

Initial Heritability Analyses of Endophenotypic Measures for Schizophrenia

The Consortium on the Genetics of Schizophrenia

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Context: Exploration of the genetic architecture of specific endophenotypes may be a powerful strategy for understanding the genetic basis of schizophrenia.

Objective: To characterize the genetic architecture of some key endophenotypic measures selected for their reported heritabilities in schizophrenia.

Design: Family-based heritability study.

Setting: Seven sites across the United States.

Participants: At the time of these initial data analyses, the members of 183 nuclear families ascertained through probands with schizophrenia had been assessed for these endophenotypes.

Main Outcome Measures: Variance component models were used to assess the heritability of and the environmental and genetic correlations among the endophenotypes. The Consortium on the Genetics of Schizophrenia assesses the neurophysiologic measures of prepulse inhibition of acoustic startle, P50 event-related potential suppression, and the antisaccade task for eye

movements and the neurocognitive measures of the Continuous Performance Test (Degraded Stimulus version), the California Verbal Learning Test, the Letter-Number Sequencing test, and 6 measures from the University of Pennsylvania Computerized Neurocognitive Battery. The heritabilities of these 12 measures are the focus of this article.

Results: All of the endophenotypes and the University of Pennsylvania Computerized Neurocognitive Battery measures were found to be significantly heritable ($P \leq .005$), with heritabilities ranging from 24% to 55%. Significant environmental and genetic correlations were also observed between many of the endophenotypic measures.

Conclusion: This is the first large-scale, multisite, family-based heritability study of a collection of endophenotypes for schizophrenia and suggests that endophenotypes are important measures to consider in characterizing the genetic basis of schizophrenia.

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GENETIC FACTORS PLAY A substantial role in the etiology of schizophrenia. A recent review^{1,2} of the progress of genetic research in schizophrenia revealed several replicated linkages, including evidence implicating chromosome arms 1q, 5q, 6p, 6q, 8p, 10p, 13q, 15q, and 22q. However, none of these linkage findings has led to cloning of causative genes for schizophrenia. This may be due to the modest nature of the linkage signals and the broad genetic regions they encompass and to the low penetrance, genetic heterogeneity, polygenic inheritance, and environmental effects associated with schizophrenia.

One way to dissect the underlying pathologic mechanisms of a complex disorder is through the use of phenotypes known or likely to represent the subclinical pathologic abnormalities of the disease. *Endophenotype* is often used as the descriptive term for these discrete, genetically determined, disease-related phenotypes.³⁻⁵ To be useful for genetic analyses, such endophenotypes must be reliable, stable, and heritable. The main advantage of using endophenotypes in schizophrenia research is that they relate to specific neurobiologic functions and substrates associated with the disease, so their genetic architecture is likely to be less complex than that associated with the hetero-

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geneous and more subjective criteria of schizophrenia itself as defined by the *DSM-IV-TR*.⁶ By identifying the genetic determinants of these endophenotypes, researchers may be in a position to more easily identify the genes or groups of genes that influence the expression of an endophenotype-linked disease.

The Consortium on the Genetics of Schizophrenia (COGS) explores endophenotypes as a strategy for understanding the genetic basis of schizophrenia. The COGS seeks to ascertain a minimum of 420 pedigrees from 7 sites (Harvard University, Mount Sinai School of Medicine, University of California San Diego, University of California Los Angeles, University of Colorado, University of Pennsylvania, and University of Washington) during a 5-year period.⁷ Three neurophysiologic endophenotypes (pre-pulse inhibition of the startle response [PPI], P50 event-related potential suppression, and the antisaccade task for eye movements) and 3 neurocognitive endophenotypes (the Continuous Performance Test [CPT] as a test of attention, the California Verbal Learning Test, Second Edition [CVLT], as a test of verbal declarative memory, and the Letter-Number Sequencing test [LNS] as a test of working memory) have been chosen for study. Impaired performance on these endophenotypes has been demonstrated not only in patients with schizophrenia but also in their clinically unaffected relatives, which provides evidence that these deficits may reflect part of the heritable risk of the illness.⁸⁻²⁹ In addition, 6 measures from the University of Pennsylvania Computerized Neurocognitive Battery (Penn CNB) were included to characterize the individuals and to provide additional endophenotypes for analysis: Abstraction and Mental Flexibility, Face Memory, Spatial Memory, Spatial Processing, Sensorimotor Dexterity, and Emotion Recognition.^{30,31} Complete reviews of each endophenotype, including the rationale for selection and data regarding stability, reliability, and heritability, are provided by Gur et al³² and Turetsky et al.³³

Characterizing the genetic architecture of these endophenotypic measures is likely to help determine which of these measures contribute to the heritable risk of schizophrenia. Herein we report the results of these initial heritability analyses of the 6 primary endophenotypic measures and the 6 Penn CNB measures in 183 families from the COGS. In addition to the heritability analyses, a genome scan and candidate gene interrogations will be pursued after study completion to identify specific chromosomal loci influencing variation in endophenotypic measures and *DSM-IV-TR* clinical schizophrenia. According to the outcomes of these genetic analyses, better models of the genetic and nongenetic neurobiologic bases of risk of schizophrenia can be developed.

METHODS

PARTICIPANT ASCERTAINMENT

The COGS pedigrees have been ascertained through the identification of probands at each site who meet the *DSM-IV-TR* criteria for schizophrenia via administration of the Diagnostic Interview for Genetic Studies³⁴ and the Family Interview for Genetic Studies.³⁵ The COGS probands and family members range in age from 18 to 65 years. All the participants receive

urine toxicologic screens for drugs of abuse before phenotyping. The ascertainment and screening procedures, inclusion and exclusion criteria, and descriptive statistics of the sample are discussed in detail by Calkins et al.⁷

The minimal requirements for pedigree ascertainment in the COGS are a schizophrenia proband, both parents, and at least 1 unaffected sibling. This sampling strategy was pursued to provide greater potential for phenotypic contrasts between and among the siblings for quantitative statistical genetic analyses. Data on additional affected and unaffected siblings are collected when available. This is in contrast to other studies that focus exclusively on affected sibling pairs or other related designs. Because the COGS focuses on exploring the genetic architecture of quantitative endophenotypes underlying schizophrenia susceptibility, not necessarily the genetic basis of schizophrenia itself, unaffected and affected siblings in a family are needed to maximize the probability of gathering sufficient variation in the proposed endophenotypes for analysis purposes. In addition, to understand how a particular endophenotype contributes to schizophrenia, individuals with and without schizophrenia are needed to relate the endophenotype to the disease as a whole. Of the 183 families described thus far, 70% are sibships of 2, 17% are sibships of 3, 8% are sibships of 4, and 5% are sibships of 5 or more.

PHENOTYPING

The COGS has established common diagnostic and phenotyping methods across all 7 participating sites, which includes data reduction and central data storage for all endophenotypes collected. Standardization of phenotyping is maintained through yearly on-site visits and a yearly 3-day retraining workshop for diagnosticians and phenotypers at the director/administrative site at the University of California, San Diego. To ensure quality assurance, data for each endophenotypic measure are monitored regularly by investigators at a designated COGS site who have expertise in the relevant endophenotype (for complete details, see the study by Calkins et al⁷).

Each endophenotype is described briefly herein, but a more detailed description of the assessment procedure for each endophenotype is provided elsewhere.⁷ The following 3 neurophysiologic endophenotypes have been analyzed. First, PPI was measured as the percentage of inhibition of the startle reflex in response to a weak prestimulus using a 60-millisecond interstimulus interval.^{36,37} Second, P50 suppression was measured as the ratio of the amplitudes of the P50 event-related potentials generated in response to the conditioning and test stimuli that are presented with a 500-millisecond interstimulus interval.³⁸ Third, the hallmark test of oculomotor inhibition, the antisaccade task, requires participants to fixate on a central target and respond to a peripheral cue by looking in the opposite direction at the same distance and is measured as the ratio of correct antisaccades to total interpretable saccades.³⁹

We also analyzed the following 3 neurocognitive endophenotypes. First, the Degraded Stimulus version of the CPT is a widely used measure of deficits in sustained, focused attention with a high perceptual load whose assessment is based on correct target detections and incorrect responses to nontargets.^{40,41} Second, for the assessment of verbal learning and memory, we used the CVLT, an established list-learning test measured as the total recall score of a list of 16 verbally presented items summed across 5 trials.⁴² Third, the LNS, a prototypical, commonly used task to measure working memory information storage with manipulation, is measured as the correct reordering of intermixed numbers and letters.^{29,43}

To fully characterize the patients with schizophrenia, we also used a modified version of the Penn CNB,^{30,31} excluding measures of attention and verbal and working memory, which were

assessed as detailed in the previous paragraph. The measures were evaluated using this battery. The test for Abstraction and Mental Flexibility presents 4 objects from which the participant must choose the 1 that does not belong. The assessment of Face Memory requires participants to recognize 20 previously presented target faces among 20 distracter faces. The assessment of Spatial Memory uses euclidean shapes as learning stimuli in a recognition paradigm identical to that used for Face Memory. Spatial Processing is assessed using 2 lines presented at an angle, and the corresponding lines must be identified on a simultaneously presented array. The test of Sensorimotor Dexterity requires the participant to click as quickly as possible using the computer mouse on a target that gets increasingly smaller. The assessment of Emotion Recognition involves the correct identification of a variety of facial expressions of emotion. Each test of the Penn CNB is measured as "efficiency," a combination of accuracy (percentage correct) and speed (median response time in milliseconds), which is calculated as $\text{accuracy}/\log_{10}(\text{speed})$ and is expressed as standard equivalents (z scores).

STATISTICAL ANALYSES

Variance component models have a long history in human genetics.^{44,45} Such methods, as implemented in the SOLAR version 2.1.2 linkage analysis package, were exploited to obtain heritability (h^2) estimates for each of the endophenotypes.⁴⁶ This maximum likelihood method assumes a multivariate normal distribution of phenotypes in a pedigree and can accommodate a defined set of covariates. The null hypothesis of no heritability ($h^2=0$) is tested by comparing a "full" model, which assumes that some fraction of the phenotypic variation is explained by genetic factors, with a "reduced" model, which assumes that no variation is explained by genes, using likelihood ratio tests. Although the variance component method is robust to violations of multivariate normality within pedigrees,⁴⁷⁻⁵⁰ the distribution of values for each measure was analyzed to eliminate large departures. In the case of PPI, 2 individuals with trait values greater than 3 SDs from the mean (ie, outliers) were removed to improve the distribution of this endophenotype.

Factors that were likely to affect the endophenotype in question, such as age, sex, and site of endophenotype collection, were screened using SOLAR for significance as covariates for each endophenotype. Only factors that showed a significant ($P < .05$) association with a particular endophenotype were retained in the heritability analysis of that endophenotype because controlling for the effects of a known covariate is important for obtaining an accurate estimate of heritability. Level of education and IQ were not pursued as covariates because, although they may be associated with many of the endophenotypes in question, they are also powerfully affected by schizophrenia.

A correction was also made for ascertainment bias because the families were recruited through the identification of a proband with schizophrenia and thus are not representative of the general population. The type of correction scheme implemented in SOLAR involves conditioning on the trait values of the probands under the assumption that the probands are, in fact, randomly selected.⁴⁷ Because this method does not depend on the specification of a particular threshold value for ascertainment for which the correction will be based, it is more flexible than other methods and appropriate for these analyses.

Bivariate genetic and environmental correlations were also computed using SOLAR.^{51,52} The genetic correlation between 2 endophenotypes is the component of the overall correlation that is due to pleiotropy (ie, the effect of a gene or set of genes on both endophenotypes simultaneously), which is obtained from the kinship information in the pedigree. The environmental cor-

relation between 2 endophenotypes is the component of the correlation due to environmental factors that affect both endophenotypes, which is obtained from the individual-specific error.

According to the considerations of Schork,⁴⁴ this study has more than adequate power to detect an additive genetic effect of approximately 15% or greater in the present sample of 183 families with the previously mentioned sibship size distribution and ample power to assess the genetic and environmental correlations among the endophenotypes. These estimates of power assume a random collection of families. The present families are ascertained through schizophrenia probands who are likely to have atypical endophenotype scores, creating within-pedigree contrasts and increasing the power of detection. **Table 1** provides the performance on each endophenotype and data on age, level of education, and Wide Range Achievement Test standard score⁵³ for the probands and their affected and unaffected first-degree relatives.

RESULTS

HERITABILITY

We conducted heritability analyses to explore how much of the variation in each endophenotype can be attributed to inherited genetic factors (**Table 2**). Although multiple endophenotypic measures were tested, these endophenotypes are not independent, so the appropriate correction for multiple testing is not known. In addition, given the exploratory nature of the analysis, multiple comparisons corrections may not be necessary.⁵⁴

Of the primary endophenotypic measures that have been collected thus far, PPI, the antisaccade task, CPT, CVLT, and LNS were found to be significantly heritable ($P < .001$), with heritability estimates ranging from 25% for the CVLT to 42% for the antisaccade task. All of the measures from the Penn CNB (Abstraction and Mental Flexibility, Face Memory, Spatial Memory, Spatial Processing, Sensorimotor Dexterity, and Emotion Recognition) were also found to be significantly heritable ($P < .001$), with heritability estimates ranging from 24% for Spatial Memory to 55% for Spatial Processing. Age was found to be a highly significant covariate for all endophenotypes except P50, and sex was a significant covariate for PPI, CVLT, Spatial Processing, Sensorimotor Dexterity, and Emotion Recognition.

P50 suppression, measured as the test to conditioning amplitude ratio, was not found to be significantly heritable in these quantitative genetic analyses. Because of the problematic nature of ratios for statistical analysis (ie, a skewed distribution from 0 to values many times greater than the median), other genetic studies^{38,55} of the P50 sensory gating paradigm have dichotomized the values into normal and abnormal. After completion of the initial analyses, a study by Anokhin et al⁵⁶ suggested that the difference between the test and conditioning amplitudes, an alternative measure often used with paired stimulus paradigms,⁵⁷ was more heritable than the ratio in a twin analysis. We thus repeated the P50 analysis using this difference measure and found it to be heritable in this sample (28%; $P = .004$).

Multiple secondary measures have been collected in addition to the originally designated primary measures described herein, including, among many others, the LNS

Table 1. Descriptive Statistics for the 6 Primary Endophenotypes and the 6 Penn CNB Measures in Probands and Their Affected and Unaffected First-Degree Relatives

	Affected				Unaffected			
	Probands		Siblings		Siblings		Parents	
	No. ^a	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD	No.	Mean ± SD
Age, y	183	34.2 ± 10.8	7	45.0 ± 12.9	265	36.9 ± 11.4	303	62.3 ± 10.6
Education, y	183	13.5 ± 2.1	7	12.4 ± 2.1	265	15.5 ± 2.5	268	15.1 ± 3.2
WRAT standard score	172	100.5 ± 12.5	7	91.0 ± 18.9	250	106.0 ± 10.3	155	104.9 ± 13.8
Primary endophenotypes								
PPI	122	44.6 ± 26.3	6	45.9 ± 20.2	183	43.4 ± 25.1	100	36.7 ± 26.9
P50 suppression	113	0.6 ± 0.5	4	0.4 ± 0.4	169	0.5 ± 0.3	92	0.5 ± 0.4
Antisaccade task	158	0.6 ± 0.3	6	0.4 ± 0.4	230	0.8 ± 0.2	134	0.7 ± 0.2
CPT	167	2.3 ± 1.1	6	2.1 ± 1.1	254	2.7 ± 1.0	154	2.2 ± 0.9
CVLT	180	42.4 ± 11.7	7	40.4 ± 19.6	259	55.8 ± 9.7	155	50.2 ± 10.4
LNS	181	9.2 ± 2.7	7	7.3 ± 3.3	258	11.1 ± 2.4	153	10.0 ± 2.6
Penn CNB measures								
ABF	159	-0.4 ± 1.2	5	-0.6 ± 1.2	229	0.2 ± 1.0	152	-0.5 ± 1.0
FMEM	159	-0.8 ± 1.2	6	-1.0 ± 1.4	224	0.2 ± 0.9	147	-0.4 ± 1.0
SMEM	155	-0.6 ± 0.9	5	-0.3 ± 0.9	223	0.1 ± 0.8	141	-0.4 ± 0.8
SPA	141	-0.6 ± 1.2	4	-1.3 ± 0.5	207	-0.2 ± 0.9	124	-0.5 ± 1.0
S-M	154	-0.7 ± 1.3	6	-1.2 ± 1.6	220	-0.1 ± 0.9	145	-0.6 ± 1.0
EMO	155	-1.2 ± 0.9	5	-1.5 ± 1.2	222	-0.4 ± 0.6	139	-0.9 ± 0.8

Abbreviations: ABF, Abstraction and Mental Flexibility; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; EMO, Emotion Recognition; FMEM, Face Memory; LNS, Letter-Number Sequencing test; Penn CNB, University of Pennsylvania Computerized Neurocognitive Battery; PPI, prepulse inhibition of the startle response; S-M, Sensorimotor Dexterity; SMEM, Spatial Memory; SPA, Spatial Processing; WRAT, Wide Range Achievement Test.

^aAlthough 183 probands were ascertained, the sample size of each endophenotype varied owing to differences in endophenotype-specific exclusion criteria (eg, hearing threshold for PPI and visual acuity for the CPT), interpretable data (ie, P50 and PPI waveforms), and availability of data for each measure.

Table 2. Heritability Estimates of the Primary Endophenotypes and the Penn CNB Measures as Assessed in the Pedigrees

Endophenotype	No.	h ² ± SE	95% CI	P Value	Covariate P Value ^a	
					Age	Sex
PPI ^b	401	0.32 ± 0.13	0.06 to 0.57	.005	.04	<.001
P50 suppression ^c	389	0.10 ± 0.18	-0.25 to 0.45	.18	.61	.67
Antisaccade task	525	0.42 ± 0.08	0.27 to 0.57	<.001	<.001	.93
CPT ^b	587	0.38 ± 0.07	0.23 to 0.52	<.001	<.001	.59
CVLT ^b	609	0.25 ± 0.08	0.11 to 0.40	<.001	<.001	<.001
LNS ^b	605	0.39 ± 0.07	0.25 to 0.52	<.001	<.001	.29
ABF ^b	543	0.28 ± 0.07	0.13 to 0.43	<.001	<.001	.73
FMEM ^b	533	0.27 ± 0.07	0.13 to 0.41	<.001	<.001	.25
SMEM ^b	520	0.24 ± 0.08	0.08 to 0.40	<.001	<.001	.45
SPA ^b	469	0.55 ± 0.08	0.39 to 0.71	<.001	<.001	<.001
S-M ^b	521	0.39 ± 0.08	0.23 to 0.55	<.001	<.001	.007
EMO ^b	516	0.32 ± 0.07	0.18 to 0.46	<.001	<.001	.002

Abbreviations: ABF, Abstraction and Mental Flexibility; CI, confidence interval; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; EMO, Emotion Recognition; FMEM, Face Memory; h², residual heritability after variance due to covariates is removed; LNS, Letter-Number Sequencing test; Penn CNB, University of Pennsylvania Computerized Neurocognitive Battery; PPI, prepulse inhibition of the startle response; S-M, Sensorimotor Dexterity; SMEM, Spatial Memory; SPA, Spatial Processing.

^aNote that for each endophenotype, only significant covariates were accommodated in the heritability analysis.

^bSignificantly heritable endophenotypes ($P < .05$).

^cAn alternative measure of P50 suppression, the conditioning-test amplitude difference, was found to be significantly heritable ($h^2 = 0.28 \pm 0.11$; $P = .004$) in this sample.

forward condition, baseline startle for PPI, the identical pairs version of the CPT, and measures of accuracy and efficiency for each Penn CNB measure. Although we focused on the primary measures in this study, heritability estimates for these and other secondary measures of the endophenotypes will be presented in future publications or made available to the scientific community on the COGS Web site (<http://www.npistat.com/cogs/>).

CORRELATIONS

The bivariate correlations, as given in **Table 3** and **Table 4**, are estimates of the strength of the components of the observed correlations between each pair of endophenotypes that can be attributable to genetic and environmental factors. Although a larger genetic correlation is indicative of increased evidence of shared genes

Table 3. Bivariate Genetic Correlations Between the Primary Endophenotypes and the Penn CNB Measures as Assessed in the Pedigrees^a

	PPI	Antisaccade Task	CPT	CVLT	LNS	ABF	FMEM	SMEM	SPA	S-M
Antisaccade task	-0.10±0.20									
CPT	0.07±0.21	0.42±0.13 ^b								
CVLT	0.04±0.26	0.06±0.19	0.34±0.18							
LNS	0.09±0.20	0.45±0.14 ^b	0.35±0.15 ^b	0.38±0.17 ^c						
ABF	0.19±0.26	0.34±0.17	0.40±1.80 ^b	0.34±0.21	0.42±1.80 ^b					
FMEM	0.20±0.24	0.29±0.16	0.32±0.16	0.38±0.20 ^b	0.26±0.17	0.22±0.19				
SMEM	0.21±0.34	0.31±0.17	0.43±0.21 ^b	0.68±0.23 ^b	0.38±0.21	0.87±0.27 ^c	0.61±0.22 ^b			
SPA	0.41±0.18 ^b	0.46±0.13 ^c	0.57±0.12 ^c	0.49±0.16 ^b	0.45±0.13 ^c	0.76±0.16 ^c	0.46±0.16 ^b	0.49±0.20 ^b		
S-M	-0.10±0.21	0.16±0.15	0.19±0.15	-0.23±0.19	0.08±0.15	0.15±0.18	0.10±0.17	0.20±0.21	0.13±0.15	
EMO	0.12±0.23	0.32±0.15	0.32±0.16	0.30±0.19	0.34±0.16 ^b	0.34±0.19	0.58±0.14 ^b	0.56±0.24 ^b	0.47±0.15 ^b	0.21±0.17

Abbreviations: ABF, Abstraction and Mental Flexibility; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; EMO, Emotion Recognition; FMEM, Face Memory; LNS, Letter-Number Sequencing test; Penn CNB, University of Pennsylvania Computerized Neurocognitive Battery; PPI, prepulse inhibition of the startle response; S-M, Sensorimotor Dexterity; SMEM, Spatial Memory; SPA, Spatial Processing.

^aCorrelation estimates and their standard errors (mean±SE) are indicated for each pair of endophenotypes.

^bCorrelations significant at $P < .05$.

^cCorrelations significant at $P < .001$ that remain significant after correction for multiple testing.

Table 4. Bivariate Environmental Correlations Between the Primary Endophenotypes and the Penn CNB Measures as Assessed in the Pedigrees^a

	PPI	Antisaccade Task	CPT	CVLT	LNS	ABF	FMEM	SMEM	SPA	S-M
Antisaccade task	0.12±0.12									
CPT	0.26±0.10 ^b	0.34±0.08 ^c								
CVLT	-0.03±0.10	0.23±0.09 ^b	0.14±0.08							
LNS	0.16±0.10	0.17±0.17	0.19±0.08 ^b	0.28±0.08 ^b						
ABF	-0.03±0.12	0.21±0.09 ^b	0.17±0.08 ^b	0.22±0.08 ^b	0.14±0.08					
FMEM	0.03±0.10	0.34±0.08 ^c	0.28±0.08 ^c	0.30±0.08 ^c	0.17±0.08 ^b	0.30±0.08 ^c				
SMEM	-0.11±0.11	0.31±0.09 ^c	0.08±0.09	0.17±0.08 ^b	0.04±0.09	0.04±0.08	0.24±0.08 ^b			
SPA	-0.12±0.38	0.26±0.11 ^b	0.01±0.11	0.22±0.10 ^b	0.18±0.10	0.22±0.09 ^b	0.17±0.10	0.15±0.10		
S-M	-0.13±0.28	0.36±0.09 ^c	0.31±0.09 ^c	0.33±0.08 ^c	0.21±0.09 ^b	0.26±0.09 ^b	0.34±0.08 ^c	0.20±0.09 ^b	0.30±0.11 ^b	
EMO	0.00±0.01	0.27±0.09 ^b	0.17±0.08	0.23±0.08 ^b	0.15±0.09	0.23±0.08 ^b	0.35±0.07 ^c	0.06±0.08	0.17±0.10	0.29±0.08 ^c

Abbreviations: ABF, Abstraction and Mental Flexibility; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; EMO, Emotion Recognition; FMEM, Face Memory; LNS, Letter-Number Sequencing test; Penn CNB, University of Pennsylvania Computerized Neurocognitive Battery; PPI, prepulse inhibition of the startle response; S-M, Sensorimotor Dexterity; SMEM, Spatial Memory; SPA, Spatial Processing.

^aCorrelation estimates and their standard errors (mean±SE) are indicated for each pair of endophenotypes.

^bCorrelations significant at $P < .05$.

^cCorrelations significant at $P < .001$ that remain significant after correction for multiple testing.

(pleiotropy), this statistic is merely an estimate, and thus a high correlation value may not necessarily be significant owing to the standard error associated with its estimation. Correction for multiple testing is not trivial for these analyses or necessarily appropriate⁵⁴ because of the extensive correlations observed between the endophenotypes. Nevertheless, we have given an indication of the effect of correction for multiple testing using the conservative Bonferroni method. The endophenotypic measure of P50 suppression was not included in these analyses because it was not found to be significantly heritable.

Significant ($P < .05$) genetic correlations were observed between many of the endophenotypes, particularly between the neurocognitive measures. Spatial Processing seems to be genetically correlated with all of the other endophenotypes tested, including PPI, except for Sen-

sorimotor Dexterity, which did not reveal significant genetic correlations with any endophenotype. The genetic correlations observed between the CVLT and LNS, between Abstraction and Mental Flexibility and Spatial Memory, and between Spatial Processing and the antisaccade task, CPT, LNS, and Abstraction and Mental Flexibility were significant at the $P < .001$ level and remained significant after correction for multiple testing. These results suggest that overlapping genetic architecture (pleiotropy) underlies some of these endophenotypes.

We also observed significant ($P < .05$) environmental correlations between many of the endophenotypes. The PPI did not reveal a significant environmental correlation with any endophenotype other than the CPT. Conversely, the antisaccade task, CVLT, and Face Memory revealed environmental correlations with nearly every

other endophenotype. In contrast to the genetic correlations, Sensorimotor Dexterity revealed significant environmental correlations with all of the other endophenotypes except for PPI. Many of the environmental correlations involving these endophenotypes were significant at the $P < .001$ level and remained significant after correction for multiple testing.

COMMENT

By identifying the genetic determinants of endophenotypes known or likely to represent the subclinical pathologic abnormalities of a disease, researchers may be able to more easily identify the genes or groups of genes that affect the actual manifestations of that disease.^{3,4,58} All of these endophenotypes, which were selected for their heritability in schizophrenia, are significantly heritable in this sample. The heritability of these measures partially reflects the rigorous quality control and standardization used to reduce variability between COGS data collection sites that could otherwise have created noise in the data and obscured heritability estimates.⁷ Because the site of endophenotype collection was not a significant covariate in these analyses and because site effects have not been observed in the analyses of the individual endophenotypes (other data to be presented separately),^{39,59} efforts of the COGS to standardize phenotyping across all 7 sites seem to have been successful. In addition to evidence of the lack of site effects, estimates of reliability and stability for these endophenotypes are presented individually elsewhere.^{39,59}

P50 suppression, as measured by means of the test to conditioning amplitude ratio, was shown to be highly heritable in several studies of patients with schizophrenia,^{38,60} and investigations of this measure in healthy twins estimated the heritability of P50 suppression to be 0.68⁶¹ and 0.44 to 1.00.⁶² Despite this evidence of heritability, initial analyses of this endophenotype did not reveal significant heritability in this sample. Several alternatives to the P50 ratio have been examined, of which the difference between conditioning and test amplitude was found to have the most promising metric properties.⁶³ This measure also exhibited higher heritability than the ratio in a recent twin study.³⁶ As predicted from this recent study, this difference as an alternative P50 suppression measure in the present sample revealed significant heritability (28%). Several factors may affect the heritability of this endophenotype, as measured by ratios and difference scores (see discussions of pedigree ascertainment bias and antipsychotic medication use that follow). Future studies in the complete sample with perhaps more sophisticated methods are necessary before any firm conclusions can be drawn.

Comparison of our results with those in the literature reveals consistencies and discrepancies. Although twin studies of PPI have demonstrated that heritability accounts for more than 50% of PPI variance,⁶⁴ the present estimate of PPI is lower at 32%. The present heritability estimate of 42% for the antisaccade task is also lower than the estimate of 57% observed in a large twin study.⁶⁵ For a Degraded Stimulus condition of the CPT

similar to that presented herein, heritability estimates of 51% to 79% have been observed,^{66,67} whereas other heritability estimates for the CPT range between 30% and 62%,⁶⁸ consistent with the present estimate of 38% for the Degraded Stimulus version of the CPT. Although 1 twin study⁶⁹ of the CVLT reported heritability of 56% for learning and memory, another study involving patients with schizophrenia and their first-degree biological relatives reported a small effect size (0.21) for recall on trials 1 to 5 of the CVLT, consistent with the heritability estimate of 25% presented herein. Heritability estimates for verbal and visual working memory are moderately high in nonclinical samples (43%-49%)^{70,71} and comparable in schizophrenia (36%-42%),^{72,73} consistent with the present observed heritability of 39% for the LNS. A large, multisite family study⁷⁴ estimated the heritability of accuracy and speed for Face Memory to be 33% and 25%, respectively, and the heritability of an emotion intensity discrimination test to be 37.3%. These estimates correlate reasonably well with the present heritability estimates of 23% for Face Memory and 33% for Emotion Recognition. Many of the previously mentioned heritability estimates derive from twin studies in healthy individuals, a sample composition different from that presented herein, and many of the sample sizes were small. However, although sample differences may account for some of the discrepancies between the present heritability estimates and those previously reported, other factors may have contributed, as discussed in detail later herein.

As noted by Calkins et al,⁷ the particular recruitment strategy of families used by the COGS may result in cohort effects due to familial "intactness" and the selection of family members willing to participate in lengthy research sessions. Such an ascertainment scheme may have led to the preferential selection of patients with schizophrenia and families with less genetic loading for pathologic endophenotypic values, which would lower, but not undermine, the estimates of heritability. Therefore, it is possible that a sample of "singleton" patients may show greater deficits and greater heritability of the endophenotypes if their families could be studied. Correction for this type of ascertainment bias is not trivial, nor is it feasible, and it is possible that this conundrum has had a negative impact on the power of detection as far as heritability. Future research involving the comparison of the effect size of endophenotypic deficits in singletons recruited for other studies vs probands in the COGS sample will inform us regarding these issues.

We included schizophrenia probands in this study because their endophenotypic values are likely to be in pathologic ranges, which allows for analysis of these endophenotypes with respect to schizophrenia. Although this is a common practice that simply requires an appropriate statistical accommodation,⁷⁵ it is likely to have affected the heritability results. This inclusion also introduced a potentially confounding factor into these analyses. Both PPI and P50 suppression were shown in other studies to be at least partially normalized by the use of atypical (second-generation) antipsychotic medications in patients with schizophrenia.^{37,60,76-78} Because 85% of the present schizophrenia probands were taking atypical an-

tipsychotic medications at the time of endophenotype testing, this “normalization” effect of atypical antipsychotic medications complicates the interpretation of heritability data for these endophenotypes in the context of the COGS. It is possible that other endophenotypes are susceptible to the effects of atypical antipsychotic medications as well. This is an indication that some of these endophenotypes will require more probands, including unmedicated patients, and a more precise, advanced statistical approach that will account for medication use in the assessment of heritability.

It is also possible that shared environmental influences have affected these heritability calculations. However, the participants in the present study tend to be older and are not as likely to be sharing a current environment with their family members. We do not have accurate information regarding the shared environment of the siblings in childhood and adolescence, and it is unclear what impact early shared environment might have on later manifestations of these endophenotypes.

The observed heritabilities for these endophenotypes are lower than the highest heritability of 80% observed for schizophrenia itself.⁷⁹ However, we suspect that by assessing endophenotype heritabilities, we are parsing the entire heritability of schizophrenia into components with specific underlying neurobiologic features. For this reason, we do not necessarily expect to find a single endophenotype that is more heritable than schizophrenia but rather a series of endophenotypes that additively approach the heritability of schizophrenia and relate to the specific neurobiologic features of schizophrenia as an epigenetic puzzle.⁸⁰

The analyses reported herein can be used to generate hypotheses about the relationships between the endophenotypes at the genetic level and suggest that not only are they heritable but they also show evidence of genetic correlations. These correlations make sense from a phenomenologic and neural substrate level, as many of these measures have similar psychological, genetic, and neurobiologic underpinnings. The fact that the endophenotypes are not 100% coheritable suggests that there are subtypes of schizophrenia with different endophenotypic profiles. These genetic correlations offer an exciting and challenging opportunity to explore the potential common underlying genetic and neurobiologic substrates of these endophenotypic measures, which will be possible as genetic data become available. The lack of genetic correlations between many of the endophenotypes is also interesting and suggests that different genes contribute to endophenotypic expression. Although these results require replication, they should stimulate exploration of the reported relationships.

The insights gleaned from these results will help guide us in future analyses that will focus on understanding the complex genetic architecture of schizophrenia using these endophenotypes, alone or in combination, in even larger samples gathered by the COGS in the future. Ultimately, we will use DNA already obtained from the study participants to search for influential loci in a 5800–single nucleotide polymorphism genomewide linkage panel and for additional candidate gene studies. This strategy should position us to dissect the polygenic basis of

risk of schizophrenia and to identify molecular deficits,^{5,81} which can serve as potential therapeutic targets for the development of new, genetically informed psychopharmacologic treatments for schizophrenia.

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