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Polygenic Risk for Schizophrenia Is Associated with Cognitive Change Between Childhood and Old Age

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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 at age 11 and with the Moray House Test 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. Schizophrenia polygenic risk profile scores were calculated using information from the Psychiatric GWAS Consortium on Schizophrenia GWAS.

Results: In LBC1936, polygenic risk for schizophrenia was negatively associated with IQ at age 70 but not at 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 aging and risk of schizophrenia.

Key Words: Aging, cognition, dementia, schizophrenia

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 single nucleotide polymorphisms (SNPs). Whether these genetic risk factors confer a long-term, stable deficit in cognitive ability, a 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 $>.6$ between measures of IQ taken at ages 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 tested 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. While 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 (LBC1936) (14) whose participants have cognitive function data in childhood and old age and genome-wide SNP data. We used information from the latest available genome-wide association study (GWAS) of the Psychiatric GWAS Consortium on Schizophrenia (PGC-SCZ) release to provide individual polygenic risk profile scores (15).

Methods and Materials

Subjects

The Lothian Birth Cohort 1936 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 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 (SD .8). These assessments are referred to as ages 11 and 70 throughout. All subjects were asked questions about their medical history.

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Cognitive Testing

Most LBC1936 participants undertook the Moray House Test (MHT) at age 11 (14). They retook 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. Moray House Test 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-Third Edition (18) and Wechsler Memory Scale-Third Edition (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 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, California). Single nucleotide polymorphisms 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 .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 (Centre for Statistical Genetics, University of Michigan; <http://www.sph.umich.edu/csg/abecasis/MACH>) and then converted back to PLINK (MAP/PED; <http://pngu.mgh.harvard.edu/purcell/plink/>) format for later analysis.

Summary results from the most recent international GWAS of 9394 individuals with schizophrenia (21) and 12,462 control subjects 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 $p < .5$, $p < .1$, $p < .05$, and $p < .01$. 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. 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 that 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. Single nucleotide polymorphisms 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 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 (R Project for Statistical Computing; www.r-project.org), 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 to adversely affect cognition or cognitive aging (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, 937 people provided data for analysis.

We examined the relationship between polygenic risk profile scores for schizophrenia and participants' relative cognitive change between childhood and old age. This long-term cognitive change was derived as follows. The relationship between IQ at ages 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 years. The MHT number 12 was administered at age 11 and again at age 79, when Raven *et al.* (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 four 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 in which 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 sixty-nine people (39%) had a history of hypertension, 82 (9%) had a history of diabetes, and 46 (5%) had a history of previous stroke. We adjusted for these variables in all subsequent analyses.

Table 1. Polygene Scores and Cognitive Ability at Age 70 in 937 People from LBC1936

Threshold	Cognitive Ability at Age 70 from MHT	Cognitive Ability at Age 70 from Six Wechsler Tests
$p = .5$	Beta = $-.06$, $t = -1.68$, $p = .09$, $R^2 = .3$	Beta = $-.10$, $t = -2.80$, $p = .005$, $R^2 = .8$
$p = .1$	Beta = $-.06$, $t = -1.74$, $p = .08$, $R^2 = .3$	Beta = $-.09$, $t = -2.46$, $p = .01$, $R^2 = .6$
$p = .05$	Beta = $-.03$, $t = -.97$, $p = .33$, $R^2 = .1$	Beta = $-.08$, $t = -2.45$, $p = .01$, $R^2 = .6$
$p = .01$	Beta = $-.05$, $t = -1.40$, $p = .16$, $R^2 = .2$	Beta = $-.08$, $t = -2.30$, $p = .02$, $R^2 = .6$

Beta, standardized regression coefficient representing change in dependent variable for unit change in polygene profile scores, where both are measured in standard deviation units; LBC1936, Lothian Birth Cohort 1936; MHT, Moray House Test; R^2 , estimate of variance in cognitive ability explained by polygene score in %.

Relationship of Polygenic Score to Cognition

Polygenic risk for schizophrenia (derived separately using four significance thresholds) was not associated with IQ at age 11 (Table S1 in Supplement 1). Polygenic risk for schizophrenia showed a weak, nonsignificant association with MHT-derived IQ at age 70 at p thresholds of .5 (Table 1: beta = $-.06$, $p = .09$) and .1 (Table 1: beta = $-.06$, $p = .08$). Polygenic risk for schizophrenia was significantly associated with general cognitive ability at age 70, as based on the six nonverbal subtests from the Wechsler battery, at all four GWAS thresholds (range of p values .005 to .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 $p = .01$ (beta = $-.07$, $p = .03$). A trend was observed for the threshold of $p = .1$ (Table 2: beta = $-.07$, $p = .05$). When lifetime cognitive change was derived from the six Wechsler nonverbal 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 .004 to .008; Table 2). Judged by the change in the model R^2 statistic, the proportion of variance in cognitive ability change between ages 11 and 70 (using the Wechsler tests) explained by polygenic risk for schizophrenia was between .8% at a GWAS threshold of $p = .5$ to .9% at the threshold of $p = .005$.

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 $p = .01$ additionally showed a significant negative association with general cognitive ability at age 79 (Table 3: standardized beta = $-.11$, $p = .03$) 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 $p = .01$ and relative change in cognitive ability measured using the MHT in LBC1936 was also in

the same direction in LBC1921 (standardized beta = $-.04$, $p = .38$).

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 $p = .5$ (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 (significant negative association with general cognitive ability at GWAS thresholds .1, .05, and .01; Table 3). Polygenic risk for schizophrenia was also significantly and negatively associated with change in cognitive ability from ages 11 to 70 or 79 using the MHT (GWAS threshold $p = .01$: standardized beta = $-.06$, $p = .036$). 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 .1, .05, and .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 when the verbal reasoning dominated Moray House Test was used and when using a more extensive cognitive battery that incorporated nonverbal, 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 $p = .01$. The direction of each statistically significant effect in LBC1936 was broadly replicated in LBC1921 for all but the most liberal of the GWAS thresholds ($p = .5$). Meta-analysis of the findings from both LBC1921 and LBC1936 also supported a significant negative

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 Age 11 to Age 70 from MHT	Change in Cognitive Ability from Age 11 to Age 70 from Six Wechsler Tests
$p = .5$	Beta = $-.04$, $t = -1.12$, $p = .26$, $R^2 = .1$	Beta = $-.08$, $t = -2.44$, $p = .015$, $R^2 = .6$
$p = .1$	Beta = $-.07$, $t = -1.93$, $p = .05$, $R^2 = .4$	Beta = $-.09$, $t = -2.68$, $p = .007$, $R^2 = .8$
$p = .05$	Beta = $-.04$, $t = -1.19$, $p = .23$, $R^2 = .2$	Beta = $-.10$, $t = -2.89$, $p = .004$, $R^2 = .9$
$p = .01$	Beta = $-.07$, $t = -2.14$, $p = .03$, $R^2 = .5$	Beta = $-.10$, $t = -2.93$, $p = .003$, $R^2 = .9$

Beta, standardized regression coefficient; LBC1936, Lothian Birth Cohort 1936; MHT, Moray House Test; 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 ($n = 1434$)

Threshold	Cognitive Ability at Age 79 from Four Tests in LBC1921	Meta-Analysis of LBC1921 and LBC1936 Fixed Effects Estimate
$p = .5$	Beta = .045, SE = .050, $t = .91$, $p = .36$	Beta = $-.05$, $z = -1.92$, $p = .054$
$p = .1$	Beta = $-.083$, SE = .0497, $t = -1.66$, $p = .097$	Beta = $-.08$, $z = -3.43$, $p = .0006$
$p = .05$	Beta = $-.065$, SE = .050, $t = -1.30$, $p = .20$	Beta = $-.08$, $z = -2.68$, $p = .007$
$p = .01$	Beta = $-.11$, SE = .0519, $t = -2.17$, $p = .03$	Beta = $-.09$, $z = -3.08$, $p = .002$
	Change in Cognitive Ability from Age 11 to Age 79 from MHT in LBC1921	Meta-Analysis of LBC1921 and LBC1936 Fixed Effects Estimate
$p = .01$	Beta = $-.04$, SE = .050, $t = -.89$, $p = .38$	Beta = $-.06$, $z = -2.10$, $p = .036$
	Change in Cognitive Ability from Age 11 to Age 79 from Four Tests in LBC1921	Meta-Analysis of LBC1921 and LBC1936 Fixed Effects Estimate
$p = .5$	Beta = .05, SE = .049, $t = .99$, $p = .32$	Beta = $-.04$, $z = -1.42$, $p = .15$
$p = .1$	Beta = $-.03$, SE = .049, $t = -.65$, $p = .52$	Beta = $-.07$, $z = -2.52$, $p = .01$
$p = .05$	Beta = $-.02$, SE = .050, $t = -.40$, $p = .69$	Beta = $-.07$, $z = -2.66$, $p = .008$
$p = .01$	Beta = $-.06$, SE = .052, $t = -1.24$, $p = .21$	Beta = $-.09$, $z = -3.01$, $p = .003$

Beta, standardized regression coefficient; LBC1921, Lothian Birth Cohort 1921; LBC1936, Lothian Birth Cohort 1936; MHT, Moray House Test; SE, standard error.

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, while 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 aging 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.* (33) have shown that up to 25% of the risk for schizophrenia can be attributed to variants that do not reach whole-genome significance. This implies that a polygenic approach to estimating individualized risk, taking in SNPs with p values $< .5$, may be able to provide better phenotype predictions. This may be especially true in adult samples where general cognitive ability may be more strongly influenced 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 pre-morbid intelligence is modest (35) and less than initially expected (9). Fowler *et al.* (35) 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 aging explained by polygenic risk of schizophrenia can also be expected to increase. This has important implications for the eventual clinical usefulness of polygenic profiling in schizophrenia, although future studies will also need to address the diagnostic specificity of these findings.

The present study has some potential limitations. First, 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 provided more accurate estimates of cognitive ability. However, previous studies have demonstrated a very high correlation (.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). Second, 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 nonverbal Wechsler subtests. The finding of greater cognitive aging using the general cognitive battery would have survived false discovery rate correction (40) at all four GWAS *p* value thresholds. Third, it should 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 aging, 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 with 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 aging 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 aging could aid the mechanistic understanding of both cognitive aging and schizophrenia and the link between them.

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1. McGuffin P, Farmer AE, Gottesman II, Murray RM, Reveley AM (1984): Twin concordance for operationally defined schizophrenia. Confirmation of familiarity and heritability. *Arch Gen Psychiatry* 41:541–545.
2. Sharma T, Harvey P (2000): *Cognition in Schizophrenia: Impairments, Importance and Treatment Strategies*. London: Oxford University Press.
3. Jones P, Rodgers B, Murray R, Marmot M (1994): Child developmental risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 334:1393–1402.
4. David AS, Malmberg A, Brandt L, Allebeck P, Lewis G (1997): IQ and risk for schizophrenia: A population-based cohort study. *Psychol Med* 27:1311–1323.
5. Zammit S, Allebeck P, David AS, Dalman C, Hemmingsson T, Lundberg I, Lewis G (2004): A longitudinal study of premorbid IQ

score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry* 61: 354–360.

6. Byrne M, Hodges A, Grant E, Owens DC, Johnstone EC (1999): Neuropsychological assessment of young people at high genetic risk for developing schizophrenia compare with controls: Preliminary findings of the Edinburgh High Risk Study (EHRS). *Psychol Med* 29: 1161–1173.
7. Cosway R, Byrne M, Clafferty R, Hodges A, Grant E, Abukmeil SS, *et al.* (2000): Neuropsychological change in young people at high risk for schizophrenia: Results from the first two neuropsychological assessments of the Edinburgh High Risk Study. *Psychol Med* 30:1111–1121.
8. McIntosh AM, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2005): Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. *Br J Psychiatry* 186: 378–385.
9. Touloupoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, Muuurray R (2007): Substantial genetic overlap between neurocognition and schizophrenia: Genetic modeling in twin samples. *Arch Gen Psychiatry* 64:1348–1355.
10. Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, *et al.* (2007): Adjudicating neurocognitive endophenotypes for schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 144:242–249.
11. Deary IJ, Yang J, Davies G, Harris SE, Tenesa A, Liewald D, *et al.* (2012): Genetic contributions to stability and change in intelligence from childhood to old age. *Nature* 482:212–215.
12. Davies G, Tenesa A, Payton A, Yang J, Harris SE, Liewald D, *et al.* (2011): Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Mol Psychiatry* 16:996–1005.
13. Deary IJ, Johnson W, Houlihan LM (2009): Genetic foundations of human intelligence. *Hum Genet* 126:215–232.
14. Deary IJ, Gow AJ, Taylor MD, Corley J, Brett C, Wilson V, *et al.* (2007): The Lothian Birth Cohort 1936: A study to examine influences on cognitive ageing from age 11 to age 70 and beyond. *BMC Geriatr* 7:28.
15. International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, *et al.* (2009): Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 460:748–752.
16. Deary IJ, Gow AJ, Pattie A, Starr JM (2012): Cohort profile: The Lothian Birth Cohorts of 1921 and 1936. *Int J Epidemiol* 41:1576–1584.
17. Gow AJ, Corley J, Starr JM, Deary IJ (2012): Reverse causation in activity-cognitive ability associations: The Lothian Birth Cohort 1936. *Psychol Aging* 27:250–255.
18. Wechsler D (1998): *WAIS-IIIUK Administration and Scoring Manual*. London: Psychological Corporation.
19. Wechsler D (1998): *WMS-IIIUK Administration and Scoring Manual*. London: Psychological Corporation.
20. Corley J, Jia X, Kyle JA, Gow AJ, Brett CE, Starr JM, *et al.* (2010): Caffeine consumption and cognitive function at age 70: The Lothian Birth Cohort 1936 study. *Psychosom Med* 72:206–214.
21. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (2011): Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 43:969–976.
22. Biessels GJ, Deary IJ, Ryan CM (2008): Cognition and diabetes: A lifespan perspective. *Lancet Neurol* 7:184–190.
23. Kilander L, Nyman H, Boberg M, Hansson L, Lithell H (1998): Hypertension is related to cognitive impairment: A 20-year follow-up of 999 men. *Hypertension* 31:780–786.
24. Mok VC, Wong A, Lam WW, Fan YH, Tang WK, Kwok T, *et al.* (2004): Cognitive impairment and functional outcome after stroke associated with small vessel disease. *J Neurol Neurosurg Psychiatry* 75:560–566.
25. Gow AJ, Johnson W, Pattie A, Brett CE, Roberts B, Starr JM, Deary IJ (2011): Stability and change in intelligence from age 11 to ages 70, 79, and 87: The Lothian Birth Cohorts of 1921 and 1936. *Psychol Aging* 26: 232–240.
26. Raven JC, Court JH, Raven J (1977): *Manual for Raven's Progressive Matrices and Vocabulary Scales*. London: H. K. Lewis.
27. Lezak MD (1995): *Neuropsychological Assessment*. New York: Oxford University Press.
28. Wechsler D (1987): *Wechsler Memory Scale-Revised*. San Antonio, TX: Psychological Corporation.
29. Aylward E, Walker E, Bettes B (1984): Intelligence in schizophrenia: Meta-analysis of the research. *Schizophr Bull* 10:430–459.

30. Walters JT, Corvin A, Owen MJ, Williams H, Dragovic M, Quinn EM, *et al.* (2010): Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Arch Gen Psychiatry* 67: 692–700.
31. Hall J, Whalley HC, Job DE, Baig BJ, McIntosh AM, Evans KL, *et al.* (2006): A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. *Nat Neurosci* 9:1477–1478.
32. Porteous DJ, Thomson P, Brandon NJ, Millar JK (2006): The genetics and biology of DISC1—an emerging role in psychosis and cognition. *Biol Psychiatry* 60:123–131.
33. Lee SH, DeCandia TR, Ripke S, Yang J, Schizophrenia Psychiatric Genome-Wide Association Study Consortium (PGC-SCZ) J, International Schizophrenia Consortium (ISC) J, *et al.* (2012): Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nat Genet* 44:247–250.
34. Posthuma D, Mulder EJ, Boomsma DI, de Geus EJ (2002): Genetic analysis of IQ, processing speed and stimulus-response incongruency effects. *Biol Psychol* 61:157–182.
35. Fowler T, Zammit S, Owen MJ, Rasmussen F (2012): A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. *Arch Gen Psychiatry* 69:460–466.
36. Glahn DC, Curran JE, Winkler AM, Carless MA, Kent JW Jr, Charlesworth JC, *et al.* (2012): High dimensional endophenotype ranking in the search for major depression risk genes. *Biol Psychiatry* 71:6–14.
37. Scottish Council for Research in Education. (1933): *The Intelligence of Scottish Children: A National Survey of an Age-Group*. London: University of London Press.
38. Deary IJ, Johnson W, Starr JM (2010): Are processing speed tasks biomarkers of cognitive aging? *Psychol Aging* 25:219–228.
39. Deary IJ, Whiteman MC, Starr JM, Whalley LJ, Fox HC (2004): The impact of childhood intelligence on later life: Following up the Scottish mental surveys of 1932 and 1947. *J Pers Soc Psychol* 86:130–147.
40. Benjamini Y, Hochberg Y (1995): Controlling the false discovery rate - a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol* 57:289–300.
41. Beddington J, Cooper CL, Field J, Goswami U, Huppert FA, Jenkins R, *et al.* (2008): The mental wealth of nations. *Nature* 455:1057–1060.
42. Harris SE, Deary IJ (2011): The genetics of cognitive ability and cognitive ageing in healthy older people. *Trends Cogn Sci* 15:388–394.