ORIGINAL ARTICLE

Substantial Genetic Overlap Between Neurocognition and Schizophrenia

Genetic Modeling in Twin Samples

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Context: The use of endophenotypes, biological traits that increase the liability to a disorder, represents one strategy to facilitate the detection of susceptibility genes for complex behavioral disorders such as schizophrenia. Establishing that a candidate trait is both heritable and linked genetically to schizophrenia is integral to its validity as an endophenotypic marker. Neurocognitive deficits are among the most promising indicators of increased risk for schizophrenia; however, it is not clear to what extent these deficits are genetically linked to the disorder.

Objectives: To quantify the genetic and environmental contributions to the variability of selected neurocognitive measures and to estimate the genetic relationship between these and schizophrenia.

Design: Genetic model fitting to monozygotic and dizygotic twin data.

Setting: United Kingdom psychiatric research institute.

Participants: Two hundred sixty-seven monozygotic and dizygotic twins concordant and discordant for schizophrenia, and healthy monozygotic and dizygotic control twin pairs.

Main Outcome Measures: The heritabilities of intelligence, working memory, processing speed, perceptual organization, and verbal comprehension were estimated, and the genetic relationship between each of these and schizophrenia was quantified.

Results: Genetic influences contributed substantially to all of the cognitive domains, but intelligence and working memory were the most heritable. A significant correlation was found between intelligence and schizophrenia (r=–0.61; 95% confidence interval, –0.71 to –0.48), with shared genetic variance accounting for 92% of the covariance between the two. Genetic influences also explained most of the covariance between working memory and schizophrenia. Significant but lesser portions of covariance between the other cognitive domains and schizophrenia were also found to be genetically shared. Environmental effects, although separately linked to neurocognition and schizophrenia, did not generally contribute to their covariance.

Conclusion: Genomewide searches using factorial designs stratifying for levels of intelligence and working memory will assist in the search for finding quantitative trait loci for schizophrenia.

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BEHIND THE CATEGORICAL diagnosis of complex disorders, there are probably continuously distributed liability traits that could provide more power to discover relevant quantitative trait loci than the clinical phenotypes of the disorders themselves.[1] Schizophrenia, like hypertension for example, is increasingly viewed as representing the extreme end of a set of quantitative traits that are continuously distributed in the population from normal to abnormal.[1-3] Given this, one promising strategy is to decompose the disorder into more basic constructs that reflect increased liability in order to identify the alleles associated with normal variation of these traits, effectively identifying the genes that contribute to the development of schizophrenia.

Neurocognitive deficits are among the most promising of the possible indicators of this liability. This is suggested by the evidence that cognitive impairment (1) is present in first-episode schizophrenia; (2) remains relatively stable throughout the course of illness; (3) cannot be totally explained by the effect of symptoms or medication; (4) appears to be present before the onset of the disorder; and (5) is even found among some healthy relatives of patients with schizophrenia. In relation to the last point, prospective high-risk and family studies suggest a familial impairment in several cognitive domains, and in general intellectual function, among the relatives of patients with schizophrenia.[4-9] However, family and high-risk studies cannot differentiate between shared environmental or genetic factors. Twin studies are the most powerful design to clarify this question, but to

our knowledge there have been only a handful of published studies on neurocognitive performance in twins who have schizophrenia.[10-13] None of these have used genetic modeling to explore whether the well-recognized correlation between schizophrenia and cognitive impairment is in fact due to shared genetic factors. If so, neurocognition could be considered a valid marker for future molecular genetic studies.

Structural equation modeling, or genetic modeling, separates the covariance between 2 variables (eg, schizophrenia and intelligence) into genetic and environmental components. The former indicates the degree to which the same genes influence the 2 traits, and the latter reflects the level to which the same phenotypic covariance is induced by the environment.[1,14] For the first time to our knowledge, we applied this approach to neurocognitive data from monozygotic (MZ) and dizygotic (DZ) twins with and without schizophrenia.

More specifically, in a sample of 267 twins varying in zygosity, concordance for schizophrenia, and disease status, we assessed the following: (1) differences in intelligence, working memory, processing speed, perceptual organization, and verbal comprehension using linear regression models to get an indication of the performance of the MZ and DZ pairs who were concordant and discordant for schizophrenia against control twins before proceeding with the more sophisticated structural equation modeling approach; (2) the genetic (ie, heritability) and environmental sources of variation for intelligence and the other cognitive domains; and (3) the extent to which the covariation between schizophrenia and neurocognition is due to genetic overlap or common environmental effects. In particular, genetic model fitting was used, which applies the method of maximum likelihood to directly estimate model parameters (additive genetic effects, A; environmental effects that are shared between twins, C; and influences that twins do not share, E) from the observed variance-covariance matrices of MZ and DZ twins.

We hypothesized the following: (1) cognitive impairment in schizophrenia would be genetically influenced so that the closer the genetic relationship of the co-twins (MZ vs DZ) is, the greater the cognitive dysfunction is; (2) the cognitive domains would be moderately to highly heritable; (3) genetic variation relevant to normal differences in intelligence would substantially overlap with that related to liability to schizophrenia; and (4) those domains of cognitive function that are less prone to improvement, such as working memory, will be more heritable and more genetically linked to schizophrenia. The first hypothesis is based on the regression models, whereas the others can be tested from the genetic models.

METHODS

PARTICIPANTS

Probands with schizophrenia were recruited nationally throughout the United Kingdom from National Health Service treatment centers through referrals by their treating psychiatrist. In the United Kingdom, the National Health Service is a comprehensive national treatment service funded centrally and free at the point of delivery for all aspects of health care. By virtue of its financial and organizational structure, it is hugely inclusive and as a consequence cares for most patients with schizophrenia, making it a very representative system from which to recruit. Control twins were recruited from a volunteer twin register held at the Institute of Psychiatry, London, England. Exclusion criteria applied to all of the groups were age younger than 18 years, a history of a neurological disorder or of a systemic illness with known neurological complications, a history of significant head injury associated with loss of consciousness for more than 1 minute, and current harmful substance use or dependence (defined as within the last 12 months). No candidate included in the study had a psychotic illness directly attributable to the harmful use of illicit substances. The study was approved by the UK Multicenter Research Ethics Committee and all of the subjects gave written informed consent before participating.

CLINICAL ASSESSMENT

The *DSM-IV* diagnoses were made using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version,[15] supplemented by information from medical notes or by using the Structured Clinical Interview for *DSM-IV*.[16] Psychotic symptoms in the probands in the month before testing were assessed using the Scale for the Assessment of Positive Symptoms[17] (SAPS) and the Scale for the Assessment of Negative Symptoms[18] (SANS). Zygosity was determined by assessment of 12 highly polymorphic microsatellite markers and a standardized twin likeness questionnaire. Medication status was recorded at the time of the assessment, and age at first contact with psychiatric services was ascertained to serve as a proxy index of age at illness onset.

In concordant pairs, both members fulfilled criteria for *DSM-IV* schizophrenia or schizoaffective disorder. In discordant pairs, 1 member was diagnosed with *DSM-IV* schizophrenia, whereas the co-twin was free of any psychotic illness. In control pairs, both members were free of personal or family history of psychosis or schizophrenia spectrum disorder. The probability that any of the discordant pairs would become concordant for schizophrenia in the future was low given that a mean (SD) of 12.54 (10.19) years had elapsed since the onset of illness in the patients.

NEUROCOGNITIVE ASSESSMENTS

The full UK version of the Wechsler Adult Intelligence Scale third edition was administered to all of the participants.[19] This consists of 14 subtests each designed to engage a distinct aspect of cognitive behavior. In addition to full-scale IQ, the subtests of the Wechsler Adult Intelligence Scale third edition can be organized to provide indexes of the following 4 more refined domains of cognitive function: (1) working memory, the composite score of arithmetic, digit span, and letter-number sequencing subtests; (2) processing speed, the composite score of digit symbol and symbol search subtests; (3) perceptual organization, the composite score of picture completion, block design, and matrix reasoning subtests; and (4) verbal comprehension, the composite score of vocabulary, similarities, and information subtests. The validity of these 4 indexes has been established.[20]

ANALYSES

Regression Models to Compare Adjusted Mean Differences Between Groups

Data drawn from members of the same family can correlate and are not considered to be independent, violating the assumption of independence made in analyses of variance. As a result, mean comparisons were analyzed using the regress command in Stata

version 8 statistical software (Stata Corp, College Station, Texas). This allows for nonindependence of observations by using a robust sandwich estimator to calculate standard errors. After establishing a main effect of group, planned post hoc tests between MZ concordant pairs, probands from MZ discordant pairs, and unaffected co-twins from discordant pairs were compared with MZ control twins. Similarly, affected and unaffected members of DZ pairs discordant for schizophrenia were compared with DZ control twins. All of the scores were age adjusted and sex was included as a covariate in the analyses.

Preparation of Data Prior to Model Fitting

As is customary, prior to model fitting, all of the sources of variation in cognitive function that were considered to represent a cause of nuisance or noise variance in the trait were partitioned out. Consequently, the effects of age, sex, and education were regressed out in the Stata program. Even though educational level is confounded by several variables, including the presence of psychiatric disorder, we felt that the most conservative strategy was to regress out these effects before twin modeling given that educational attainment is highly predictive of cognitive performance. In this way, interpretation of the results is more straightforward. Because simultaneous analyses of dichotomous and continuous data could not be performed, both schizophrenia, which was scored as a dichotomous attribute, and cognition, which was scored as a continuous variable, were modeled as threshold traits. Accordingly, each cognitive measure was ordinalized into 5 equal classes in terms of proportions, which captured most of the information in the continuous data, in the Stata program before transferring data into MX software for statistical modeling (Michael Neale, Department of Psychiatry, Virginia Commonwealth University, Richmond; http://www.vcu.edu/mx).

Background to Twin Modeling

Because of the difference in genetic proximity between twins with different zygosities, identical twins correlate 1 for additive genetic effects (A) (also known as narrow heritability, h^2), representing the combined effect of alleles at a locus and across loci that add up to affect behavior, whereas nonidentical twins correlate half of that (ie, 0.5).[3] Conversely, both types of twins correlate equally as 1 for environmental effects that both twins share (C or c^2), such as parenting, whereas unique environmental effects or influences (E or e^2) that twins do not share, such as accidents, are modeled in both twin types as 0. As a consequence of these different degrees of genetic correlations between MZ and DZ twins but the same degree of correlation in environmental influences, a higher correlation in MZ twins than in DZ twins would represent the effect of the higher proportion of genes shared among MZ twins.[21]

Bivariate Twin Modeling

Bivariate models are concerned with estimating A, C, and E of the individual variables due to the MZ to DZ cross-twin within-trait (trait A in twin 1 with that of the co-twin) correlation, as well as with partitioning the covariance between the 2 traits into A, C, and E by means of the cross-twin cross-trait (trait A in twin 1 with trait B of the co-twin) MZ to DZ correlation ratios. Significant cross-twin within- or cross-trait covariances imply that common etiological factors between the 2 traits are familial. Whether these common familial etiological influences are genetic or environmental in origin is inferred by the MZ to DZ ratio of the cross-twin within- or cross-trait covariances.[21] For example, if the cross-twin cross-trait correlation was greater for MZ twins than for DZ twins at about 2 to 1, respectively, this would imply that A contributes to the phenotypic correlation between the 2 traits. A ratio of 1:1 suggests that the same influences of C are inducing a correlation between the 2 traits. Nonsignificant cross-twin cross-trait correlations suggest that the shared etiological influences on the 2 traits are due to E and therefore not due to familial effects.

The partitioning of the covariation between schizophrenia and each cognitive measure into the genetic, shared environmental, and unique environmental sources of covariation yields genetic (r_g), common environmental (r_c), and individual-specific environmental (r_e) correlations, respectively. The r_g indicates the extent to which the same genetic effects influence both schizophrenia and neurocognition, whereas the r_c reflects the degree to which the environmental effects inducing a shared environmental correlation for 1 trait (eg, working memory) are the same as those in the second trait (eg, schizophrenia). The level to which the unique environmental influences are common in both traits is given by the r_e. A genetic correlation of 1.0 would suggest that all of the additive genetic influences that act on 1 trait also influence the second. Similarly, an environmental correlation of 0 would imply that the environmental influences on, say, the liability to schizophrenia are independent of the environmental effects on intelligence.

As the r_g, r_c, and r_e correlations do not take into account the heritability of either trait, it is possible for a large genetic correlation to actually explain a very small portion of the observed covariation between these 2 traits. Combining the information from the r_g, r_c, and r_e with the heritabilities c^2 and e^2 of each trait, we can establish the genetic ($r_{ph\text{-}a}$), common environmental ($r_{ph\text{-}c}$), and unique environmental ($r_{ph\text{-}e}$) contributions to the total phenotypic correlation (r_{ph}) between 2 traits.

The bivariate models assumed a continuum of genetic risk that is normally distributed with the disorder occurring only when a certain threshold of liability is exceeded. Both affected and unaffected individuals were assumed to be part of the same distribution of liability to the disorder, with each individual being either below or above the threshold. Because data were from twin pairs selected for schizophrenia rather than from a random sample and therefore the heritability of schizophrenia could not be estimated, the model parameters for schizophrenia were fixed to values estimated by a meta-analysis[22] and the threshold to the population prevalence. Accordingly, the model parameters for schizophrenia were fixed to the point estimates of the meta-analyses as follows: $h^2=0.81$, $c^2=0.11$, $e^2=0.08$. The analyses were repeated using a different genetic model for schizophrenia based on the lower limit of the 95% confidence interval (CI) of heritability in liability to schizophrenia, $h^2=0.73$, $c^2=0.19$, $e^2=0.08$, of the same meta-analyses. However, as the different parameter estimates for schizophrenia had virtually no effect on the main results of the study, we report the findings of the first analyses. The lifetime prevalence of schizophrenia was set to 1%.

The variance of individual scores on a trait and the within-pair covariances in the same trait or across traits were summarized by a series of structural equations in MX. From these equations it was possible to estimate the maximum-likelihood genetic and environmental variance components of the neurocognitive measures and the covariance between these measures with the genetic liability to schizophrenia. A goodness-of-fit index (χ^2) was obtained by computing the difference in likelihoods and the degrees of freedom between the genetic ACE model and the observed variance-covariance matrices. More information on these models can be found in the articles by Rijsdijk et al[23] and Hall et al.[24]

Polychoric Correlations

To estimate the MZ and DZ twin correlation within each cognitive test and across each cognitive test and schizophrenia, we fit-

Table 1. Demographics of Twins

Characteristic	MZ CC Twins With Schizophrenia (n=48)	MZ DC Twins With Schizophrenia (n=14)	Healthy MZ DC Twins (n=12)	DZ DC Twins With Schizophrenia (n=11)	Healthy DZ DC Twins (n=11)	MZ Control Twins (n=111)	DZ Control Twins (n=60)
Age, range, y	22-60	20-53	20-53	21-60	21-60	20-62	21-58
Age, mean (SD), y	37.77 (1.53)	29.71 (2.32)	29.71 (2.32)	37.64 (3.65)	37.64 (3.65)	40.94 (1.09)	44.00 (1.30)
Female, No. (%)	12 (25.0)	5 (35.7)	4 (33.3)	6 (54.5)	7 (63.6)	87 (78.4)	52 (86.7)
Education, mean (SD), y	14.09 (0.47)	12.64 (0.55)	13.08 (0.75)	14.00 (0.83)	15.36 (0.82)	13.86 (0.27)	14.67 (0.30)

Abbreviations: CC, concordant; DC, discordant; DZ, dizygotic; MZ, monozygotic.

Table 2. Summary Statistics of Means and Standard Deviations

	Score, Mean (SD)						
WAIS Subscale	MZ CC Twins With Schizophrenia	MZ DC Twins With Schizophrenia	Healthy MZ DC Twins	MZ Control Twins	DZ DC Twins With Schizophrenia	Healthy DZ DC Twins	DZ Control Twins
Full-scale IQ	85.5 (14.6)	82.7 (17.0)	89.9 (17.0)	111.6 (15.7)	92.0 (18.8)	106.7 (13.7)	112.7 (13.3)
Verbal comprehension	89.8 (14.4)	87.0 (14.4)	90.4 (14.4)	109.5 (16.5)	95.8 (18.7)	106.4 (12.4)	109.4 (14.3)
Perceptual organization	85.4 (14.9)	86.8 (22.4)	98.1 (20.1)	112.9 (15.5)	95.3 (17.7)	102.2 (15.4)	115.2 (16.7)
Processing speed	81.9 (12.2)	75.4 (9.8)	88.0 (14.1)	107.8 (13.4)	90.6 (17.2)	99.2 (20.0)	109.1 (14.0)
Working memory	88.7 (14.4)	81.0 (16.0)	87.4 (18.7)	106.1 (16.4)	91.8 (23.6)	110.0 (16.0)	108.7 (13.7)

Abbreviations: CC, concordant; DC, discordant; DZ, dizygotic; MZ, monozygotic; WAIS, Wechsler Adult Intelligence Scale.

ted a constrained correlational model to the MZ and DZ data to get 1 within-twin cross-trait correlation (eg, intelligence with liability to schizophrenia) equal across all of the individuals in the sample regardless of their zygosity and birth order, 1 MZ and 1 DZ cross-twin cross-trait correlation, and 1 MZ and 1 DZ cross-twin within-cognitive-test correlation. In line with the correction for selection described earlier, in each correlational model for schizophrenia, the MZ and DZ cross-twin correlations were fixed according to the point estimates of the meta-analysis, r_{MZ}=0.92 and r_{DZ}=0.52.

RESULTS

DEMOGRAPHIC AND CLINICAL VARIABLES

Two hundred sixty-seven twins contributed to the study, 185 MZ and 82 DZ. There were 48 members from 24 MZ concordant twin pairs, 26 members from 14 MZ discordant pairs (14 probands, 12 co-twins), 111 members from 56 MZ control twin pairs, 22 members from 11 DZ discordant twin pairs, and 60 members from 30 DZ control pairs. Data were excluded from 3 participants who were unable to complete the assessment due to fatigue. **Table 1** summarizes the demographic data. Among the 23 nonschizophrenic co-twins of the discordant pairs, 16 met criteria for historical *DSM-IV* Axis I diagnosis: 4 with depression only, 2 with depression and panic disorder, 2 with depression and generalized anxiety disorder, 1 with depression, panic disorder, and agoraphobia, 1 with depression, panic disorder, and generalized anxiety disorder, 1 with depression and phobia, 1 with depression, alcohol and substance abuse, and obsessive-compulsive disorder (OCD), 1 with depression and alcohol abuse, 1 with depression, drug abuse, and panic disorder, 1 with alcohol abuse, and 1 with manic episode, panic disorder, and OCD. Among the control twins, 15 individuals met criteria for historical *DSM-IV* Axis I diagnosis: 11 with depression, 1 with depression, panic disorder, OCD, and agoraphobia, 1 with panic disorder and generalized anxiety disorder, 1 with depression, mania, panic disorder, and OCD, and 1 with depression, panic disorder, OCD, and phobia. No co-twins without schizophrenia or healthy control subjects were unwell at the time of testing, none were under medical supervision, and none were receiving any psychotropic medication at the time of assessment.

RESULTS FROM THE REGRESSION ANALYSES

The summary statistics are given in **Table 2**, whereas **Table 3** presents the results of the regression analyses. Patients irrespective of zygosity or concordance performed worse than control subjects on all of the measures. The nonpsychotic co-twins from MZ discordant pairs also scored significantly worse than control subjects on all of the tests, whereas their DZ counterparts did not score significantly differently from controls on any measure except perceptual organization.

RESULTS FROM THE BIVARIATE TWIN MODELING ANALYSES

Standardized Estimates for Each Neurocognitive Domain

The cross-twin within-trait correlations are given in **Table 4**. All of the within-pair covariances were greater for MZ twins than for DZ twins, and in the case of MZ pairs, every correlation was significant. In the DZ pairs, 2 of the covariances were statistically significant, those for verbal comprehension and working memory. **Table 5** shows the additive genetic effects (h^2), shared environ-

Table 3. Adjusted Mean Comparisons

WAIS Subscale	MZ CC Twins With Schizophrenia vs Control Twins, *t* Score (*P* Value)	MZ DC Twins With Schizophrenia vs Control Twins, *t* Score (*P* Value)	Healthy MZ DC Twins vs Control Twins, *t* Score (*P* Value)	DZ DC Twins With Schizophrenia vs Control Twins, *t* Score (*P* Value)	Healthy DZ DC Twins vs Control Twins, *t* Score (*P* Value)
Full-scale IQ	–6.48 (<.001)	–6.30 (<.001)	–4.43 (<.001)	–3.79 (<.001)	–1.44 (.15)
Verbal comprehension	–4.80 (<.001)	–5.60 (<.001)	–4.32 (<.001)	–2.37 (.02)	–0.78 (.44)
Perceptual organization	–6.67 (<.001)	–4.80 (<.001)	–2.89 (.004)	–3.91 (<.001)	–2.55 (.01)
Processing speed	–6.92 (<.001)	–8.70 (<.001)	–3.90 (<.001)	–3.11 (.002)	–1.51 (.13)
Working memory	–5.28 (<.001)	–6.04 (<.001)	–4.02 (<.001)	–2.84 (.005)	–0.11 (.92)

Abbreviations: CC, concordant; DC, discordant; DZ, dizygotic; MZ, monozygotic; WAIS, Wechsler Adult Intelligence Scale.

Table 4. Cross-twin Within-trait and Cross-twin Cross-trait Correlations[a]

WAIS Subscale	Cross-twin Within-trait Correlation for MZ Twins, *r* (95% CI)[b]	Cross-twin Within-trait Correlation for DZ Twins, *r* (95% CI)[b]	Cross-twin Cross-trait Correlation for MZ Twins, *r* (95% CI)[c]	Cross-twin Cross-trait Correlation for DZ Twins, *r* (95% CI)[c]
Full-scale IQ	0.73 (0.57 to 0.84)	0.30 (–0.04 to 0.58)	–0.58 (–0.70 to –0.44)	–0.32 (–0.51 to –0.10)
Verbal comprehension	0.83 (0.71 to 0.90)	0.56 (0.26 to 0.77)	–0.40 (–0.53 to –0.26)	–0.33 (–0.52 to –0.12)
Perceptual organization	0.71 (0.54 to 0.83)	0.30 (–0.06 to 0.60)	–0.52 (–0.64 to –0.39)	–0.41 (–0.61 to –0.18)
Processing speed	0.59 (0.33 to 0.77)	0.34 (–0.03 to 0.60)	–0.40 (–0.50 to –0.40)	–0.32 (–0.55 to –0.09)
Working memory	0.81 (0.68 to 0.89)	0.49 (0.17 to 0.72)	–0.45 (–0.57 to –0.31)	–0.19 (–0.39 to 0.02)

Abbreviations: CI, confidence interval; DZ, dizygotic; MZ, monozygotic; WAIS, Wechsler Adult Intelligence Scale.
[a] The 95% CIs including 0 indicate statistical nonsignificance.
[b] Correlation of twin 1 with co-twin twin 2 on the WAIS ($WAIS_{tw1}$ – $WAIS_{tw2}$). The schizophrenia cross-twin within-trait correlation (SZ_{tw1} – SZ_{tw2}) is constrained to 0.92 in MZ twins and 0.52 in DZ twins based on the genetic point estimates of a meta-analysis and a 1% prevalence.
[c] Correlation of trait A (WAIS score) of twin 1 with trait B (genetic liability to schizophrenia) of co-twin twin 2 ($WAIS_{tw1}$ – SZ_{tw2}).

Table 5. Additive Genetic, Common, and Specific Environmental Estimates of Full ACE Genetic Model for Wechsler Adult Intelligence Scale Full-Scale IQ and Indexes[a]

WAIS Subscale	h^2 Estimate (95% CI)	c^2 Estimate (95% CI)	e^2 Estimate (95% CI)
Full-scale IQ	0.70 (0.15 to 0.82)	0.01 (0.00 to 0.53)	0.29 (0.18 to 0.44)
Verbal comprehension	0.49 (0.06 to 0.88)	0.34 (0.00 to 0.72)	0.17 (0.10 to 0.29)
Perceptual organization	0.60 (0.09 to 0.81)	0.10 (0.00 to 0.54)	0.30 (0.18 to 0.47)
Processing speed	0.43 (0.004 to 0.43)	0.15 (0.00 to 0.58)	0.42 (0.24 to 0.63)
Working memory	0.65 (0.21 to 0.87)	0.17 (0.00 to 0.58)	0.18 (0.10 to 0.30)

Abbreviations: CI, confidence interval; WAIS, Wechsler Adult Intelligence Scale.
[a] h^2, c^2, and e^2 indicate heritability, shared environmental, and nonshared environmental effects, respectively. Parameters for schizophrenia are fixed based on a prevalence of 1% and the following genetic model: h^2=0.81, c^2=0.11, e^2=0.08. The 95% CIs including 0 indicate statistical nonsignificance.

mental effects (c^2), and unique environmental effects (e^2) for intelligence and for the 4 domains that underlie it. Genetic factors accounted substantially for the total variation in intelligence (h^2=0.70; 95% CI, 0.15 to 0.82), working memory (h^2=0.65; 95% CI, 0.21 to 0.87), and perceptual organization (h^2=0.60; 95% CI, 0.09 to 0.81) and moderately for verbal comprehension (h^2=0.49; 95% CI, 0.06 to 0.88) and processing speed (h^2=0.43; 95% CI, 0.004 to 0.43). Shared environment did not explain interindividual differences to a significant extent, whereas individual-specific environmental effects accounted for a significant portion of the variance in all of the measures: processing speed (e^2=0.42; 95% CI, 0.24 to 0.63), perceptual organization (e^2=0.30; 95% CI, 0.18 to 0.47), intelligence (e^2=0.29; 95% CI, 0.18 to 0.44), working memory (e^2=0.18; 95% CI, 0.10 to 0.30), and verbal comprehension (e^2=0.17; 95% CI, 0.10 to 0.29).

A, C, and E Overlap Between Each Cognitive Test and Schizophrenia

The cross-twin cross-trait covariances are given in Table 4. All of the correlations for MZ twins were greater than for DZ twins. Both zygosity types correlated significantly for all of the measures except for working memory in the DZ sample. The extent to which 2 traits share the same genetic, common environmental, and unique environmental effects is given by the correlations r_g, r_c, and r_e, respectively (**Table 6** and **Figure**). Apart from processing speed, all of the neurocognitive measures had significant genetic correlations (r_g) with schizophrenia: working memory (r_g=–0.79; 95% CI, –1.00 to –0.34), intelligence (r_g=–0.75; 95% CI, –1.00 to –0.49), and perceptual organization (r_g=–0.61; 95% CI, –1.00 to –0.39) had moderate to high r_g correlations and verbal comprehension had a small to moderate genetic correlation (r_g=–0.34; 95%

Table 6. Phenotypic Correlations Between Schizophrenia and Wechsler Adult Intelligence Scale Full-Scale IQ and Indexes and the Decomposed Sources of These Correlations as Predicted by the Full ACE Models and A, C, and E Correlation Estimates[a]

WAIS Subscale	$r_{ph\text{-}a}$	$r_{ph\text{-}c}$	$r_{ph\text{-}e}$	r_{ph} (95% CI)	r_g (95% CI)	r_c (95% CI)	r_e (95% CI)
Full-scale IQ	–0.56	–0.03	–0.01	–0.61 (–0.71 to –0.48)	–0.75 (–1.00 to –0.49)	–0.96 (–1.00 to 1.00)	–0.09 (–0.70 to 0.57)
Verbal comprehension	–0.21	–0.19	–0.02	–0.42 (–0.53 to –0.30)	–0.34 (–0.98 to –0.08)	–1.00 (–1.00 to 1.00)	–0.14 (–0.80 to 0.57)
Perceptual organization	–0.43	–0.11	0.01	–0.53 (–0.63 to –0.41)	–0.61 (–1.00 to –0.39)	–0.99 (–1.00 to 1.00)	0.03 (–0.57 to 0.62)
Processing speed	–0.27	–0.13	–0.17	–0.57 (–0.70 to –0.45)	–0.46 (–1.00 to 1.00)	–0.98 (–1.00 to 1.00)	–0.92 (–0.99 to –0.48)
Working memory	–0.57	0.11	–0.05	–0.51 (–0.62 to –0.39)	–0.79 (–1.00 to –0.34)	0.79 (–1.00 to 1.00)	–0.43 (–0.89 to 0.31)

Abbreviations: CI, confidence interval; WAIS, Wechsler Adult Intelligence Scale.
[a] $r_{ph\text{-}a}$, $r_{ph\text{-}c}$, and $r_{ph\text{-}e}$ indicate the phenotypic correlations due to additive genetic, shared environmental, and specific environmental influence, respectively. r_{ph} indicates the total phenotypic correlation. r_g, r_c, and r_e indicate the genetic, shared environmental, and specific environmental correlations, respectively. The fixed genetic model for schizophrenia used the following parameters: h^2=0.81, c^2=0.11, e^2=0.08. The 95% CIs including 0 indicate statistical nonsignificance.

CI, –0.98 to –0.08) with schizophrenia. No r_c correlations were significant, and the r_e correlations were also nonsignificant for most measures except for processing speed (r_e=–0.92; 95% CI, –0.99 to –0.48).

The phenotypic correlations (r_{ph}) suggested that increased liability to schizophrenia was associated with worsening performance in all of the measures assessed (Table 6). Intelligence (r_{ph}=–0.61) and processing speed (r_{ph}=–0.57) had the highest phenotypic correlation with schizophrenia. The parts of the phenotypic correlations that are due to shared genetic influences ($r_{ph\text{-}a}$), shared environmental effects ($r_{ph\text{-}c}$), and unique environmental effects ($r_{ph\text{-}e}$) are presented in Table 6. As with the r_g correlations, intelligence ($r_{ph\text{-}a}$=–0.56), working memory ($r_{ph\text{-}a}$=–0.57), and perceptual organization ($r_{ph\text{-}a}$=–0.43) shared the highest genetic variance with schizophrenia. For example, genetic influences that are shared by IQ and schizophrenia, (–0.56/–0.61) $\times$100, accounted for 92% of the phenotypic correlation between intelligence (Wechsler Adult Intelligence Scale full-scale IQ) and schizophrenia. In the same way, shared additive effects explained 50% of the phenotypic correlation between verbal comprehension (r_{ph}=–0.42) and schizophrenia, (–0.21/–0.42) $\times$100.

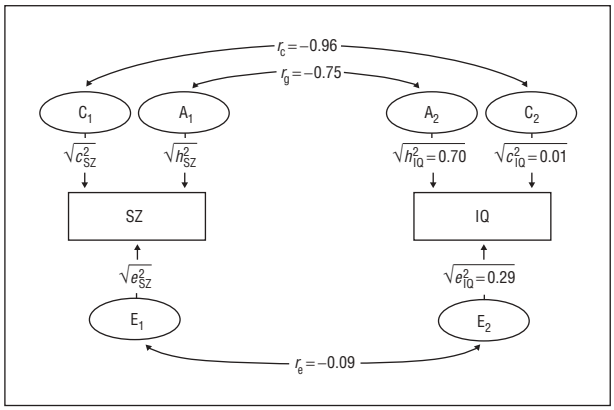

Figure. Genetic (r_g), shared environmental (r_c), and specific environmental (r_e) correlations between schizophrenia (SZ) and Wechsler Adult Intelligence Scale full-scale IQ, as well as the additive genetic (A), common environmental (C), and specific environmental (E) estimates for IQ. The parameter estimates for schizophrenia were not calculated but were based on the point estimates of a recent meta-analysis (see text): h^2=0.81, c^2=0.11, e^2=0.08.

COMMENT

Patients with schizophrenia, and to some degree their cotwins without psychosis, performed significantly worse than control subjects. While the healthy co-twins of the MZ sample had lower performances compared with control subjects on all of the measures, their DZ counterparts performed worse than control subjects in only a single measure. This is consistent with the idea that the greater the genetic loading is for schizophrenia, the larger and more dispersed is the cognitive impairment, an assumption that is consistent with the available literature.[12]

We went beyond this interpretation and quantified the strength of the relationship between neurocognition and schizophrenia using structural equation models. Based on these analyses, intelligence and working memory had the highest proportion of interindividual differences associated with genetic effects and also shared the largest genetic variance with schizophrenia. Perceptual organization was also moderately related to the disorder, whereas processing speed and verbal comprehension were the least genetically linked to schizophrenia.

As anticipated, intelligence was substantially heritable, with 70% of the total variance accounted for by additive genetic effects. The remaining variation was mainly due to individual specific environmental factors, while the effects of shared environment were almost negligible. The increase of heritability from early childhood to middle childhood to adulthood, with the expected decrease of shared environmental influences (which are more prominent in childhood), is a well replicated though poorly understood finding.[25,26]

The extent to which genetic factors are shared between intelligence and schizophrenia is expressed as r_g=–0.75 and suggests that the same genes contribute to individual differences in intelligence and to the liability to schizophrenia. As the correlation is only –0.75, [1–(–0.75^2)] or 44% of the genetic variance in schizophrenia is independent of intelligence, suggesting that both traits have some genes whose effects are specific. Similar observations have been made for attention-deficit/hyperactivity disorder and IQ, although the correlations were much lower (r_g=–0.45).[2] Analogous approaches have also been used to examine the genetic overlap between major depression and generalized anxiety disorder[27] and between neuroticism and major depression.[28]

Nonetheless, such inferences concerning the relationship between schizophrenia and intelligence rarely come without caveats. First, as has been noted before,[29] in polygenic systems genetic correlations may not always represent common genes influencing 2 or more traits. While inferences of common genes between 2 traits may indeed be true, a genetic correlation is insufficient proof for this sort of conclusion. For example, it has been shown that it is possible for 2 variables sharing all genes in common to yield low genetic correlations and for traits with only a few genes in common to have high genetic correlations.[29] Even so, it is generally accepted that these inferences about common genes are more justified when the following occur: (1) genetic correlations are substantial, (2) the assumption of additive genetic effects is correct, and (3) there is sufficient evidence to reject a major gene model,[29] all 3 of which are true in the context of this study. Second, as with any correlation, genetic correlations are not directional and therefore the path of causation cannot be inferred: lower intelligence may increase liability to schizophrenia or schizophrenia may cause lower intelligence. However, the lower scores of MZ discordant twins across the host of tests indicate that it is the genes of schizophrenia that reduce scores in our twins rather than the presence of schizophrenia. Third, it is possible that schizophrenia and intelligence correlate because both are associated separately with a third factor (ie, there is a common cause). For instance, studies have shown that schizophrenia is associated with structural brain abnormalities[23,30,31] and that intelligence is correlated with whole and gray brain matter volumes.[32] It would therefore be of interest to examine how much, if any, of the genetic correlation between schizophrenia and intelligence is explained by a genetic correlation of both traits with brain volumes.

Genetic correlations between 2 traits do not normally take account of their respective heritabilities. Consequently, it may be possible to have a genetic correlation that is very high but only explains a small portion of the observed covariance if the 2 traits are not highly heritable. To counter this, the modeling approach combined r_g with the heritability of each trait to calculate that part of the phenotypic correlation attributable to shared genetic influences. This revealed that 92% of the phenotypic correlation between intelligence and schizophrenia was due to common additive genetic factors, suggesting that quantitative trait loci studies of intelligence in healthy people may also be relevant to schizophrenia.[33-35]

Environmental factors played a negligible role in the covariation between intelligence and schizophrenia, suggesting that there is no significant overlap in environmental influences on the 2 traits or that the effects are too small to be detected in this study. Consequently, the lack of any shared environmental correlation suggests that the factors that make family members similar for intelligence are not the same as those that influence the liability to schizophrenia. Similarly, the lack of a unique environmental correlation implies that whatever makes family members different in terms of their liability to schizophrenia is not the same as that which makes them different for intelligence.

Intelligence comprises multiple abilities that normally work together seamlessly to produce a unitary outcome. Batteries designed to assess general intellectual function by and large reflect this model and consist of several subtests that are each intended to assess a different skill. While each in theory measures a distinct aspect of cognition, overlap is inevitable. In the case of the Wechsler Adult Intelligence Scale third edition, factor analyses have identified the following 4 major factors: working memory, perceptual organization, processing speed, and verbal comprehension.[19]

Working memory was both the most genetically influenced and the most genetically correlated with schizophrenia, suggesting that a portion of the interindividual variance in working memory is shared with the interindividual variance in liability to schizophrenia. Working memory is the ability to retain and manipulate information mentally and contributes substantially to Spearman g,[36,37] the process or processes that explain about 40% of the variance among tests. As with intelligence, identifying the genes relevant to working memory ability should assist in the search for the genes related to increased liability to schizophrenia.

Perceptual organization also shares some genetic variability with schizophrenia (r_g=–0.61; $r_{ph\text{-}a}$=–0.43). Perceptual organization is the ability to perceive relationships within spatial or visual components as well as social settings. Additive genetic influences explained most of the variance in perceptual organization, with about a third of the difference attributed to unique environmental effects.

The other 2 indexes, processing speed, a measure of time taken to complete certain tasks, and verbal comprehension, an index of verbal ability, were moderately influenced by environmental factors as well as by additive genetic effects. Both showed only small to moderate shared genetic variance with schizophrenia, which would make them unlikely candidates in the search for genes that increase liability to schizophrenia.

Our findings should be seen in the context of some limitations. First, most of the multivariate modeling in the psychiatric literature is based on analysis of population-based cohorts of twins, increasing confidence in the generalizability of parameter estimates. Such a design is much less feasible when integrating performance-based measures of cognition as was done here, and it would not seem appropriate to require it. The generalizability question then hinges to a large extent on the representativeness of both phenotypes (schizophrenia, cognitive function) in the twins sampled compared with those in the overall population. Despite recruiting nationally through the UK National Health Service and assessing every twin who fulfilled the study's entry criteria and consented to contribute, we do not have a way of knowing whether individuals who volunteered to take part in the study are systematically different from those who did not. Nonetheless, this aspect of volunteering or consenting to do research was present in the control twins as well, thereby reducing variability between samples due to this aspect. Second, although the genetic covariances are quite large and this constitutes a novel contribution, the 95% CIs around these estimates are also large, reflecting that the number of twin pairs available for analysis is on the border of those needed for effective application of these bivariate statistical approaches. Third, the study design is underpowered in detecting shared common environmental effects, although any shared common environmental effects cannot be greater than the common environmental effects for schizophrenia, which are small.

To summarize, applying bivariate genetic model fitting for the first time to our knowledge, this research shows that 92% of the phenotypic correlation between intelligence and schizophrenia is explained by shared genetic variability. Working memory and perceptual organization also shared substantial genetic variance with schizophrenia. Establishing a shared genetic variance between schizophrenia and intelligence or working memory is only the first step in unveiling the relation between them. The next step will be to identify specific genes that influence schizophrenia together with intelligence or working memory. Whole genome searches stratifying on the level of intelligence or working memory using comprehensive factorial designs with 4 groups, schizophrenia with high IQ, schizophrenia with low IQ, nonschizophrenia with high IQ, and nonschizophrenia with low IQ, will help to characterize genes that are specific to schizophrenia, are specific to IQ, or influence both.

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