and most comprehensively-phenotyped studies of patients with schizophrenia and their healthy siblings, which has been described in detail before (Egan *et al.*, 2001*b*). There were 227 families with a schizophrenia patient and an unaffected sibling, 189 additional families with one schizophrenia patient and no additional family members, and 55 families with one or more unaffected siblings. All participants were able to provide informed consent after the procedures had been fully explained for a protocol approved by the NIH IRB.

Measurement

Clinical assessment

All participants were medically screened and completed separate DSM-IV diagnostic interviews (First *et al.*, 1994) with two research psychiatrists. Individuals were included in the schizophrenia group if they had schizophrenia, schizoaffective disorder, psychosis not otherwise specified, or schizoid personality disorder (Dickinson *et al.*, 2011). Schizoid personality diagnosis was included as part of the schizophrenia spectrum, consistent with prior work in the PGC and with evidence of strong genetic overlap with schizophrenia. Siblings were allowed to have a history of mood/anxiety or personality disorder but no schizophrenia spectrum disorder history. Controls were not included in the study if they had first-degree relatives with schizophrenia spectrum disorders or Axis I or Axis II diagnosis history, or if they were currently on psychotropic medication. Controls were determined to be unrelated based on genome-wide identity-by-state estimation in PLINK. If identity-by-state of paired samples had PH_HAT > 0.2, one of the samples was excluded. Exclusion criteria for all participants included history of head trauma with extended loss of consciousness, alcohol, or drug abuse within the past 6 months, IQ < 70, or evidence of learning disability. Schizophrenia participants were stable and receiving neuroleptic medications at the time of the study.

Polygenic risk score

DNA was extracted from blood using standard procedures, and genotyping was done using various Illumina Bead Chips including 510K/610K/660K/2.5M. We divided samples into two groups according to genotyping chips: one group included samples genotyped with low-resolution BeadChips (510K/610K/660K), and the other included samples genotyped with high-resolution BeadChips (2.5 M). For each type of chip, both cases and controls were genotyped. There are many reasons that the different chips are unlikely to influence our results—these include: very high genotyping and imputation accuracies; we used only common SNPs for the analyses; and the fact that we ran several samples on most chips and observed genotype concordance rates $> 99.5\%$. Imputation was performed separately for these two groups. To control for the use of two different imputations, we included genotyping batch label as a covariate in the statistical analysis. Quality control was performed before imputation using PLINK (version 1.07; http://pngu.mgh.harvard.edu/purcell/plink/), as reported by the PGC (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The quality control parameters for retaining SNPs and subjects were: SNP missingness < 0.05 (before sample removal); subject missingness < 0.02; autosomal heterozygosity deviation ($|Fhet| < 0.2$); SNP missingness < 0.02 (after sample removal); difference in SNP missingness between cases and controls < 0.02; and SNP Hardy-Weinberg equilibrium ($P > 10^{-6}$ in controls or $P > 10^{-10}$ in cases). Pre-phasing was done before imputation with SHAPEIT, and imputation was done with IMPUTE2 using 1000 Genome Phase 1 as reference panel. SNPs were clumped using PLINK. In each step of clumping, if two SNPs are within 500 kb and with $r^2 \geqslant 0.1$, the more significant SNP was kept. To control for population stratification in the association analysis, the first 10 principal components of the whole genome data were calculated using EIGENSOFT v5.01 (EIGENSOFT, http://www.hsph.harvard.edu/alkes-price/software/).

To assess cumulative polygenic risk at the genomic level, we used the results from the 2014 PGC schizophrenia meta-analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), after excluding

the present sample, to construct *PRS* in our sample using R scripts. Thus, the data comprised 36 573 cases and 112 468 controls. Polygenic risk was estimated in each individual separately by adding up the number of risk alleles (0, 1, 2) of each SNP that was found to be associated with schizophrenia in the PGC sample multiplied by the logarithm of the SNP's odds ratio as described before (Vassos *et al.*, 2017). Ten different *PRS* levels were calculated based on the SNPs associated with schizophrenia at different *P*-value thresholds ($P_T < 5 \times 10^{-8}$, 10^{-6}, 10^{-4}, 10^{-3}, 0.01, 0.05, 0.1, 0.2, 0.5, 1). *PRS* was standardized using the mean and variance of the control group for all subsequent analysis.

Neuropsychological assessment and cognitive factors

All participants were administered a comprehensive neuropsychological battery of assessments, previously reported to be consistently and commensurately impaired in schizophrenia (Dickinson *et al.*, 2011). Guided by principal components analysis, composites were created reflecting six broad cognitive domains: verbal memory [cognitive factor (CF) 1], *n*-back (CF 2), visual memory (CF 3), processing speed (CF 4), card sorting (CF 5) and digit span (CF 6). All cognitive composites were standardized using the mean and variance of the control group. Using similar methodology, a single composite measure, *g*, was also created as one estimate of general cognitive ability (Dickinson *et al.*, 2011) (used in correlation analyses, described below). However, in the current study, we focused on the six domain-specific cognitive factors as the key indices of the cognitive effects of schizophrenia, and modelled general cognitive ability as a latent variable underlying performance in these domains [see 'Bivariate non-causal and causal models (Cholesky)' section below]. The main advantage of using several cognitive domains is the ability to model a latent variable that is free of measurement error. Using a measurement model when attempting to infer direction of causation ensures parameter estimates will be unbiased, rather than being attenuated by unknown varying degrees of measurement error (Duffy and Martin, 1994).

Correlations

Prior to model fitting we ran correlational analysis to illustrate the relationship among key variables. Pearson correlations between two continuous variables (e.g. *g* and *PRS*) were estimated using SPSS 23.0 (Corp, 2015). The biserial correlation was estimated between a dichotomous and a continuous variable (e.g. schizophrenia and PRS; schizophrenia and *g*) using OpenMx (Boker *et al.*, 2011). While the cases include family members, ignoring non-independence among data points does not introduce bias to the estimates of correlation coefficients, but will produce standard errors and *P*-values that are too small. We therefore randomly selected one member from each family to run such analysis.

Model fitting

We used causal modelling of family and control data to explore the underlying relationships between schizophrenia, cognitive deficit and PRS. These complex models are based on the following assumptions. Both genetic (*A*) and environmental (*E*) components contribute to the variance of the phenotypes (e.g. schizophrenia or cognition), while half of the genetic variance contributes to the covariance between siblings. Specifically, the relatedness between patients and their siblings is incorporated into the standard error of the mean (SEM) through the correlations between their additive components (set to be 0.5 as appropriate for first degree relatives). This is equivalent to a random effects model with pre-specified correlational structure. As in twin studies, the reciprocal causal relationships between two phenotypes can be estimated from sibling data, assuming that each phenotype has specific *A* and *E* components (Duffy and Martin, 1994). Because patients were recruited based on their clinical status, our subjects do not represent a random sample of the population. Since parameter estimates (e.g. heritability) obtained from non-random data would be misleading unless ascertainment is correctly modelled, we do not attempt to estimate the model parameters for schizophrenia but assume values supported by the literature, an approach adopted in previous studies (Toulopoulou *et al.*, 2007, 2010*a*, 2015). Thus, we assume a liability threshold model for schizophrenia, where the liability is normally distributed with mean 0, variance 1, with a threshold that corresponds to a lifetime population prevalence of 1% (Sullivan *et al.*, 2003*a*), and components of variance $A = 0.82$ and $E = 0.18$ (Cardno *et al.*, 1999). This is a standard procedure used for analysing samples ascertained to contain affected family members. Figure 1 shows the causal paths between schizophrenia and cognition. The observed phenotype, e.g. schizophrenia diagnosis labelled as *SCZ*, is denoted by a square, while the latent variable *L-SZ* in the circle represents schizophrenia liability and is continuous. The arrow pointing from *L-SZ* to *SCZ* is fixed to unity, which denotes that *SCZ* is obtained directly from *L-SZ* through a liability-threshold model.

The genetic components of cognition are estimated from the data. Even though the data were ascertained from families with schizophrenia, we have previously shown (by theory and simulation studies) that unbiased estimates can be obtained when the parameters of the phenotype responsible for ascertainment (i.e. schizophrenia in our study) are correctly specified (Rijsdijk *et al.*, 2005).

Bivariate non-causal and causal models (Cholesky)

To build the causal model, and before incorporating molecular genetic data, we first checked that the data are consistent

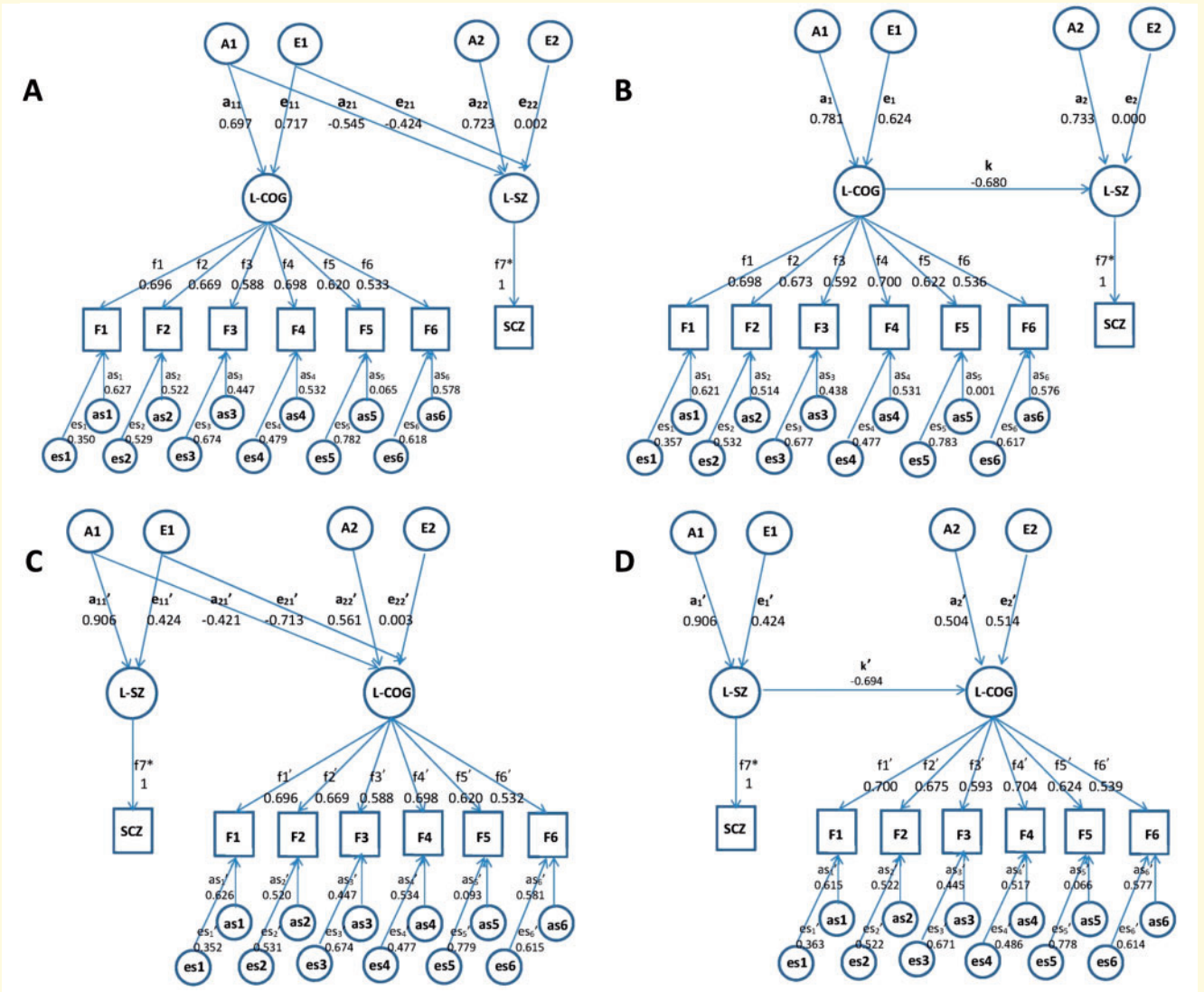

Figure 1 Testing causal paths between schizophrenia and cognition. Bivariate non-causal and causal models (Cholesky) with observed variables: *SCZ* = schizophrenia and *F1–6* = cognitive factors 1–6 (*F1*: verbal memory; *F2*: N back; *F3*: visual memory; *F4*: processing speed; *F5*: card sorting; *F6*: digit span), and latent variables: *L-SZ* = schizophrenia liability; *L-COG* = general cognitive factor; *A* = genetic component; *E* = environmental component; for each observed cognitive factor, variance could be explained by both shared (*L-COG*) and specific components, including genetic (*as*1–6) and environmental (es1–6); the path coefficients a_{mn} in lowercase is the path coefficient from the m^{th} genetic factor to the n^{th} latent variable; the path coefficients from *L-COG* to *F1–6* are shown as *f1–6*; path coefficients *f1* and *f1'* from *L-COG* to *F1* are set to unity to identify the model; all path coefficients are standardized after model fitting; parameters labelled with an asterisk have been fixed to 1. The overall genetic variance to *L-SZ* is constrained to 0.82 (see 'Materials and methods' section). Models **A** and **C** are equivalent Cholesky models with different ordering of *L-SZ* and *L-COG*; Models **B** and **D** are both sub-models (nested models) of Cholesky model, representing different directions of causation between *L-SZ* and *L-COG*; the parameters estimates obtained are such that in Model **B** a_1 and e_1 multiplied by *k* are approximately equal to a_{21} and e_{21}, whereas in Model **D** a_1' and e_1' are far from proportional to a_{21}' and e_{21}'; thus, one would expect Model **D** to be rejected, as is indeed the case.

with our earlier work that showed genetic overlap between schizophrenia and cognition due to a potentially causal relationship between the two phenotypes. Specifically, we employed bivariate models (Neale and Cardon, 1992) to explore the covariance between the two phenotypes, schizophrenia and cognition, a necessary feature to infer causation. These models consider every variance and covariance between all pairs of variables in the sibling data, and provide the baseline for causation models. In the Cholesky decomposition, a_{mn} is the path coefficient from the m^{th} genetic factor to the n^{th} latent phenotype (Fig. 1A and C). When modelling the relationship between schizophrenia and cognition (six cognitive factors), two latent (unobserved, statistically-defined) variables are employed to build the bivariate model. As shown in Fig. 1, one latent variable is *L-SZ*, representing schizophrenia

liability in a liability threshold model, and the other is *L-COG*, reflecting shared influences on the six broad cognitive domains mentioned above, *F1–6*.

Models A and C in Fig. 1 are assumed to be statistically equivalent while testing different ordering of the variables cognition and schizophrenia; the order of the variables (here *L-SZ* and *L-COG*) being arbitrary in the Cholesky decomposition. In total, 29 parameters are estimated in the full bivariate model: three genetic parameters (a_{11}, a_{21}, a_{22}), three environmental parameters (e_{11}, e_{21}, e_{22}), five factor loadings *f2–6* from *L-COG* to *F2–6* (*f1* is set to unity as customary), six genetic and six environmental residual parameters ($as_{1–6}$, $es_{1–6}$), and six means of cognitive factors ($M_{F1–6}$) ($M_{F1–6}$ not shown in Fig. 1). All the path coefficients are standardized such that all variables have unit variance after model fitting.

Causal model

The models above describe the covariance between two phenotypes but cannot provide information on the direction of causation. The causal model attempts to explore their causal relationship. The full reciprocal causal models, represented in Fig. 1B and C include two opposite arrows between two latent variables, the causal path k pointing from *L-COG*→*L-SZ* and k' pointing from *L-SZ*→*L-COG*. The full reciprocal causal model with two causal paths between two latent phenotypes would estimate all the variance and covariance between them, which is in principle the same as the Cholesky model, and therefore their model fit would be the same. The significance of causal paths k and k' can be tested by examining sub-models, representing different directions of causation between *L-SZ* and *L-COG*, shown in Fig. 1B and D dropping one causal path at a time, then comparing the outcome with the full reciprocal causal model (see 'Results' section).

The models with one causal path are considered as nested models of the Cholesky model, because the causal arrow imposes a certain constraint in the genetic and environmental components. In the Cholesky model, genetic contribution to the covariance between *L-SZ* and *L-COG* is expressed as $a_{11} \times a_{21}$, and environmental contribution is $e_{11} \times e_{21}$, and the proportion of *A* and *E* component is freely estimated, expressed as $(a_{11}/e_{11}) \times (a_{21}/e_{21})$. In the sub-model with causal path k (Fig. 1B), the proportion of genetic and environmental covariance is related to $(a_1/e_1)^2$, with genetic contribution $a_1 \times a_1 \times k$, and environmental contribution $e_1 \times e_1 \times k$. If the sub-model could describe the genetic architecture of variables, the value of $a_1 \times k$ and $e_1 \times k$, representing A_1 and E_1 contribution to the second latent variables *L-SZ*, should be close to a_{21} and e_{21} in the Cholesky model, respectively. On the other hand, they could be discrepant with each other, which would mean that the causation model is not suitable to describe the data.

The genetic and environmental components of schizophrenia liability should be set to a specific value, here 0.82 and 0.18 as described above. In this scenario, more than one genetic or environmental single-headed arrow is pointing to *L-SZ*. As shown in Fig. 1, in the Cholesky model, both a_{21} and a_{22} (e_{21} and e_{22}) contribute to *L-SZ*'s genetic (environmental) variance, the genetic and environmental parts are constrained as $a_{21}^2 + a_{22}^2 = 0.82$, $e_{21}^2 + e_{22}^2 = 0.18$. While in the causation model, both k and a_2 (k and e_2) contribute to *A* (*E*) components, so the genetic and environmental parts are constrained as $(a_1 \times k)^2 \times a_2^2 = 0.82$ and $(e_1 \times k)^2 \times e_2^2 = 0.18$. In this situation, all of the genetic and environmental parameters (*ep*) are freely estimated, and the observed statistics (*os*) would decrease by 2 because of the constraints, so the degrees of freedom (*df*) is calculated as $df = os - ep$.

In the other scenario, when testing the causation model with causal path k' (i.e. schizophrenia is causal of cognitive deficit) (Fig, 1D), only one genetic (environmental) path a_1' (e_1') is pointing to *L-SZ*, and the comparable full model (the Cholesky model) shown in the Fig. 1C, also has one single-headed arrow pointing to *L-SZ*. Therefore, only parameters a_{11}' and e_{11}' (a_1' and e_1') contribute to the genetic and environmental components of *L-SZ*, and $a_{11}'^2$ and $e_{11}'^2$ ($a_1'^2$ and $e_1'^2$) could be directly set to 0.82 and 0.18. In this situation, the number of *ep* could decrease by 2, so *df* is the same as the first scenario. Though the Cholesky model in Fig. 1A and C has different constraint methods and different order of the variables in the figures, they are identical with the same $-2LL$ (minus 2 log likelihood) and *df* (degree of freedom). Therefore, they would be the full models and provide the baseline for the causal models with different causal direction.

If the causal model is not significantly worse than the Cholesky model, it would mean that the bivariate causal model fits the data well and with fewer parameters, meaning that it would represent the best model to describe the relationship between schizophrenia liability and cognition. Otherwise, the Cholesky model would be the more appropriate, which does not implicate a specific order of variables.

Trivariate causal model

The trivariate model incorporates molecular genetic data, and forms a more detailed description of the full dataset, compared to the bivariate models, to explore the underlying causal relationships between schizophrenia, cognition and PRS. Figure 2 shows the causal relationships between key variables. Latent PRS (*L-PRS*) determines the observed phenotype [i.e. *PRS* threshold ($P_T < 0.05$)] while *L-COG* and *L-SZ* reflect latent variables as described before. In our model, the PRS is treated as a phenotype (just as schizophrenia and cognition). However, PRS is special in that it is calculated from individuals' genotypes in an additive fashion, and is therefore guaranteed to have a heritability of

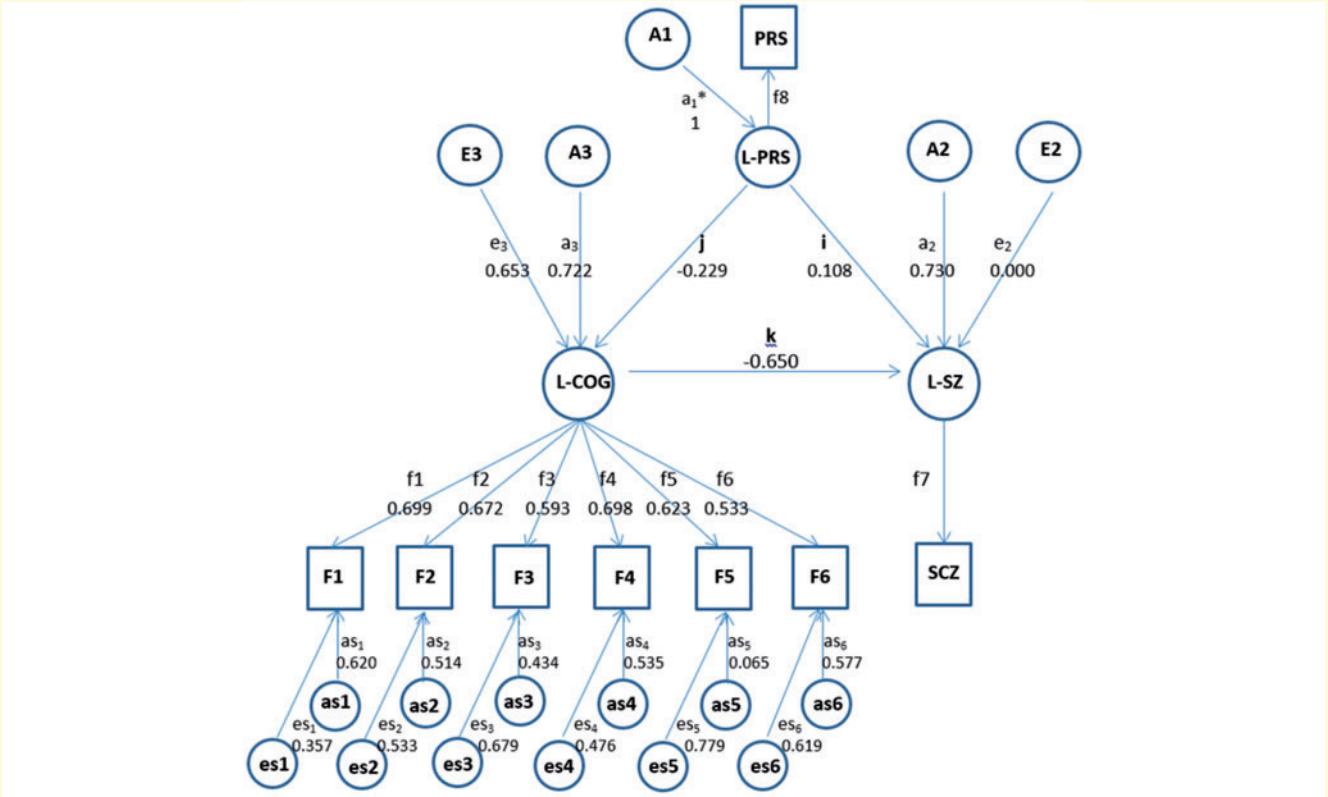

Figure 2 Model of causal relationships among polygenic risk scores, schizophrenia liability and cognition. Trivariate causal model with observed variables: *SCZ* = schizophrenia, *F1–6* = cognitive factors 1–6, and *PRS* = polygenic risk score (*P*-value threshold 0.05); and latent variables: *L-SZ* = schizophrenia liability, *L-COG* = general cognitive factor, *L-PRS* = polygenic risk score; *A* = genetic component, *E* = environmental component; for each observed cognitive factor, variance could be explained by both shared (*L-COG*) and specific components, including genetic (*as*1–6) and environmental (es1–6); the path coefficients a_m in lowercase is the path coefficient from the m^{th} genetic factor to the latent variable; the path coefficients from *L-COG* to *F1–6* are shown as *f1–6*; path coefficient *f1* from *L-COG* to *F1* is set to unity to identify the model; *i, j, k* represent causal paths: causal path *i, L-PRS* to *L-SZ*; causal path *j, L-PRS* to *L-COG*; causal path *k, L-COG* to *L-SZ*; all path coefficients are standardized after model fitting; parameters labelled with an asterisk have been fixed to 1; the overall genetic variance to *L-SZ* is constrained to 0.82. Note that *L-PRS* influences *L-SZ* both directly and indirectly (through *L-COG*).

1 and a correlation of 0.5 between siblings (and other types of first-degree relatives). As shown in Fig. 2, latent variables were modelled to be influenced through causal paths *i*, *j*, *k* and *k′* (*k′* from *L-SZ*→*L-COG* not shown in Fig. 2), and residual genetic and environmental components of latent variables, As_{1-6} and Es_{1-6}, which incorporated measurement error. Reciprocal causal models typically use two opposite single-headed arrows between each pair of latent variables to represent these potential causal relationships. Genetic causation assumes that PRS can only cause phenotypes and genotypes cannot be influenced by the phenotypes, so there is no reciprocal causation involving *L-PRS*. As with *L-COG*, the path loadings for *L-SZ* and *L-PRS* from the latent variables to the observed phenotypes were constrained to 1.

In this analysis, the full trivariate model has four causal paths at the latent variable level. The significance of each causal path would be tested by comparing nested models dropping one causal path then comparing to the full model, using the likelihood ratio chi-squared statistic. Thus, there would be four sub-models dropping single-headed arrows *i*, *j*, *k* and *k′* sequentially. Again, the model with the fewest variables is deemed the best fitting model for the data.

Multiple testing and sensitivity analysis

A number of bivariate models, some nested within others, were fitted to test the two reciprocal paths between L-SZ and L-COG. It would be reasonable and appropriate to adjust for testing two hypotheses. We regarded 0.025 as the critical *P*-value for statistical significance rather than the usual 0.05. The purpose of the trivariate model was to estimate how much of the genetic contribution of the polygenic score to schizophrenia liability is mediated through cognitive impairment. This is a single specific question and does not involve multiple testing.

In the model fitting, the genetic and environmental contributions to schizophrenia liability are assumed to be 0.82 and 0.18, respectively. Many researchers suggest that the heritability of schizophrenia ranges at 0.7–0.9 (Farmer

et al., 1987; Sullivan *et al.*, 2003*b*). To explore whether the value of heritability affects the model fitting results, we also fitted the data fixing schizophrenia heritability (a^2) ranging from 0.7 to 0.9.

Data availability

The data that support the findings of this study are available from the corresponding author, upon request.

Results

Mean comparisons

Demographics, means, standard deviations (SDs) and *P*-values for group comparisons on cognitive factors, PRSs, and the *g* composite are given in Table 1. As expected, participants with schizophrenia performed significantly worse than siblings and healthy controls, and siblings scored lower than controls (all $P < 0.001$). Patients with schizophrenia and siblings have significantly higher *PRS* than controls (all $P < 0.001$).

Polygenic risk score analysis

The means and standard deviations for *PRS* in schizophrenia, siblings and control groups calculated for the different thresholds are given in Supplementary Table 1. The numbers of SNPs for the different thresholds are shown in Supplementary Table 2. We conducted logistic regression to estimate the proportion of schizophrenia variation in case/control status that was explained by each *PRS* and found that the *P*-value threshold 0.05 accounted for more variance in our sample than *PRS* for other thresholds, about 9% of the variance in schizophrenia liability (Supplementary Table 2). This *PRS* threshold showing greatest risk prediction is consistent with results of the original PGC report (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Thus, we chose this *PRS* threshold ($P_T < 0.05$), which included 24 694 SNPs, for all our subsequent analysis.

Correlational analysis

Supplementary Fig. 1 shows the correlation coefficients between each pair of variables. Schizophrenia correlated with *g* at −0.461 (*P*-value < 0.001), and *PRS* at 0.142 (*P*-value < 0.001). The Pearson correlation between *g* and *PRS* was −0.297 (*P*-value < 0.001).

Bivariate non-causal and causal models (Cholesky)

The bivariate model fitting results are shown in the first part of Table 2. Model 1 is the baseline Cholesky model, which tests for covariation between schizophrenia liability

Table 1 Demographic, cognitive factor and PRSs

	Control			Siblings		Schizophrenia		Schizophrenia and Control group		Sibling and Control group	
n	607			290		416		-		-	
Male, *n*	285			122		316		-		-	
Age, mean (SD)	31.05 (9.78)			35.58* (9.64)		34.38* (9.89)		-		-	
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*P*-value	*P*-value
PRS	607	0	1	286	0.31	0.94	416	0.78	1.05	4.10×10^{-31}	1.37×10^{-5}
Verbal memory (F1)	598	0	1	284	−0.38	1.08	415	−2.00	1.33	7.97×10^{-114}	4.97×10^{-7}
n-back (F2)	561	0	1	216	−0.57	1.31	282	−1.82	1.53	4.38×10^{-62}	8.51×10^{-9}
Visual memory (F3)	345	0	1	280	−0.10	1.36	405	−1.92	2.32	3.96×10^{-45}	0.33
Processing speed (F4)	603	0	1	283	−0.53	1.06	416	−1.98	1.1	2.36×10^{-137}	1.20×10^{-12}
Card sorting (F5)	583	0	1	279	−0.47	1.24	391	−1.80	1.65	8.14×10^{-71}	3.16×10^{-8}
Span (F6)	523	0	1	286	−0.27*	1.04	414	−1.15*^	1.13	3.95×10^{-54}	2.71×10^{-4}
g	594	0	1	277	−0.60*	1.16	412	−2.96*^	1.72	3.90×10^{-151}	2.86×10^{-13}

PRS = PRS with *P*-value cut-off at 0.05. Data on PRS and cognitive variables have been standardized according to the mean and standard deviation of the control group. *Indicates $P < -0.001$ when compared to controls; ^indicates $P < 0.001$ when compared to siblings.

Table 2 Model fitting results

	ep	−2LL	*df*	AIC	Δ−2LL	Δ*df*	*P*	Comparison model
Bivariate model								
1: Cholesky	29	26 072.78	8446	9179.78	–	–	–	–
2: L-COG↔L-SZ	29	26 072.78	8446	9179.78	–	–	–	–
3: Dropping L-SZ→L-COG	28	26 074.57	8447	9179.57	1.79	1	0.18	1 and 2
4: Dropping L-COG→L-SZ	28	26 092.64	8447	9197.64	19.85	1	<0.01	1 and 2
Trivariate model								
1: Full	32	29 736.61	9752	10 232.61	–	–	–	–
2: Dropping PRs→L-COG (*j*)	31	29 759.54	9753	10 253.54	22.94	1	<0.01	1
3: Dropping PRS→L-SZ (*i*)	31	29 751.26	9753	10 245.26	14.65	1	<0.01	1
4: Dropping L-SZ→L-COG (*k*′)	31	29 737.85	9753	10 231.85	1.24	1	0.26	1
5: Dropping L-COG→L-SZ (*k*)	31	29 758.10	9753	10 252.10	21.49	1	<0.01	1

Δ − 2LL = the difference of minus 2 log likelihood between two models; Δ*df* = the difference of the degrees of freedom; −2LL = minus 2 log likelihood; AIC = Akaike information criterion; *ep* = estimate parameter; *df* = degree of freedom; *P* = *P*-value, when *P*-value < 0.05 (*P*-value < 0.025 for bivariate), the model is significantly worse than the comparison model.
The overall genetic variance to *L-SZ* is constrained to 0.82.

and cognition. Model 2 (full reciprocal causal model) with two causal paths has an identical fit, as expected, as the two models are created to be equivalent (see above). Model 3, a nested model, which drops the causal path k' (*L-SZ→L-COG*), was not significantly worse (*P*-value = 0.18) than Models 1 and 2. While Model 4, which drops path k (*L-COG→L-SZ*), was significantly worse (*P*-value < 0.01) compared with Models 1 and 2, suggesting that the causal path k was important and could not be dropped. Therefore, Model 3 fitted the data well and with fewer parameters, supporting our earlier work in a pan-European twin with schizophrenia sample that found cognition to be upstream of schizophrenia liability (Toulopoulou *et al.*, 2015).

The same model fitting was performed assuming different heritability levels, from 0.7 to 0.9, and the model fitting results are presented in Supplementary Table 3. When heritability, a^2 is 0.7 to 0.8, Model 4, which drops path *L-COG→L-SZ*, deteriorates statistically significantly from baseline models, while Model 3, which drops path *L-SZ→L-COG*, is not significantly worse and thus the model with the best fit for the data. When a^2 is 0.9, both Models 3 and 4 are significantly worse than the baseline model (Model 2), and Model 3 is still chosen due to the smaller Akaike information criterion (AIC). Thus, the model fitting results do not change with different heritability levels.

According to the chosen Model 3 (Fig. 1B), *A* contributes 61% ($0.781^2 = 0.61 \times 100\% = 61\%$; CI 0.748–0.814%) to the variance in cognition, and it is moderately heritable. The causal path k from *L-COG→L-SZ* is −0.680, which suggests that 46% [$(-0.680)^2 = 0.46 \times 100\% = 46\%$; CI −0.711 to −0.674] of variance in schizophrenia liability is explained by variation in cognition.

Figure 1B and D illustrate the two nested models with opposite direction of causation, and based on the two Cholesky models (Fig. 1A and C), which are equivalent. The parameter estimation in the nested model that describes the relationship best would be closer to the equivalent Cholesky. In Fig. 1, the upper part illustrates the nested model (Fig. 1B) from cognition to schizophrenia liability (*L-COG→L-SZ*), and its comparable Cholesky model (Fig. 1A). A_1 would affect both of the phenotypes simultaneously, and its contribution on the variance of the second phenotype *L-SZ* is $a_{21}{}^2$ (0.55^2) in the Cholesky model (Fig. 1A), and $(a_1 \times k)^2$ [$(0.781 \times 0.680)^2 = 0.53^2$] in the causal model (Fig. 1B). Figure 1 also illustrates the causal model *L-SZ→L-COG* (Fig. 1D), and its comparable Cholesky model (Fig. 1C). The contribution of A_1 on variance of *L-COG* is $a_{21}{}'^2$ (0.42^2) in the Cholesky model and $(a_1' \times k')^2$ [$(0.906 \times 0.694)^2 = 0.63^2$] in the nested model. The path estimates are closer between a_{21} (0.55) and $a_1 \times k$ (0.53) [e_{21} (0.42) and $e_1 \times k$ (0.42)] (Fig. 1A and B), comparing with the path estimates between a_{21}' (0.42) and $a_1' \times k'$ (0.63) [e_{21}' (0.71) and $e_1' \times k'$ (0.29)] (Fig. 1C and D). Thus, the value of A_1 and E_1 contribution on the second phenotype is closer between the Cholesky model and nested model *L-COG→L-SZ*. This result is concordant with our assumption, and duplicates and verifies the results of the model fitting comparison (above), which supports a direction of causation from cognition to schizophrenia liability. The details of parameter comparison, such as the value of a_{21} and $a_1 \times k$, at different schizophrenia heritability levels, and the corresponding confidence intervals, can be found in Supplementary Table 4.

Trivariate causal model

The model fitting comparison results are listed in the second part of Table 2. Model 1 is the full model with four causal paths, i, j, k and k' among three latent variables. When the causal path k' is dropped ($k' = 0$), the model (Model 4) is not significantly different from the full model (Model 1). In contrast, when we drop the

causal path *k*, which indicates that the *L-SZ* is accounted for by variation in *L-COG* (*L-COG*→*L-SZ*) (Model 5), the model fit deteriorated significantly compared to its base model (Model 1). Models 2 and 3 show that causal paths *j* and *i* could not be dropped, thus *L-PRS* contributes significantly to both *L-SZ* and *L-COG*.

The model fitting results at different schizophrenia heritability levels (0.7–0.9) are presented in Supplementary Table 3. When the heritability of schizophrenia is set to 0.7 and 0.8, the model fitting results are similar and model selections are the same as the results when the heritability of schizophrenia as 0.82. When it is fixed to 0.9, all nested models (Models 2–5) are significantly worse than Model 1, and could not select the model according to *P*-value; however, Model 4 still has the smallest AIC among them, and fit the data best.

Figure 2 shows the parameter estimates of the best fitting model (Model 5) with three significant causal paths (*i*, *j*, *k*) at heritability of schizophrenia as 0.82. Table 3 shows the corresponding genetic variance components of schizophrenia liability including those that 'pass through' cognition. In total, *L-PRS* explained 8.07% (CI 5.45–10.74%) of the genetic variance components of schizophrenia liability, directly and indirectly through *L-COG*. *L-PRS* affected *L-SZ* directly by causal path *i* (Fig. 2), with 1.43% (CI 0.46–3.08%) of genetic variance in schizophrenia liability explained by *L-PRS*. *L-PRS* also explained 2.71% (CI 2.41–3.85%) of genetic variance of schizophrenia liability indirectly through *L-COG*. The remainder 3.93% (CI 2.37–4.48%) reflected correlated variation in which variation in *L-SZ* was attributed to variation from cognition and vice versa. Of the remaining genetic variance components of schizophrenia liability 26.87% (CI 21.45–32.57%) was accounted for by *L-COG*-relevant pathways not captured by *L-PRS* and 65.06% (CI 59.96–70.95%) was through paths other than *L-COG* and *L-PRS* (Table 3). The parameter estimates of the other models, based on different heritability assumptions are shown in the Supplementary material.

The parameter estimates of Model 4 with a^2 of schizophrenia fixed to 0.7, 0.8 and 0.9 are shown in Supplementary Fig. 2. The corresponding amounts and percentages of genetic variance components of schizophrenia liability contributed by *L-PRS* at different schizophrenia heritability levels are provided in Supplementary Table 5. As shown in Supplementary Fig. 2 when schizophrenia heritability a^2 increases, genetic parameters (a_2 and a_3) increase and environmental parameters (e_2 and e_3) decrease. Accordingly, when heritability is set at $a^2 = 0.7$ the genetic (a_3) and environmental (e_3) path loadings for *L-COG* are $a_3 = 0.662$ and $e_3 = 0.748$ respectively, while at $a^2 = 0.9$, the equivalent path loadings change to $a_3 = 0.843$ and $e_3 = 0.488$. Because the total variance of schizophrenia is fixed, including genetic and environmental part, the environmental path loading of *L-SZ* (e_2) decreases with increasing a^2, and becomes nearly 0 when a^2 is at 0.82. Thus, when heritability of schizophrenia is fixed to 0.82 and above, the environmental variance is totally through the environmental component of *L-COG*. As shown in Supplementary Table 5 the amount of every component of schizophrenia genetic variance accounted by *L-PRS* is similar at different a^2 levels, with percentages decreasing as a^2 increases: 9.3% of schizophrenia genetic variance is explained by *L-PRS* at $a^2 = 0.7$, and 7.4% at $a^2 = 0.9$. The genetic variance components of schizophrenia liability related *L-COG* at different schizophrenia heritability levels are shown in Supplementary Table 6. The total variance related to *L-COG* increases as a^2 increases from 0.7 to 0.9. Thus at $a^2 = 0.7$, 31.68% (CI 23.20–42.60%) of overall genetic risk is mediated through influences on cognition, and at $a^2 = 0.9$, 39.23% (CI 36.35–50.90%).

Discussion

Recent studies have shown genetic overlap between schizophrenia and cognition; however, the direction of causation remains unclear. We used causal modelling to address this question. A central aim of the current work was to determine whether and to what extent cognitive deficit mediates the influence of common genetic variants on schizophrenia. Results of modelling incorporating molecular genetic data, in the form of PRSs, were consistent with earlier statistical modelling in twin data—both approaches suggest that genetics, in part, move through cognition to exert an effect on schizophrenia risk (Toulopoulou *et al.*, 2015). More

Table 3 Genetic variance components of schizophrenia liability

Expression	Variance component	Estimate, %	CIs, %
$(i \times a_1)^2/(1 - k \times k')^2$	*L-PRS* contributed directly	1.43	0.46–3.08
$(k \times j)^2 \times a_1{}^2/(1 - k \times k')^2$	*L-PRS* through *L-COG*	2.71	2.41–3.85
$2 \times k \times j \times i \times a_1{}^2/(1 - k \times k')^2$	Covariance between *L-PRS* and *L-COG*	3.93	2.37–4.48
$k^2 \times a_3{}^2/(1 - k \times k')^2$	From *L-COG* excluded *L-PRS*	26.87	21.45–32.57
$a_2{}^2/(1 - k \times k')^2$	*L-SZ* independently	65.06	59.96–70.95

% = percentage of variance in liability to schizophrenia explained by additive genetic differences; latent variables: *L-SZ* = schizophrenia liability; *L-COG* = general cognitive factor; *L-PRS* = polygenic risk score; *i*, *j*, *k* represent causal paths: causal path *i*, *L-PRS* to *L-SZ*; causal path *j*, *L-PRS* to *L-COG*; causal path *k*, *L-COG* to *L-SZ*, causal path *k'*, *L-SZ* to *L-COG*; $a_m{}^2$ is the path coefficient from the m^{th} genetic factor to the latent variable in Fig. 2. Genetic variance to *L-SZ* is constrained to 0.82. Confidence intervals that do not include 0 are significant.

specifically, current analyses indicated that, out of 8.07% of the variation in schizophrenia explained by PRS, more than one-third of that variation, i.e. 2.71% was mediated through cognitive deficit. We found that this model fit the data better than one with opposite directionality, which represented schizophrenia as mediating the relationship between PRS and cognitive deficit. Further parsing of genetics variance components based on family data (e.g. siblings) suggested that cognitive deficit mediated an even greater part of the genetic influences on schizophrenia, beyond what is accounted for by the PRS (i.e. 26.87% of the inherited liability to schizophrenia not captured in the modelling by PRS).

The findings have implications for the question of whether many genes could act through a constrained set of pathways (Geschwind and Flint, 2015). Specifically, results suggested that as much as 33.51% of the overall heritable liability to schizophrenia may be mediated through cognitive operations. Only a modest portion of this is captured by current *PRS*. It is not clear that rare variant or epigenetic influences can be reflected in a PRS type scheme. Nevertheless, results were robust, and changes in the value of schizophrenia's heritability did not appreciably affect model fitting. Further study of the molecular and cellular genetic basis of variation in cognition, which involves the basic mechanisms of brain development and function (Birnbaum and Weinberger, 2017), will likely provide insights about the mechanisms by which risk genes bias the brain toward inefficient cognition in schizophrenia.

Interpreting the polygenic effects of risk variants in terms of disease mechanisms will require integration of genetic, biological, and circuit levels of analysis (Gandal *et al.*, 2016), but recent attempts have highlighted the role of histone methylation, dendritic spines, calcium signalling, glutamatergic transmission, plasticity, neurogenesis, synaptic pruning, and immunity (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, 2015; Gandal *et al.*, 2016). Most of the risk variants are regulatory, exerting their influence through modifications in gene expression (e.g. in the context of gene environment interactions) (Birnbaum and Weinberger, 2017; Ursini *et al.*, 2018). A possibility highlighted by our findings is that some of the aforementioned processes first influence alterations in cognition and have later effects contributing to the more acute symptoms of schizophrenia. At the same time, we found that about 65% of the genetic influences on schizophrenia were not related to genetic influences on cognition and PRS, highlighting the challenges to the current approach to identifying intermediate phenotypes.

One finding consistent with current genome wide heritability estimates (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) is that most of the heritable influence on schizophrenia is independent of current PRS. Even though polygenic risk was calculated based on the large PGC dataset (36 573 schizophrenia cases and 112 468 controls), PRS is still an incomplete measure of risk. As mentioned earlier, PRS derived from the current state of the art GWAS and accounts for part of the variation in schizophrenia liability (~7%), less than the estimated additive heritability from twin studies (Wray *et al.*, 2014).

We modelled general cognition as a latent trait, reflecting the covariance of six broad cognitive domains that are consistently altered in schizophrenia. Similar latent cognition variables have been widely used in genetic studies (Dickinson *et al.*, 2014; Trampush *et al.*, 2017). Latent cognition correlated robustly with PRS and had the added advantage of facilitating model fitting by reducing the number of variables for analysis. When cognitive factors were modelled separately in exploratory bivariate models, individual analyses were consistent with the main findings, but results were generally weaker. These observations are in line with earlier reports from statistical modelling of twin and sibling data that suggested a stronger link between schizophrenia and general cognition than between schizophrenia and individual cognitive abilities (Toulopoulou *et al.*, 2007, 2010*b*, 2015; Owens *et al.*, 2011*a*, 2012).

Findings from the current study suggest that cognitive deficit mediates (or causes) part of the observed association between schizophrenia and genetic factors. Although it is unlikely that cognitive deficit can 'cause' psychotic symptoms in a straightforward mechanistic sense, it is possible that poor cognition might leave an individual with fewer resources to combat psychotic symptoms. Alternatively, poor cognition can be viewed as a necessary but not sufficient component of an altered developmental trajectory that may involve psychosis-related neural functions as a later emerging component (Birnbaum and Weinberger, 2017). Thus, some individuals may have cognitive compromise but not sufficient developmental deviation to manifest psychosis, or alternatively, some individuals with mild psychotic symptoms might not develop clinical schizophrenia unless their cognition is also impaired. By either scenario, cognitive deficit would be in the causative chain from genetic risk to schizophrenia, in combination with other factors.

It has been a long-standing assumption that cognitive deficit and schizophrenia both reflect abnormal neurodevelopment. Indeed, recent findings that several of the risk variants predict expression in brain of genes that are more likely to be expressed prenatally, are consistent with evidence of an early developmental contribution to risk (Birnbaum *et al.*, 2015). Literature addressing the antecedents of schizophrenia suggest that some developmental programming connected to schizophrenia occurs early in life and affects cognitive development in childhood, well before the onset of acute psychotic symptoms. Other developmental programming, in adolescence, may further hamper cognitive development, and also generate psychotic phenomena. The current modelling cannot address these intertwined developmental hypotheses but offer clearer support for an aetiological trajectory through cognitive deficit toward schizophrenia.

Our results should be viewed in light of several limitations. First, while the cumulative effect of the genome-wide schizophrenia-associated common risk loci identified in the latest studies provides an optimal starting point for exploring the role of cognition as an intermediate disease mechanism, the risk scores, as mentioned earlier, represent only part of the heritable variation that contributes to schizophrenia. Second, the PRS includes SNPs that may not be causative variants. As discussed by others (Wray *et al.*, 2014) schizophrenia-associated SNPs correlate with many other variants, which could be the true risk-conferring ones. Third, we constructed PRSs based on the standard methodology. The methodology is robust; however, other approaches, such as empirical Bayes, which applies an automatic PRS weighting, might capture risk better (So and Sham, 2017). Fourth, our estimates are limited to the cognitive assessments used, participant characteristics, and study design. Other assessments, participants, or study designs could yield different results. It would be of interest to model both the more upstream (i.e. earlier in the sequence of cognitive operations) and downstream cognitive processes that recent research has highlighted as important in schizophrenia (e.g. source memory, prediction error, motivational salience, and social cognition). Fifth, the models are limited by the validity of the assumptions we made. With three variables (schizophrenia, cognition, and PRS) in our causative models, we effectively assumed that there was no other reason for these three variables to correlate than each other, which is likely an oversimplification of reality. For example, in our models, we assumed that genes cause increases in liability for schizophrenia and reductions in cognitive function. These assumptions are appropriate, but there might be other reasons that cognition and schizophrenia correlate with each other, other than in relation to the PRS. Sixth, cognition was defined as a latent variable with continuous indicators, while schizophrenia as a binary outcome variable. This difference in measurement approaches could lead to differences in statistical power to detect the two reciprocal causal paths. Indeed, in the bivariate model where both paths are estimated, the path from *L-SZ* to *L-COG* has a wider 95% CI than the path from *L-COG* to *L-SZ*. Thus, while our results support a causal relationship from *L-COG* to *L-SZ*, we cannot exclude the possibility of type 2 error in relation to the path from *L-SZ* to *L-COG*. Seventh, we estimated the *E* component in our models, as studies do not attribute significance to shared environment (*C*) for both schizophrenia (Sullivan *et al.*, 2003*a*) and cognition (Bouchard, 2013). However, the study design cannot differentiate between *C* and *E* (for this, we would need twin data); thus, *E* should be better interpreted as both common environment and unique environment. Eighth, to assess PRS we used the results from the latest PGC schizophrenia meta-analysis. As the PGC schizophrenia meta-analysis did not stratify on environmental risk (e.g. obstetrical complications) we cannot know the extent to which risk variants may be dependent on the environment. Ninth, causal modelling evaluates consistency of various models to the data, and does not provide absolute proof of causality. A longitudinal design, starting before illness onset, would be more informative and definitive. Alternatively, Mendelian randomization may also be a powerful approach. However, to perform a robust Mendelian randomization, it is preferable to use individual SNPs as multiple instruments (as opposed to PRSs applied here), and to control for some of these SNPs being pleiotropic (Davey Smith and Hemani, 2014; Hemani *et al.*, 2018; Verbanck *et al.*, 2018). Finally, when PGC sample size is further enlarged to produce a PRS that captures a greater proportion of the variance in schizophrenia liability, it is uncertain whether the proportion of variance mediated through cognitive impairment will remain unchanged.

In conclusion, the underlying biology of polygenic risk in schizophrenia is poorly understood. One strategy to translate polygenic burden into brain mechanisms of disease is to examine the causal relationships between schizophrenia, PRS, and proposed biological associations of risk, i.e. intermediate phenotypes that presumably lie on the chain of causation from gene to phenotype (e.g. cognitive deficit). We showed that cognitive deficit partially mediates the relationship between PRS and the disorder. Modelling sibling data suggested an even greater role for cognition in transmitting genetic influences on schizophrenia risk. Other genetic influences on diagnosis are more independent of cognition. Further discovery and analysis will be needed to understand more fully the degree to which genetic risk for schizophrenia is mediated through cognition.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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