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Polygenic risk for schizophrenia is associated with cognitive change between childhood and old age

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Abstract

Background

Genome-wide association studies (GWAS) have shown a polygenic component to the risk of schizophrenia. The disorder is associated with impairments in general cognitive ability that also have a substantial genetic contribution. No study has determined whether cognitive impairments can be attributed to schizophrenia's polygenic architecture using data from GWAS.

Methods

Members of the Lothian Birth Cohort 1936 (LBC1936, N=937) were assessed using the Moray House Test (MHT) at age 11 and with the MHT and a further cognitive battery at age 70. To create polygenic risk scores for schizophrenia, we obtained data from the latest GWAS of the Psychiatric GWAS Consortium on Schizophrenia (PGC-SCZ). Schizophrenia polygenic risk profile scores were calculated using information from the PGC-SCZ GWAS.

Results

In LBC1936, polygenic risk for schizophrenia was negatively associated with IQ at age 70, but not age 11. Greater polygenic risk for schizophrenia was associated with more relative decline in IQ between these ages. These findings were maintained when the

results of LBC1936 were combined with that of the independent Lothian Birth Cohort 1921 (N=517) in a meta-analysis.

Conclusions

Increased polygenic risk of schizophrenia is associated with lower cognitive ability at age 70, and greater relative decline in general cognitive ability between the ages of 11 and 70. Common genetic variants may underlie both cognitive ageing and risk of schizophrenia.

Introduction

Schizophrenia is a familial disorder in which genetic factors account for approximately 80% of the total variation in liability(1). Schizophrenia is frequently associated with lifelong disability and with impaired cognitive test performance that is not effectively treated with current antipsychotic treatments(2). Reduced general cognitive ability has also been found in children who later develop schizophrenia(3-5), in people at high genetic risk of psychosis(6, 7) and studies of unaffected adult relatives(8). Bivariate genetic studies (in affected patients and their families) suggest that the phenotypic correlation between cognitive ability and risk of schizophrenia is substantial and up to 92% of their covariance is due to common genetic factors(9, 10). These shared genetic causes have not yet been attributed to sets of specific SNPs. Whether these genetic risk factors confer a long-term, stable deficit in cognitive ability, or greater risk of cognitive decline over time, or both, is also not known.

General cognitive ability is substantially stable over time, with a correlation of >0.6 between measures of IQ taken at age 11 and 70(11). General cognitive ability also has a strong genetic basis(12, 13). By adolescence and throughout adulthood, well over 50% of its variation is due to genetic factors(12). Using genome-wide SNP data, we have estimated that common variants account for 24% of

the change in general cognitive ability from age 11 to age 70. These findings warrant a search for genetic variants that influence both the enduring stable trait of cognitive ability, and its change across the life course after childhood.

In the present study we test the hypothesis that having more of the common, risk-associated genetic variants for schizophrenia is associated with lower cognitive ability in childhood and old age, and relatively more decline in between. Whilst a relationship between genetic risk of schizophrenia and cognition has been based largely on studies of affected individuals, we sought to address this issue in a sample of individuals from the healthy population. We studied the Lothian Birth Cohort 1936(14) whose participants have cognitive function data in childhood and old age, and genome-wide SNP data. We used information from the latest-available Psychiatric GWAS consortium (PGC-SCZ) release to provide individual polygenic risk profile scores(15).

Materials and Methods

Subjects

The Lothian Birth Cohort 1936 (LBC1936) comprises 1091 community-dwelling individuals without dementia (548 men and 543 women), residing in or around the city of Edinburgh, Scotland(14, 16). Most of the LBC1936 had participated in the Scottish Mental Survey 1947 (SMS1947) at a mean age of 10.9 years and then in a follow up assessment approximately 59 years later at a mean age of 69.5 years old (SD 0.8). These assessments are referred to as ages 11 and 70 throughout. All subjects were asked questions about their medical history.

Cognitive testing

Most LBC1936 participants undertook the Moray House Test (MHT) at age 11(14). They re-took the MHT at about age 70. The MHT is a group-administered, paper-and-pencil test that has a time limit of 45 minutes and has a preponderance of verbal reasoning items with some arithmetical and abstract items also. MHT scores were converted into an IQ-type scale, with a mean of 100 and SD = 15, as we have done elsewhere(17). At age 70, participants completed an additional cognitive test battery of psychometric tests from the Wechsler Adult Intelligence Scale (WAIS)-III(18) and Wechsler Memory Scale (WMS)-III(19), including Digit Symbol Coding, Block Design, Matrix Reasoning, Digit Span Backwards, Symbol Search

and Letter-number sequencing. The additional tasks resulted in a measure of cognitive ability at age 70 that had a greater number of fluid-type tasks. Principal Component Analysis (PCA)-derived scores were then computed for general cognitive ability, memory, and processing speed(20).

Genotyping and risk profile score calculation

Details of the GWAS sample collection, processing and quality control have been described elsewhere(12). Genomic DNA was extracted from venous blood of members of LBC1936. Genotyping was conducted at the Wellcome Trust Clinical Research Facility, Edinburgh, United Kingdom (www.wtcrf.ed.ac.uk) and used the Illumina 610-Quadv1 whole-genome SNP array (San Diego, CA, USA). SNPs were excluded from the polygenic analysis where the minor allele frequency was less than 2%, if the call rate was less than 98% or if the Chi-squared test for Hardy–Weinberg Equilibrium was less than 0.001. Strand ambiguous SNPs were also removed. The resulting SNP set was then used to calculate four multidimensional scaling (MDS) components to assess for population stratification and adjust for this in later analyses. The data were then imputed to HapMap version 3 using MACH software (http://www.sph.umich.edu/csg/abecasis/MACH) and then converted back to plink (map/ped) format for later analysis.

Summary results from the most recent international GWAS of 9,394 individuals with schizophrenia(21) and 12,462 controls were obtained from PGC-SCZ. Details of the methods used by the consortium are given elsewhere(21). Polygenic profile scores were calculated according to the methods described by Purcell et al(15). Four lists of significant SNPs were generated from the PGC-SCZ association data, at significance thresholds of $p<0.5$, $p<0.1$, $p<0.05$ and $p<0.01$. These were used to select SNPs with a minor allele frequency of at least 2% from our LBC1936 GWAS data set, resulting in four separate files that contained the genotypes of each individual. In order to identify polygenic effects due to independent SNPs in linkage equilibrium with one another, each SNP set was then pruned using the variance inflation factor which is equivalent to $1/(1-R^2)$ (where R is the multiple regression coefficient for a SNP being regressed on all other SNPs simultaneously). Linkage equilibrium-based SNP pruning was conducted in a sliding window of 50 SNPs with each calculation performed iteratively by moving the window by five SNPs. SNPs were conservatively selected on the basis of a variance inflation factor of 2 or less. Finally, to obtain polygenic risk profile scores for schizophrenia, these four SNP sets were then scored using the sum of the number of reference alleles multiplied by the logarithm of the odds ratio for schizophrenia across the whole genome.

All analyses were performed in Plink with the exception of imputation to HapMap version 3 and data manipulation, which were performed in Mach (www.sph.umich.edu/csg/abecasis/MACH) and R software, respectively.

Statistical analyses

All statistical analyses were conducted in the R statistical software package (http://www.r-project.org/) using linear regression models that were adjusted for the first four MDS components measuring population stratification, for gender, and for a previous history of diabetes, stroke or hypertension as these conditions have previously been shown adversely to affect cognition or cognitive ageing(22-24). We examined the association between polygenic risk profile scores for schizophrenia at all four thresholds and cognitive ability in childhood IQ from the MHT at age 11) and cognitive ability in old age (IQ from the MHT at age 70 and then from six tests at age 70). In total, nine hundred and thirty seven people provided data for analysis.

We examined the relationship between polygenic risk profile scores for schizophrenia and participant's relative cognitive change between childhood and old age. This long-term cognitive change was derived as follows. The relationship between IQ at age 11 and 70 could be summarized using a linear regression model in which

the residual value reflected the observed deviation in IQ at age 70 based on that predicted by IQ at age 11. They represent an estimate of cognitive change for each LBC1936 participant with the relevant data. Negative values reflect a decline in function relative to that of others in the sample. Change scores were also estimated for general cognitive ability after adjustment for age 11 IQ.

Replication sample

Significant relationships between polygenic risk for schizophrenia and cognitive ability or cognitive ability change were then examined in the smaller Lothian Birth Cohort of 1921 (LBC1921)(25). The LBC1921 sample contributed 517 individuals to the current analysis who participated in the Scottish Mental Survey of 1932 when they were aged 11. The MHT number No. 12 was administered at age 11 and again at age 79, when Raven's(26) Standard Progressive Matrices, verbal Fluency(27) and Logical Memory(28) tests were also administered. General cognitive ability was measured using the MHT alone, and from the first principal component of the four cognitive tests at age 79. Processing methods and the subsequent analyses, including GWAS, were nearly identical to the methods used in LBC1936. The analyses were all adjusted for gender, the first 4 GWAS-MDS components and for the presence of a previous diagnosis of diabetes, hypertension or vascular disease.

In addition for testing for replication of significant findings across the two cohorts LBC1936 and LBC1921, we also conducted a meta-analysis of the results from the two studies. A fixed effects model was used which used the standardized regression coefficients were weighted by the inverse of their squared standard error and pooled to provide a summary estimate across both cohorts.

Results

A total sample of 937 (479 women and 458 men) individuals contributed both genome-wide and cognitive data to the analysis of the LBC1936, none of whom were known to suffer from schizophrenia. Three hundred and sixty-nine people (39%) had a history of hypertension, 82 had a history of diabetes (9%), and 46 (5%) had a history of previous stroke. We adjusted for these variables in all subsequent analyses.

Relationship of polygenic score to cognition

Polygenic risk for schizophrenia (derived separately using four significance thresholds) was not associated with IQ at age 11 (Supplementary Table 1). Polygenic risk for schizophrenia showed a weak, non-significant association with MHT-derived IQ at age 70 at p-thresholds of 0.5 (Table 1: beta = -0.06, p = 0.09) and 0.1 (Table 1: beta = -0.06, p = 0.08). Polygenic risk for schizophrenia was significantly associated with general cognitive ability at age 70 as based on the six non-verbal subtests from the Wechsler battery, at all four GWAS thresholds (range of p-values 0.005 to 0.02, Table 1).

Relationship of polygenic score to change in cognition

Greater polygenic risk for schizophrenia was associated with relatively greater decline in IQ from age 11 to age 70 (based on

MHT scores adjusted for IQ at age 11) at the GWAS threshold of p=0.01 (beta = -0.07, p = 0.03). A trend was observed for the threshold of p=0.1 (Table 2: beta = -0.07, p = 0.05). When lifetime cognitive change was derived from the six Wechsler non-verbal tests at age 70 adjusted for IQ at age 11, polygenic risk for schizophrenia was associated with lower than expected general cognitive ability at all four GWAS significance thresholds (range of p-values 0.004 to 0.008, Table 2). Judged by the change in the model R^2 statistic, the proportion of variance in cognitive ability change between age 11 and 70 (using the Wechsler tests) explained by polygenic risk for schizophrenia was between 0.8% at a GWAS threshold of P = 0.5 to 0.9% at the threshold of P = 0.005.

Replication in LBC1921

Three out of four of the significant associations between polygenic risk for schizophrenia and general cognitive ability at age 70 in LBC1936 were in the same direction in the smaller LBC1921 cohort at age 79. Polygenic risk for schizophrenia at the GWAS threshold of p = 0.01 additionally showed a significant negative association with general cognitive ability at age 79 (Table 3, Standardised beta = -0.11, p = 0.03) in LBC1921. This finding replicated the association found in LBC1936 in both direction and significance.

The significant negative association between polygenic risk of schizophrenia at a threshold of p = 0.01 and relative change in cognitive ability measured using the MHT in LBC1936 was also in the same direction in LBC1921 (standardised beta = -0.04, p = 0.38). When IQ was determined using four tests in LBC1921, the negative associations between polygenic risk of schizophrenia and change in cognitive ability remained in the same direction for all but the GWAS threshold of p = 0.5 (Table 3). None of these findings were individually significant in LBC1921 (which has a much smaller sample size).

Fixed effects meta-analysis using data from both cohorts showed a significant negative association between polygenic risk for schizophrenia and general cognitive ability in the eighth decade using the composite measure derived from four or six separate tests (Table 3: significant negative association with general cognitive ability at GWAS thresholds 0.1, 0.05 and 0.01). Polygenic risk for schizophrenia was also significantly and negatively associated with change in cognitive ability from 11 to 70 or 79 using the MHT (GWAS threshold p = 0.01: standardised beta = -0.06, p = 0.036). This negative association was also found using the estimate of change in cognitive ability based upon the four or six tests at GWAS thresholds of 0.1, 0.05 and 0.01 (Table 3).

Discussion

Greater polygenic risk for schizophrenia is associated with lower fluid-type general cognitive ability at age 70, but not at age 11. Furthermore, greater polygenic risk for schizophrenia is associated with a greater relative decline in general cognitive functioning between age 11 and age 70. These results were significant with the verbal-reasoning-dominated Moray House Test was used and when using a more extensive cognitive battery that incorporated non-verbal, fluid-intelligence-type tests from the Wechsler battery.

The association of polygenic risk for schizophrenia with cognitive ability at age 70 independently replicated partially in LBC1921 at age 79, at the GWAS threshold of $p = 0.01$. The direction of each statistically significant effect in LBC1936 was broadly replicated in LBC1921 for all but the most liberal of the GWAS thresholds ($p = 0.5$). Meta-analysis of the findings from both LBC1921 and LBC1936 also supported a significant negative association between polygenic risk for schizophrenia and both general cognitive ability in old age and cognitive ability change from childhood to old age.

Cognition is impaired in schizophrenia(29) and more recent studies have demonstrated that cognitive deficits may be seen pre-morbidly and in the unaffected close relatives of people with schizophrenia(5, 8). We are not aware of any studies that have serially-measured

cognition over time in a population-based cohort and then related these measurements to polygenic risk of schizophrenia. These cognitive changes occurred between age 11 and the eighth decade of life, and the precise timing and trajectory of these changes could not be determined in the current study. Therefore, whilst these changes are likely to be related to brain plasticity, it is not possible to identify whether the changes were related specifically to neurodevelopmental factors. Because the LBC1936 is a year-of-birth sample of mainly healthy people living in the community, these findings suggest that common genetic risk variants for schizophrenia may accelerate cognitive ageing independent of the clinical illness.

Studies of specific genetic risk factors, such as those identified in *DISC1* or *NRG1*, as well as some genome-wide significant variants, have demonstrated an association between the risk allele and cognitive impairment in one or more domains(30-32). It is likely, however, that these variants individually capture less than 1% of the total risk to schizophrenia and cumulatively less than 5% of the total risk to the disorder(21). A significant proportion of the 'missing heritability' to schizophrenia may lie in the variants that do not survive multiple testing corrections across the whole genome in GWAS studies. Recently Lee et al have shown that up to 25% of the risk for schizophrenia can be attributed to variants that do not reach

whole-genome significance(33). This implies that a polygenic approach to estimating individualized risk, taking in SNPs with p-vales <0.5, may be able to provide better phenotype predictions. This may be especially true in adult samples where general cognitive ability may be more strongly influence by genetic factors than in children(34).

The current findings suggest that common risk variants for schizophrenia are in combination associated with greater decline in general cognitive ability between age 11 and age 70. This builds upon a large body of literature showing a decline in general cognitive function over time in people at high genetic risk who later develop schizophrenia(3, 7), and upon studies that show a reduction over time in cognitive function in well relatives and affected patients. The proportion of genetic variance for schizophrenia shared with that for premorbid intelligence is modest(35) and less than initially expected(9). Fowler et al (2012) suggested that the phenotypic correlation between intelligence and schizophrenia might be caused by the onset of psychosis. However, that study was not in a position to test the phenotypic correlation between psychosis and age-related cognitive change, or the proportion of genetic variance that they share. The present study points to cognitive change and not prior cognition as the companion of schizophrenia risk.

Identifying traits that are genetically correlated with schizophrenia may also have statistical advantages for the identification of new quantitative trait loci(36). It is also possible, as GWAS samples increase and more of the heritability is captured by genotyping, that polygenic profiling will capture a greater proportion of variance in risk of schizophrenia. Assuming a constant genetic correlation with cognitive ability, the proportion of variance in cognition and cognitive ageing explained by polygenetic risk of schizophrenia can also be expected to increase. This has important implications for the eventual clinical usefulness of polygenetic profiling in schizophrenia, although future studies will also need to address the diagnostic specificity of these findings.

The present study has some potential limitations. Firstly, the cognitive test applied at age 11 (the Moray House Test) is not one that is in common use today and contemporary tests of cognition may have provide more accurate estimate of cognitive ability. However, previous studies have demonstrated a very high correlation (0.8 or more) between the MHT scores and individually administered cognitive assessments in childhood (Binet tests)(37) and old age (Wechsler tests)(38) suggesting that its use as a measure of general intelligence has concurrent validity across the

life course(39). Secondly, some of the results reported here would not survive stringent multiple testing corrections. However, the study's principal hypothesis concerned an association between polygenic risk profile scores and a decline in general cognitive ability, and was supported using data from both the MHT and a general cognitive factor derived from six non-verbal Wechsler subtests. The finding of greater cognitive ageing using the general cognitive battery would have survived false discovery rate correction(40) at all four GWAS p-values thresholds. It should thirdly be noted that the effects sizes reported in the current study are small and do not imply that the overlap in genetic architecture between cognitive ability, cognitive ageing and schizophrenia is substantial.

The failure to replicate the significant association in LBC1936 between polygenic risk for schizophrenia and change in cognitive ability in LBC1921 may also be seen as a limitation. The substantially smaller sample size in LBC1921 compared to LBC1936, as well as their more advanced years and greater comorbidity, may explain this apparent discrepancy. Nevertheless, the meta-analysis of findings from both studies supports our overall findings and conclusions.

The current study finds that polygenic risk for schizophrenia determined from GWAS contributes significantly to variation in the age-related decline of general cognitive ability in a community-dwelling sample assessed at age 11 and age 70. These findings were made in predominantly healthy, community-dwelling individuals and were therefore not simply due to the effects of chronic psychosis or its treatment. Cognitive ageing is growing in importance as a personal, social and economic burden on societies(41). It appears to be partly heritable(11), yet the specific genes are elusive(42). This new clue to the location of some of the genetic variation in cognitive ageing could aid the mechanistic understanding of both cognitive ageing and schizophrenia, and the link between them.

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Table 1: Polygene scores and cognitive ability age 70 in 937 people from LBC1936

Threshold	Cognitive ability at age 70 from MHT	Cognitive ability at age 70 from ability from six Wechsler tests
P = 0.5	Beta = -0.06, t = -1.68, p = 0.09, R^2 = 0.3	Beta = -0.10, t = -2.80, p = 0.005, R^2 = 0.8
P = 0.1	Beta = -0.06, t = -1.74, p = 0.08, R^2 = 0.3	Beta = -0.09, t = -2.46, p = 0.01, R^2 = 0.6
P = 0.05	Beta = -0.03, t = -0.97, p = 0.33, R^2 = 0.1	Beta = -0.08, t = -2.45, p = 0.01, R^2 = 0.6
P = 0.01	Beta = -0.05, t = -1.40, p = 0.16, R^2 = 0.2	Beta = -0.08, t = -2.30, p = 0.02, R^2 = 0.6

Beta: Standardized regression coefficient representing change in dependent variable for unit change in polygene profile scores, where both are measured in standard deviation units. R^2: Estimate of variance in cognitive ability explained by polygene score in %

Table 2: Polygenic scores and cognitive ability change between age 11 and age 70 in 937 people from LBC1936

Threshold	Change in cognitive ability from 11 to 70 from MHT	Change in cognitive ability from 11 to 70 from six Wechsler tests
P = 0.5	Beta = -0.04, t =-1.12, p = 0.26, R^2 = 0.1	Beta = -0.08, t = -2.44, p = 0.015, R^2 = 0.6
P = 0.1	Beta = -0.07, t = -1.93, p = 0.05, R^2 = 0.4	Beta = -0.09, t = -2.68, p = 0.007, R^2 = 0.8
P = 0.05	Beta = -0.04, t = -1.19, p = 0.23, R^2 = 0.2	Beta = -0.10, t = -2.89, p = 0.004, R^2 = 0.9
P = 0.01	Beta = -0.07, t = -2.14, p = 0.03 , R^2 = 0.5	Beta = -0.10, t = -2.93, p = 0.003, R^2 = 0.9

Beta: Standardized regression coefficient. R^2: Estimate of variance in cognitive ability change explained by polygene score. R^2: Estimate of variance in cognitive ability explained by polygene score in %

Table 3: Polygenic scores and cognitive ability in 517 people from LBC1921 and LBC1921 and LBC1936 combined (N=1,434)

Threshold	Cognitive ability at age 79 from four tests in LBC1921	Meta-analysis of LBC1921 and LBC1936 Fixed Effects Estimate
P = 0.5	Beta = 0.045, SE = 0.050, t = 0.91, p =0.36	Beta = -0.05, z = -1.92, p = 0.054
P = 0.1	Beta = -0.083, SE = 0.0497, t = -1.66, p = 0.097	Beta = -0.08, z = -3.43, p = 0.0006
P = 0.05	Beta = -0.065, SE = 0.050, t = -1.30, p = 0.20	Beta = -0.08, z = -2.68, p = 0.007
P = 0.01	Beta = -0.11, SE = 0.0519, t = -2.17, p = 0.03	Beta = -0.09, z = -3.08, p = 0.002
	Change in cognitive ability from 11 to 79 from MHT in LBC1921	**Meta-analysis of LBC1921 and LBC1936 Fixed Effects Estimate**
P = 0.01	Beta = -0.04, SE = 0.050, t = -0.89, p = 0.38	Beta = -0.06, z = -2.10, p = 0.036
	Change in cognitive ability from 11 to 79 from four tests in LBC1921	**Meta-analysis of LBC1921 and LBC1936 Fixed Effects Estimate**
P = 0.5	Beta = 0.05, SE = 0.049, t = 0.99, p = 0.32	Beta = -0.04, z = -1.42, p = 0.15
P = 0.1	Beta = -0.03, SE = 0.049, t = -0.65, p = 0.52	Beta = -0.07, z = -2.52, p = 0.01
P = 0.05	Beta = -0.02, SE = 0.050, t = -0.40, p = 0.69	Beta = -0.07, z = -2.66, p = 0.008
P = 0.01	Beta = -0.06, SE = 0.052, t = -1.24, p = 0.21	Beta = -0.09, z = -3.01, p = 0.003

Beta: Standardized regression coefficient

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