Impaired Intellect and Memory

A Missing Link Between Genetic Risk and Schizophrenia?

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Content: The DSM-IV concept of schizophrenia offers diagnostic reliability but etiologic and pathologic heterogeneity, which probably contributes to the inconsistencies in genetic studies. One solution is to identify intermediate phenotypes, “narrower” constructs of liability, that hypothetically share genetic risk with the disorder. Although a variety of candidate intermediate phenotypes have emerged, few have explicitly quantified the extent of their genetic overlap with schizophrenia.

Objective: To quantify the net-shared genetic effects between schizophrenia and specific cognitive candidate intermediate phenotypes.

Design: Twin and family design.

Setting: Adult psychiatric research centers in the United States and the United Kingdom.

Participants: A total of 2056 participants: 657 patients with schizophrenia, 674 first-degree relatives (including co-twins), and 725 controls.

Main Outcome Measures: (1) Latent factors capturing the common variance between cognitive tasks, (2) separation of the latent factors into their genetic and environmental components, and (3) estimation of the net-shared genetic variance between the latent cognitive factors or intelligence and schizophrenia.

Results: Genetic factors contributed substantially to the total variance in cognition (immediate recall latent factor: 0.66; 95% confidence interval [CI], 0.62 to 0.85; delayed recall latent factor: 0.48; 0.42 to 0.55; and intelligence: 0.66; 0.62 to 0.71). The latent common factors for modality-specific immediate and delayed recall and intelligence showed similar levels of phenotypic covariance with schizophrenia (immediate recall: −0.35; delayed recall: −0.37; and intelligence: −0.38), with 72%, 86%, and 89%, respectively, due to shared genetic effects with schizophrenia. Environmental effects accounted for little phenotypic correlation between cognition and schizophrenia.

Conclusions: Using the largest international familial schizophrenia cohort to date, we showed that a substantial portion of the phenotypic correlation between schizophrenia and cognition is caused by shared genetic effects. However, because the phenotypic and genetic correlations are far from unity, the genetics of schizophrenia are clearly not merely the genetics of cognition.

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Schizophrenia is a complex, multifactorial disorder with multiple genetic and environmental effects. However, few consistent results have been published from more than 1000 genetic association studies; a 2008 meta-analysis identified 16 nominally significant genes, with a mean summary odds ratio of only 1.23. Genome-wide searches examining single nucleotide polymorphisms have begun to produce some results, and rare variants may also have a role. It may be that schizophrenia, as presently defined, is too etiologically and pathologically heterogeneous to serve as a useful phenotype for genetic studies and that defining individuals using biologically plausible mechanisms for disease pathogenesis (intermediate phenotypes) may be a more fruitful alternative.

Patients with schizophrenia have abnormalities in brain structure, brain function, and cognition, and these abnormalities are also found in some unaffected relatives. These deficits could represent susceptibility-related phenotypes, pathophysiologically intermediate between the genes that increase susceptibility to schizophrenia and the disorder itself. Because these intermediate phenotypes are “narrower” constructs and hypothetically closer to the genetic effects than the clinical disorder itself, they may be more useful/powerful in genetic studies. Consequently, as a means of discovering appropriate phenotypes for...
genetic studies and of understanding the pathogenesis of these disorders, intermediate phenotypes have attracted a great deal of research interest.\textsuperscript{3–13} Intermediate phenotypes, or endophenotypes, should be (1) associated with the disease in the relevant population, (2) state independent, (3) heritable, (4) cosegregated with the disorder in families, and (5) found more frequently in unaffected relatives than in the general population.\textsuperscript{14}

Schizophrenia is associated with impaired cognition,\textsuperscript{13} with impairments in memory\textsuperscript{11,16–18} and general intelligence\textsuperscript{10,20} being among the best candidate intermediate phenotypes for the disorder. Despite a wealth of evidence showing that cognitive impairment is related to familial risk of schizophrenia,\textsuperscript{21} it has been impossible to determine whether that covariance is caused by common genetic or environmental effects. Multivariate statistical modeling approaches can help us address this question in twin and family data. Unlike molecular genetic approaches, which estimate the effect of observed allelic variants on phenotypic variance, genetic modeling quantifies the net-shared genetic effects between the intermediate phenotype and the illness, giving a broader estimate of their genetic and environmental overlap.

In this study, we applied genetic modeling to a combined family and twin sample to quantify the extent to which increased liability to schizophrenia overlaps genetically with cognitive impairment. These data are from the largest international familial cohort in schizophrenia in which memory and intelligence have been characterized. To our knowledge, this is the first study to use a combined family and twin design to (1) identify latent factors that capture the variations common in the performance of standard cognitive tasks and separate them into their genetic and environmental components and (2) quantify the covariance between schizophrenia and cognitive function caused by shared genetic and environmental effects. The use of family designs overcomes some of the limitations of the classic twin design because adding parents and siblings reduces parameter bias and increases statistical power.\textsuperscript{22} We hypothesized that a considerable proportion of the variance in memory and intelligence is explained by genetic effects that, in turn, share substantial genetic variance with schizophrenia.

**METHODS**

**PARTICIPANTS**

Data were collected at 3 sites—(1) the Institute of Psychiatry (IoP), King's College London, which contributed the Maudsley Family (MFS) and the Maudsley Twin (MTS) studies; (2) the National Institutes of Health (NIH), Bethesda, Maryland, with the NIH Sibling Study (NIHSS); and (3) Harvard University, Boston, Massachusetts, with the Harvard Neuropsychology Family Study (HNFS). Recruitment at each site has been described in detail elsewhere.\textsuperscript{10,16,23–26} Briefly, the IoP recruited participants with schizophrenia and their relatives from throughout the United Kingdom through voluntary support groups and by referral from National Health Service treatment centers. At the NIH, patients and their relatives were recruited from local and national sources, whereas at Harvard, patients were recruited from various hospitals in eastern Massachusetts, including Boston, and their nonpsychotic relatives through their respective probands. Patients were prescribed a variety of psychotropic medications at assessment. Controls were recruited through local advertisements, from community sources, and from existing volunteer databases. All the sites contributed patients, first-degree relatives, and controls. The exclusion criteria for all participants were head trauma resulting in loss of consciousness, current harmful substance use or dependence, history of a systemic illness with known neurologic complications, and not having English as a primary language. Controls had no personal or family history of psychotic illness. Controls and unaffected relatives with a nonpsychotic psychiatric diagnosis were included. All the studies were approved by their respective institutional review boards, and all the participants gave written informed consent before participating.

**ASSESSMENTS**

**Verbal Memory and Learning**

All the studies contributed data on Logical Memory, a widely used subtest of the Wechsler Memory Scale that measures verbal recall. The recall occurs immediately after the story presentation or after a 30-minute delay. The MFS and part of the HNFS used the original form of the stories\textsuperscript{27} but added a 30-minute delayed recall (DR) trial. The MTS, the NIHSS, and the rest of the HNFS used the stories from the Wechsler Memory Scale–Revised.\textsuperscript{28} The Associate Learning test, or the Verbal Paired Associates test as it is called in the Wechsler Memory Scale–Revised, was used to measure verbal learning. The task involves oral presentations of easy or difficult word pairs each followed by a recall trial to assess rate of learning. The revised version was used in the MTS and the NIHSS. The other 2 studies used the original scale, which does not include a DR condition but is otherwise similar to the revised version.

**Visual Memory**

The MFS, the MTS, and the NIHSS also contributed visual memory data as measured using the Visual Reproduction subtest of the Wechsler Memory Scale. The test entails exposure to a design card followed by a drawing trial. The MFS used the original form, and the other 2 studies used the revised version. Because there is no delayed condition in the original version, the MFS did not contribute visual DR data.

**Intelligence**

Intelligence, or IQ, was assessed using well-established and validated short forms of the Wechsler Adult Intelligence Scale–Revised\textsuperscript{29} (MFS, NIHSS, and HNFS) or its successor, the Wechsler Adult Intelligence Scale–Third Edition\textsuperscript{30} (MTS). Diagnoses were made using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version\textsuperscript{31} (MFS, MTS, and HNFS) or the Structured Clinical Interview for DSM-IV Axis I Disorders\textsuperscript{32} (NIHSS).

**DATA ANALYSES**

**Comparability Analyses**

Data were acquired from 3 sites and, in some cases, using different versions of the same test. To ensure compatibility, we standardized the data to controls in the same site or study. For each test version, we pooled the control data and fitted a regression model that incorporated the effects of site, age, sex, and education as well as 2-way interactions between these variables. All 2-way interactions turned out to be nonsignificant after accounting for multiple testing; therefore, fitted regression models for each site were used with only the main effects, including the constants, to
obtain standardized residuals for each test version in each site, that is: (test score – predicted test score)/residual standard deviation. The regression model for the MTS also included zygosity as an independent variable. This standardization procedure was performed on all the participant groups and ensured that all standardized variables have a mean of 0 and variance of 1 in the control groups of all the sites.

Regression Analyses: Group Comparisons

To assess differences in cognitive function between patients or relatives and controls, regression analyses were performed. Data from members of the same family share a variety of characteristics and are not independent of each other, violating the assumption of independence made in analyses of variance or regression. To account for this, robust Hubert-White sandwich estimators were used to adjust standard errors and, hence, confidence intervals and P values of regression analyses. Group, sex, and education were included as independent variables. Interactions between group and age and education were included if they significantly affected the outcome variable. After a significant main effect of group, planned post hoc tests were performed between patients and controls and between relatives and controls. Because age and education were centered, pairwise comparisons of analysis with interaction are evaluated at mean age (37 years) or mean years of education (13.5 years).

Model-Fitting Analyses

Structural equation modeling was used to specify a model by which the variance of the cognitive traits, and the covariance between those and schizophrenia, was partitioned between genetic and environmental causes. Relatives resemble each other because they share genetic and environmental factors. Additive genetic factors (A) represent the effects of genes that add up to affect behavior; common environment (C) represents nongenetic factors that are shared by members of the same family, such as diet. The unique environment (E) represents environmental factors that make members of the same family different from each other, for example, accidents. To study the contribution of genes and environment to the covariance between cognition and schizophrenia, we looked at the cross-trait correlation between cognition for participant 1 and liability to schizophrenia of his or her relative. For example, if the cross-trait correlation is greater for monozygotic than for dizygotic twins, this would imply that A contributes to the phenotypic correlation between the 2 traits, suggesting that the same genetic factors that increase the susceptibility to schizophrenia cause the cognitive impairment associated with the disease.

Polychoric Correlations

First, we fitted a correlational model to estimate the familial correlations across each cognitive domain and schizophrenia. Because data were from twin pairs and siblings selected for schizophrenia rather than from a random sample, the correlations for schizophrenia were fixed according to the estimates in population samples (rmonozygote = 0.92 and rdizygote = 0.32) as a means of correcting for ascertainment. The threshold was fixed to the population lifetime prevalence (1%). The correlational model yielded (1) phenotypic cross-trait correlations (eg, memory with liability to schizophrenia), (2) cross-relative cross-trait correlations, and (3) cross-relative within–cognitive trait correlations.

Bivariate and Multivariate Genetic Analyses

We performed bivariate and complex multivariate genetic analyses. We used estimates of schizophrenia from an earlier meta-analysis (h² = 0.81, c² = 0.11, and e² = 0.08) and refitted the model using the lower limits of the confidence intervals from the same meta-analysis (h² = 0.73, c² = 0.11, and e² = 0.08). Changing the variance components for schizophrenia did not substantially change the estimates, and the results are available on request. First, the bivariate genetic models between schizophrenia and cognition separated the variance of each individual measure into its components A, C, and E, represented by the parameters h², c², and e², respectively. The partitioning of the covariation between schizophrenia and each cognitive measure into the genetic and environmental sources of covariation yielded a genetic (r̂g), common environmental (r̂e), and unique environmental (r̂u) correlation. The r̂e indicates the extent to which the same genetic effects affect schizophrenia and cognitive function, whereas the r̂u reflects the level to which the familial environmental effects in the first trait (eg, memory) are the same with those in the second trait (eg, liability to schizophrenia). The degree to which the same unique environmental effects are common in both traits is given by the r̂e. A genetic correlation of 1.0 would imply that the 2 traits have all additive genetic effects in common, whereas an environmental correlation of 0 would suggest that the environmental effects on, for example, the liability for schizophrenia are independent of the environmental effects on cognitive function. Combining the information from the r̂g, r̂e, and r̂u with the h², c², and e² of each trait allowed us to separate the phenotypic correlation into genetic and environmental components: r̂ph-c, r̂ph-u, and r̂ph-c. The path diagram of the bivariate genetic model is depicted in Figure 1A.

Second, we performed multivariate analyses to obtain the latent factor that captures the variance common to all the immediate recall (IR) and DR memory tasks. Under this model, the variance due to error or specific to each task was separated from the reliable variance common to all the tasks. In this way, the specific and common variances were separated into their genetic and environmental components. After this, the genetic and environmental correlations between schizophrenia and the common memory factors (IR or DR) were estimated. Third, we used the multivariate approach to estimate the genetic and environmental correlations between memory and schizophrenia and between IQ and schizophrenia simultaneously in the same model. The path diagram in Figure 1B illustrates this model. On the latent factor level, we fitted a trivariate genetic model. This 3-vari-ate analysis (trivariate genetic) had 2 major advantages: first, it increased the statistical power and, therefore, the reliability of the parameter estimates; second, it allowed us to explicitly test the equality of the genetic correlations of memory and IQ with schizophrenia. This test was performed by fitting a submodel in which the 2 genetic correlations were constrained to be equal, and the difference between the full and the restricted models was tested using a likelihood ratio test with 1 df. Due to limitations in the Mx program with respect to the number of categorical variables that it can accommodate in the threshold model, the maximum family size was reduced to proband, mother, first sister, and first brother. Because the trivariate genetic approach is more comprehensive than is repeating the bivariate analyses for each cognitive variable separately, we report only the results of the trivariate genetic analyses.

Model Estimation and Evaluation

The effects of potential sources of variation or noise (age, sex, and education) were partialled out before the analyses. To fit the genetic models to the data, we performed structural equation modeling with maximum likelihood estimation of parameters using the Mx program. The fit of the genetic models was compared with that of the correlational models by subtracting the difference in −2 log-likelihood, obtaining a χ² sta-
Results

Table 1. Demographic Characteristics of the 2056 Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=657)</th>
<th>Relatives (n=674)</th>
<th>Controls (n=725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>37.14 (10.19)</td>
<td>41.79 (13.92)</td>
<td>38.92 (12.88)</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>183 (27.9)</td>
<td>411 (61.0)</td>
<td>428 (59.0)</td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>13.43 (2.60)</td>
<td>14.73 (2.82)</td>
<td>15.00 (3.07)</td>
</tr>
</tbody>
</table>

The pairwise comparisons are given in Table 2. Patients and their relatives had significantly lower IQs than did the control group. For all 6 tasks, patients scored significantly worse than did the control group, and their relatives scored significantly worse in 3 of the 4 verbal tasks (verbal memory in IR and verbal memory and verbal learning in DR), with no significant differences in the 2 visual memory tasks.

Twin and Family Correlations

Figure 2A, C, and E show the estimates of the correlations across relatives for each of the cognitive measures, and Figure 2B, D, and F show the cross-trait correlations between cognitive measures and schizophrenia. The within-trait correlations between pairs of relatives show the classic genetic cascade that evidences the effects of genetics in the variation of cognitive function. The cross-trait correlations are generally lower but also show a clear difference between the monozygotic resemblance and that of the other pairs of relatives. These point to a contribution of genetic factors to the phenotypic correlation between cognition and liability to schizophrenia. The actual correlations and their confidence intervals are available on request.

Genetic Models: Proportions of Variance and Covariance Explained by A, C, and E

Figure 3A shows the contributions of genetics ($h^2$), shared environment ($c^2$), and unique environment ($e^2$) to the variations in the common latent memory factors.
Figure 3B shows the breakdown of the phenotypic correlation between schizophrenia and each cognitive measure into genetic ($r_{ph-g}$) and environmental ($r_{ph-e}$ and $r_{ph-c}$) components. The parameter estimates and confidence intervals from the trivariate genetic models are given in Table 3.

**IR LATENT FACTOR**

The trivariate genetic model for IR provided an acceptable fit to the data ($\chi^2_{15}=54.06$, $P < .001$, RMSEA = 0.047, AIC = 16.06). The factor loadings of the 3 memory variables on the latent factor for IR were 0.59 for Logical Memory, 0.61 for Associate Learning, and 0.54 for Visual Reproduction. The square of these loadings provides the proportion of the variance that the latent factor explains of each of the variables: 0.35, 0.37, and 0.29, respectively. The remaining variance is specific to each of the memory tasks. Sixty-six percent of the common variance of IR is explained by genetic factors and 21.7% by unique environment. Shared environment did not account substantially for interindividual differences in this latent factor. The total covariance ($r_{ph}$) between schizophrenia and the IR latent factor was estimated to be −0.35. The estimate of the genetic correlation ($r_{g}$) between the 2 was −0.34 and of the unique environmental correla-

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**Table 2. Pairwise Comparisons Between Patients and Their Relatives vs the Control Group, With Group, Age, Years of Education, and Sex as Covariates**

<table>
<thead>
<tr>
<th></th>
<th>Patients vs Controls</th>
<th></th>
<th>Relatives vs Controls</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$b$ (95% CI)</td>
<td>$t$</td>
<td>$P$ Value</td>
<td>$b$ (95% CI)</td>
</tr>
<tr>
<td>Intelligence</td>
<td>−1.12 (−1.26 to −0.99)</td>
<td>−15.97</td>
<td>&lt;.001</td>
<td>−0.20 (−0.31 to −0.08)</td>
</tr>
<tr>
<td>Immediate recall</td>
<td>−1.27 (−1.41 to −1.12)</td>
<td>−17.32</td>
<td>&lt;.001</td>
<td>−0.32 (−0.45 to −0.19)</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>−1.35 (−1.59 to −1.11)</td>
<td>−11.10</td>
<td>&lt;.001</td>
<td>−0.07 (−0.25 to 0.11)</td>
</tr>
<tr>
<td>Visual memory</td>
<td>−2.14 (−3.04 to −1.24)</td>
<td>−4.67</td>
<td>&lt;.001</td>
<td>−0.29 (−1.00 to 0.42)</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>−1.29 (−1.42 to −1.15)</td>
<td>−18.85</td>
<td>&lt;.001</td>
<td>−0.29 (−0.41 to −0.17)</td>
</tr>
<tr>
<td>Visual memory</td>
<td>−1.42 (−1.64 to −1.20)</td>
<td>−12.59</td>
<td>&lt;.001</td>
<td>−0.09 (−0.26 to 0.08)</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>−1.00 (−1.27 to −0.73)</td>
<td>−7.15</td>
<td>&lt;.001</td>
<td>−0.36 (−0.57 to −0.14)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*P values and 95% CIs were derived using standard errors that are robust against correlations in family clusters. Models with intelligence and verbal learning in immediate and delayed recall conditions include an interaction between group and years of education, and models with visual memory in both conditions include interactions between group and years of education and between group and age. For these models, pairwise comparisons are based on mean age (37 years) and mean years of education (13.5 years) variables.

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**Figure 2.** Twin, sibling, and mother-offspring correlations. Correlations in Visual Reproduction (VR), Associate Learning (AL), and Logical Memory (LM) for monozygotic (MZ) twins, dizygotic (DZ) twins, siblings, and mother-offspring (M-O) pairs for immediate recall (A), delayed recall (C), and IQ (E). Cross-trait correlations are given between cognitive measures and schizophrenia, eg, correlations are given between VR in twin 1 with liability to schizophrenia (SCHZ) in twin 2, for immediate recall (B), delayed recall (D), and IQ (F).
tion \( (r_c) \) was \(-0.75\). The portion of the phenotypic correlation due to shared genetic effects was calculated as \( r_{ph-a} = -0.25 \), suggesting that 72% of the phenotypic correlation was due to genetic factors \( (r_{ph-a} = 0.25/ r_{ph} = 0.35 \times 100) \). Unique environment explained some of the phenotypic correlation, whereas common shared effects did not significantly account for the phenotypic correlation between IR and schizophrenia.

**DR LATENT FACTOR**

The model for DR provided an acceptable fit to the data \((\chi^2=59.305, P<.001; \text{RMSEA}=0.051, \text{AIC}=21.305)\). The factor loadings of the 3 memory variables assessing DR on the latent factor were 0.53 for Logical Memory, 0.43 for Associate Learning, and 0.61 for Visual Reproduction. This suggests that the factor explained 28%, 18%, and 37%, respectively, of the variance of each of the DR measures. Genetic factors accounted for 48% of the common variance of DR and unique environment for 37%. Shared environment explained 15% of the variance. The \( r_{ph} \) between DR and schizophrenia was estimated to be \(-0.37\). The \( r_c \) between the 2 factors was \(-0.50 \) and the \( r_e \) was \(-0.29\). Thus, approximately half of the genetic and a third of the environmental factors that affect the liability to schizophrenia also affect DR deficit. The portion of the phenotypic correlation due to shared genetic effects was calculated as \( r_{ph-a} = -0.32 \), suggesting that 86% of the phenotypic correlation was due to genetic factors. Schizophrenia and DR also shared 13.5% of their unique environment. Common environment did not significantly account for the phenotypic correlation between the latent factor for DR and schizophrenia.

**INTELLIGENCE**

Genetic factors accounted for a substantial amount of the total variance in intelligence \((A=0.66)\). Shared environmental effects explained 9% of the variance \((C=0.90)\), with individual-specific environmental effects and error accounting for the remaining variance \((E=0.25)\). The phenotypic correlation between IQ and schizophrenia was \( r_{ph} = -0.38 \), suggesting that increased liability to schizophrenia is associated with diminution in intelligence. The extent to which schizophrenia and intelligence shared genetic, common environment, and unique environment effects was given by the correlations \( r_g (-0.46) \), \( r_c (-0.00) \), and \( r_e (-0.33) \), respectively. These correlations suggest that schizophrenia shares with intelligence a statistically significant portion of genetic factors. When theheritabilities of schizophrenia and intelligence were considered, the part of the phenotypic correlation due to shared genetic effects was calculated as \( r_{ph-a} = -0.34 \), suggesting that 89% of the phenotypic correlation was due to genetic factors. Schizophrenia and intelligence also shared some of their unique environment.

**INTELLIGENCE, MEMORY, AND SCHIZOPHRENIA**

A submodel in which the \( r_{ph-SCHZ} \) was equated to \( r_{eq-SCHZ} \) fitted the data as well as the full genetic model \(( \chi^2=1.03, P=.31) \), suggesting that the genetic overlap between IQ and schizophrenia does not differ significantly from the over-

**Table 3. Parameter Estimates and CIs From the Trivariate Genetic Models**

<table>
<thead>
<tr>
<th>Variable</th>
<th>IR Latent Common Factor</th>
<th>DR Latent Common Factor</th>
<th>IQ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variance components</strong></td>
<td></td>
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</tr>
<tr>
<td>A</td>
<td>0.66 (0.62 to 0.85)</td>
<td>0.48 (0.42 to 0.55)</td>
<td>0.66 (0.62 to 0.71)</td>
</tr>
<tr>
<td>C</td>
<td>0.11 (0.05 to 0.13)</td>
<td>0.15 (0.14 to 0.20)</td>
<td>0.90 (0.08 to 0.09)</td>
</tr>
<tr>
<td>E</td>
<td>0.22 (0.07 to 0.22)</td>
<td>0.37 (0.22 to 0.42)</td>
<td>0.25 (0.22 to 0.28)</td>
</tr>
<tr>
<td><strong>Covariance components</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( r_{ph-a} )</td>
<td>-0.25 (-0.25 to -0.22)</td>
<td>-0.32 (-0.42 to -0.21)</td>
<td>-0.34 (-0.35 to -0.33)</td>
</tr>
<tr>
<td>( r_{ph-c} )</td>
<td>-0.00 (-0.00 to 0.00)</td>
<td>-0.00 (-0.00 to 0.00)</td>
<td>-0.00 (-0.003 to 0.00)</td>
</tr>
<tr>
<td>( r_{ph-e} )</td>
<td>-0.10 (-0.09 to -0.05)</td>
<td>-0.05 (-0.05 to -0.02)</td>
<td>-0.05 (-0.06 to -0.05)</td>
</tr>
<tr>
<td>( r_e )</td>
<td>-0.35 (-0.39 to -0.27)</td>
<td>-0.37 (-0.38 to -0.28)</td>
<td>-0.38 (-0.46 to -0.38)</td>
</tr>
<tr>
<td><strong>Genetic and environmental correlations</strong></td>
<td></td>
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</tr>
<tr>
<td>( r_g )</td>
<td>-0.34 (-0.37 to -0.32)</td>
<td>-0.50 (-0.67 to -0.41)</td>
<td>-0.46 (-0.52 to -0.32)</td>
</tr>
<tr>
<td>( r_c )</td>
<td>-0.00 (-0.34 to 0.00)</td>
<td>-0.00 (-0.31 to 0.00)</td>
<td>-0.00 (-0.10 to 1.00)</td>
</tr>
<tr>
<td>( r_e )</td>
<td>-0.75 (-0.77 to -0.67)</td>
<td>-0.29 (-0.47 to -0.21)</td>
<td>-0.33 (-0.36 to 0.18)</td>
</tr>
</tbody>
</table>

Abbreviations: A, additive genetic effects; C, shared environment effects; CI, confidence interval; DR, delayed recall; E, unique environment effects; IR, immediate recall; \( r_c \), common environmental correlation; \( r_e \), unique environmental correlation; \( r_g \), genetic correlation; \( r_{ph} \), total phenotypic correlation; \( r_{ph-a} \), breakdown of the phenotypic correlation into genetic components; \( r_{ph-c} \) and \( r_{ph-e} \), breakdown of the phenotypic correlation into environmental components.
The same analyses for the $r_{IR\cdot SCHZ}$ produced similar results ($\chi^2=0.00, P>.99$), suggesting that the correlation between IQ and schizophrenia is not stronger than that for DR and schizophrenia.

To date, several schizophrenia intermediate phenotypes have emerged, but the methods, samples, and statistics used in many studies simply highlight, at best, their familial component without explicitly quantifying the genetic association with the disorder. By combining family and twin data we created the largest international database of cognitive function in schizophrenia, a data set with the power to answer these exact questions. Genetic models based on maximum likelihood of directly estimated model parameters showed substantial shared genetic variance between schizophrenia and the IR and DR latent memory factors and between schizophrenia and intelligence, thus validating their roles as intermediate phenotypes for the disorder.

We confirmed that patients with schizophrenia and their unaffected relatives are significantly impaired compared with controls in their cognitive performance. However, these findings alone cannot confirm that the deficits are part of the genetic vulnerability to the illness. In this study, we went further by estimating their heritability and, finally, characterizing their relationship with liability to schizophrenia. We found that substantial portions of the cognitive measure variance were explained by genetic effects shared with schizophrenia. Whereas other studies have measured the heritability of other candidate intermediate phenotypes, such as brain structure$^{37}$ and cognition,$^{38,39}$ with broadly speaking similar results, the implications of these results are more far reaching, addressing the question of the degree of shared genetic liability between schizophrenia and cognitive impairment.

The trivariate genetic model-fitting analyses detected similar phenotypic correlations between schizophrenia and each of the common latent memory factors and intelligence (range, −0.35 to −0.38), whereas the genetic correlations suggested that the liability to schizophrenia is related to lower cognition specifically through common genetic effects. The genetic correlation ($r_g$) describes the extent to which genetic factors are shared between 2 traits and suggests that to a certain extent the same genetic effects that contribute to interindividual differences in liability to schizophrenia also contribute to interindividual differences in cognition. More specifically, of the 2 memory latent factors, DR showed the greater genetic link with schizophrenia, although this factor was the less heritable of the 2. Intelligence showed a similar genetic correlation ($r_g$) with schizophrenia liability to DR but was also more heritable. Separate analyses to explicitly test the equality of the genetic correlations of memory and IQ with schizophrenia did not suggest that any domain was more genetically correlated with schizophrenia than the others. Because $r_g$ does not account for the heritability of either schizophrenia or cognition, it is possible for a very large correlation to explain only a very small portion of the covariance between the two. When the heritability of schizophrenia and each cognitive domain was considered, the genetic ($r_{gh}$) contributions to the total phenotypic correlations ($r_{ph}$) between the 2 traits could be estimated. In the case of intelligence, these calculations suggested that 89% of the phenotypic covariance between liability to schizophrenia and intelligence was due to shared genetic factors. Similar estimates were found for the 2 latent memory factors and schizophrenia. These imply that a moderate portion of the genes that affect the liability to schizophrenia are also involved in memory and intellectual impairment. Nonetheless, given that the phenotypic and genetic correlations are far from perfect, a substantial portion of genetic variation has effects that are specific to schizophrenia and cognition.

The term intermediate phenotype explicitly implies an intermediate stage in a pathogenic mechanism. A wealth of evidence from population-based birth and cohort studies and studies of high-risk individuals confirms that cognitive deficits predate the onset of psychosis and give support to the idea that these phenotypes exist, in at least some patients, before the clinical endpoint, therefore mediating the effect of genes on schizophrenia. Nevertheless, intermediate phenotypes are evolving concepts that are redefined as novel experimental insights emerge. The present data suggest that increased liability to schizophrenia and cognition share, to some extent, the same genetic effects, compatible with the idea that cognition is an endophenotype or intermediate phenotype of the disease. Alternatively, the same genetic factors that predispose to schizophrenia might also predispose to cognitive impairment but without the latter mediating the genetic effects of the former.

It has been argued that an ideal intermediate phenotype will be highly heritable and also genetically simple. Although the genetic underpinnings of cognition are yet to be discovered, it is likely that cognition is genetically complex$^{40}$ and even in need of its own endophenotype markers. However, because cognition forms only 1 facet of the underlying genetic risk for the disorder, it might be easier to genetically dissect than the DSM-IV concept of schizophrenia, although findings from the recent genome-wide association study by Need et al$^{41}$ do not necessarily support this. Nevertheless, refining the schizophrenia phenotype by stratifying patients by their cognitive scores should assist in identifying vulnerability alleles. This could be achieved in a factorial design separating patients and controls by their cognitive performance (high and low), thereby differentiating between genetic variation specific to schizophrenia, cognition, and both. In this context, lower cognitive performance might identify a group of patients with a more homogeneous, possibly neurodevelopmental form of the disorder.

This study is limited first by the assumptions of genetic modeling.$^{10}$ Second, the study is based on clinically ascertained twins and families, thus the generalizability of the findings depends on how well the participants represent the general population. The study used strict inclusion criteria in well-defined geographic areas, which should enhance the representativeness of the participants. An alternative population-based approach would
require a huge number (probably millions) of participants to yield a study with comparable numbers of affected families and twins given the population prevalence of schizophrenia. Even if such a sample were recruited, administering neuropsychological tests on such a large scale would be unfeasible. Third, the study incorporated multinational and multisite data that could increase methodological and sampling heterogeneity. We used rigorous statistical procedures to confirm that data merging was appropriate, and every analytical decision was reviewed by at least 2 statistical experts (I.R.M., F.R., D.S., S.S.C., and P.S.). Fourth, there are important potential components to the cognitive correlates of the genetic risk for schizophrenia that we could not consider in this article. Fifth, genetic correlations are not directional, and, thus, the path of causation cannot be determined: impaired cognition may increase liability to schizophrenia, whereas schizophrenia may cause cognitive deficits. However, the lower scores of unaffected relatives across a variety of tests suggest that it is the genetic liability to schizophrenia that reduces scores rather than vice versa. Sixth, we assumed in this modeling that the prevalence and heritability of schizophrenia were known without error, which could induce a false accuracy on the parameter estimations. However, within a maximum likelihood framework, it is impossible to model the uncertainty in a fixed parameter. Furthermore, the parameters (heritability and prevalence of schizophrenia) are known to a high degree of accuracy, and the impact of the uncertainty should be small, as we have confirmed by repeating the analysis using the lower 95% confidence limit for heritability. Seventh, it is possible that the correlations between increased liability to schizophrenia and lower intelligence or memory reflect an as yet unidentified third factor shared between schizophrenia and cognition, such as brain structure, which our efforts will be directed to next.

The strengths of this study include that the sample, to our knowledge, represents the largest examination of intelligence and memory in families and twins with schizophrenia and used highly sophisticated multivariate genetic analytical models. The combination of twins and families has the further advantages of increasing the sample size, reducing sample variance due to differences in allelic frequency, and representing the true population more accurately than would a twin sample alone while also increasing the power to differentiate between additive genetic effects and shared environmental effects. Furthermore, sibling pairs who share the same degree of genetic similarity as dizygotic twin pairs have the additional advantage of lacking potential confounders related to the intrauterine disadvantages of monozygotic twins.

In summary, present-day psychiatric classification depends almost completely on clinically elicited symptoms. It is possible that this lack of etiologic validity drives at least some of the inconsistency in molecular genetic studies. Identifying intermediate constructs closer to the underlying genetic effects has the potential to powerfully advance the field of clinical psychiatry by clarifying etiology and pathogenesis, informing biologically plausible classification systems, improving the chances of early detection, and offering the chance of truly individualized treatment. To date, although we have several candidate intermediate phenotypes, it has been difficult to determine how many are genetically mediated by the risk genes for schizophrenia. By applying advanced genetic model fitting in this large twin and family sample, we showed that a substantial portion of the phenotypic correlation between schizophrenia and memory and intelligence is due to the same genetic effects. However, based on the genetic correlations, more than 50% of the genes that affect liability to schizophrenia do not affect cognition, and, therefore, the genetics of schizophrenia are more than the genetics of cognition.

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