Principal Components of Heritability From Neurocognitive Domains Differ Between Families With Schizophrenia and Control Subjects

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Objective: **Various measures of neurocognitive function show mean differences among individuals with schizophrenia (SZ), their relatives, and population controls. We use eigenvector transformations that maximize heritability of multiple neurocognitive measures, namely principal components of heritability (PCH), and evaluate how they distribute in SZ families and controls.** *Methods:* **African-Americans with SZ or schizoaffective disorder (SZA) ($n =$ 514), their relatives ($n =$ 1092), and adult controls ($n =$ 300) completed diagnostic interviews and computerized neurocognitive tests. PCH were estimated from 9 neurocognitive domains. Three PCH, PCH1–PCH3, were modeled to determine if status (SZ, relative, and control), other psychiatric covariates, and education were significant predictors of mean values. A small-scale linkage analysis was also conducted in a subset of the sample.** *Results:* **PCH1, PCH2, and PCH3 account for 72% of the genetic variance. PCH1 represents 8 of 9 neurocognitive domains, is most highly correlated with spatial processing and emotion recognition, and has unadjusted heritability of 68%. The means for PCH1 differ significantly among SZ, their relatives, and controls. PCH2, orthogonal to PCH1, is most closely correlated with working memory and has an unadjusted heritability of 45%. Mean PCH2 is different only between SZ families and controls. PCH3 apparently represents a heritable component of neurocognition similar across the 3 diagnostic groups. No significant linkage evidence to PCH1–PCH3 or individual neurocognitive measures was discovered.** *Conclusions:* **PCH1 is highly heritable and genetically correlated with SZ. It should prove useful in future genetic analyses. Mean PCH2 differentiates SZ families and controls but not SZ and unaffected family members.**

Key words: schizophrenia/cognition/heritability/principal components/linkage

Introduction

The neurocognitive performance of individuals with schizophrenia (SZ) is lower, on average, relative to the general population[1,2] and predicts prognosis and functional outcome. Notably, biological relatives of SZ patients, including psychiatrically healthy individuals, also show diminished neurocognitive performance at a mean level that is intermediate between SZ patients and the general population.[3,4] Thus, neurocognitive performance is tied to liability to SZ.

We have analyzed a spectrum of neurocognitive dimensions by using a Computerized Neurocognitive Battery (CNB, also known as Penn CNB), which records accuracy and response time[5,6] in large-scale genetic studies. In a Caucasian family-based SZ sample (Multiplex-Multigenerational Genetic Investigation, MGI),[7] patients on average had significantly more deficits than controls in measures of abstraction/mental flexibility and performed substantially worse on measures of verbal memory, face memory, spatial processing, and emotion identification.[7]

Patients were also impaired in response time for these domains. Relatives of these same SZ patients were, on average, impaired for accuracy of abstraction and spatial processing and showed reduced speed for attention, face memory, spatial processing, and sensorimotor function. The magnitude of these impairments was smaller than those observed among the patients. The heritability estimates were significant for accuracy and speed estimates for all the domains, ranging from 0.11 to 0.58.

Similar effects were observed in our study of African American SZ families[3] ascertained through the Project Among African-Americans to Explore Risks for Schizophrenia (PAARTNERS).[8] Patients with SZ or schizoaffective disorder (SZA) were less accurate and slower in the same neurocognitive domains as the Caucasian patients, although the effect sizes varied. For example, PAARTNERS SZ subjects tended to have greater impairment in accuracy measures of attention but less impairment regarding accuracy for face memory. As in the Caucasian sample, nonpsychotic relatives of the African-American patients had, on average, intermediate levels of performance compared with controls and patients. Measurements of accuracy of all domains were heritable, and the majority were greater than 0.30.

Two other large-scale studies obtained similar results, the Consortium on the Genetics of Schizophrenia,[9] which also used the Penn CNB and a combined sample from the UK and the US.[4] These studies are consistent with the literature that indicates substantial neurocognitive deficits in SZ.[10] Thus, the patterns of neurocognitive performance in patients with SZ, their relatives, and controls are not population specific. Moreover, with respect to etiology, the overall pattern is consistent with pleiotropy; genetic variation impacting multiple traits,[11] in this case liability for SZ and neurocognitive performance. Indeed, latent class analyses of the UK/US sample estimate that a substantial portion of the phenotypic correlation between schizophrenia and cognition results from shared genetic effects.[4] Still, the genetic overlap between the diagnostic phenotype and cognitive traits is substantially less than 100%.

The multidimensional nature of these quantitative neurocognitive measures presents some statistical challenges because they are interrelated and thus correlated.[7] One way of reducing dimensionality is to determine classical principal components of the correlated variables. Indeed, principal components applied to highly correlated traits will typically result in one or a few components that capture most of the phenotypic variation, each derived trait being a linear combination of the individual traits. A drawback to such an analysis is that these linear combinations of traits need not have genetic relevance.[12] An alternative approach, namely principal components of heritability (PCH), has direct relevance to genetic variation. This analysis takes into account both the family structures and the distribution of the traits within families. The analysis seeks one or more linear combination of traits with maximum heritability. The first PCH, for example, is the linear combination of traits that shows the least within-family variance relative to its between-family variance[12–14]; highly heritable traits, of course, show large between-family variance. Thus, PCH offers another and arguably sharper tool to investigate the pleiotropic connections between SZ liability and neurocognition.

We use quantitative genetics to determine highly heritable composite dimensions of neurocognitive domains from the Penn CNB and then evaluate the distribution of these heritable dimensions or PCH in SZ subjects, their relatives, and controls. We also evaluate the evidence for pleiotropy between liability to SZ and neurocognitive performance, as measured by PCH, in a somewhat different way than Toulopoulou et al.[4] The data analyzed are a uniform set of neurocognitive variables from a large African-American schizophrenia/schizoaffective family sample. Adult controls drawn from the same communities are evaluated similarly. In addition to addressing the nature of heritability, we also evaluate whether the PCH differ among diagnostic groups and perform a small-scale whole-genome linkage analysis using these PCH and the original neurocognitive domains.

Methods

The multisite PAARTNERS study includes probands with schizophrenia or schizoaffective disorder (SZ/SZA), their relatives, and controls, recruited from Southeastern and Eastern USA.[3,8] We recruited probands and their relatives in 1 of 3 family structures: trios, affected sibling pairs, or multiplex. Trio families included the proband and either 2 parents or at least one additional sibling if a parent was unavailable. Affected sib-pair (ASP) families included the proband, parents, and at least one sibling diagnosed with SZ/SZA depressed type. In trio and ASP families, half-siblings could be sampled if they were children of a parent who did not participate. Multiplex families included the proband and one or more affected first-degree relatives and a minimum of 8 additional first- to fourth-degree relatives. We also assessed healthy community comparison subjects (CCS) from the same communities as the probands. They were screened for the absence of personal and family history of psychoses.[3] All participants were self-identified as African-American and completed diagnostic and cognitive assessments. All participants provided written informed consent using protocols approved by each site's local Institutional Review Board.

Records of participants were for study inclusion criteria. PAARTNERS used the Diagnostic Interview for Genetic Studies with all participants. Interviewers incorporated medical chart information and obtained information from family members using the Family Interview for Genetic Studies. This information was synthesized and

Table 1. Tasks Used for Each of the Neurocognitive Domains Measured

Abbreviation	Neurocognitive Domain	Task
ABST	Abstraction and mental flexibility	Abstraction and Working Memory Task; Penn Conditional Exclusion Test
ATTN	Attention	Penn Continuous Performance Test—Number and Letter Version, Letter-n-back, 0-back condition
VMEM	Verbal memory	Penn List Learning Task, Computerized Penn Word Memory Test
FMEM	Face memory	Penn Face Memory Test
SMEM	Spatial memory	Visual Object Learning Test
WMEM	Working memory	Letter-n-back, 1- and 2-back conditions
LANG	Language	Penn Verbal Reasoning Test
SPA	Spatial processing	Computerized Judgment of Line Orientation
EMOD	Emotion processing	Penn Emotion Recognition Test; Penn Emotion Discrimination Task
SPRC	Sensorimotor processing	Computerized Finger-Tapping Task; Motor Praxis Test

consensus best estimate *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnosis assigned by doctoral level clinicians.[8]

The Penn CNB for large-scale studies,[3,15] was administered using clickable icons on desktop or laptop computers, allowing automated scoring. Administration time, including rest, was approximately 120 minutes. The battery uses 14 tasks to assess 10 neurocognitive domains, measuring accuracy (number of correct responses) and speed (response time for correct answers, table 1). One domain only evaluates speed. Because speed and accuracy are highly correlated, our analyses use only accuracy measures. Scores from individual tests were transformed to approximate normality using a Box-Cox transformation.[16] Transformed scores were normalized by the mean and SD from the control group.

The genetic (familial) and residual covariance components for the 9 neurocognitive domains were estimated simultaneously using a multiple trait mixed linear model. This model included covariates for sex and age as well as random effects for individuals and residuals. Kinships among individuals were used to account for familial relationships among the people in the study. To estimate the covariance components, we used the average information algorithm for restricted maximum likelihood estimation.[17] The estimated covariance components were then used to determine a canonical transformation of the original domain scores.[13,14] The canonical transformation is similar to a principal component analysis in that it yields a set of independent phenotypes; however, the canonical transformation maximizes the heritability in its main components or PCH. All phenotypes, in this case 9 neurocognitive domains, need to be known for PCH analysis. Missing data for neurocognitive domains were imputed when at least 7 of the 9 domains had an observation; individuals missing 3 or more observations ($n = 108$ individuals) were excluded from the analysis. For imputation, we used cognitive domain scores adjusted for sex and age

(see online supplementary table 1 for adjustments) and a prediction equation based on the phenotypic covariance matrix (see online supplementary material for table 2). Seventeen hundred and eight individuals had no missing data; 364 were missing one component; and 113 were missing 2. For detailed information on the distribution of missing observations across domains and evaluation of performances, please see online supplementary table 3. In brief, working memory had the greatest missingness ($n = 228$), emotional distinction the least ($n = 0$), the imputation was largely unbiased, and the accuracy similar to the error distribution of the data (see online supplementary material for table 4).

To identify predictors of estimated PCH, we first sought to reduce the number of diagnostic categories. Because individuals with schizophrenia (SZ) and schizoaffective disorder (SZA, depressed and bipolar types) did not differ significantly from each other with respect to mean cognitive phenotypes, these diagnoses were binned into one group. This reduction allowed a simple encoding of 3 mutually exclusive variables, each with binary outcomes: SZ, which includes SZA for modeling purposes (SZ/SZA); nonpsychotic relatives of an individual diagnosed with SZ/SZA (relative); and control individuals, who have no symptoms of psychosis and no close relative with SZ/SZA. Note that the binary encoding of any 2 of these variables encodes the third. We chose to fit models with a variable for SZ/SZA and relative. In this scheme, the mean attributable to controls is identified by the model mean. To capture other diagnoses of interest, we included 2 other indicator variables: (1) the "mood" group encodes major depressive disorder, other nonpsychotic mood related disorders, and a small number of bipolar I disorder cases ($n = 23$); (2) the "substance use disorders" group encodes disorders related to alcohol or substance abuse or dependence ($n = 429$). These latter 2 indicators could be '+' or '−' for an individual falling into the mutually exclusive sets (SZ/SZA, a relative, or

Table 2. Phenotypic and Genetic Correlations Between the Cognitive Domain Scores and the Principal Components of Heritability

Domain	PCH1		PCH2		PCH3	
	Phenotypic	Genetic	Phenotypic	Genetic	Phenotypic	Genetic
ABST[a]	0.62	0.84	−0.13	−0.14	−0.25	−0.23
ATTN	0.21	0.43	0.33	0.55	0.13	0.19
VMEM	0.68	0.81	0.40	0.39	0.35	0.29
FMEM	0.56	0.72	0.44	0.46	0.26	0.23
SMEM	0.47	0.72	0.32	0.40	0.23	0.24
WMEM	0.35	0.46	0.64	0.69	−0.48	−0.44
LANG	0.58	0.76	0.19	0.20	−0.24	−0.22
SPA	0.84	0.94	−0.16	−0.15	−0.17	−0.13
EMOD	0.74	0.90	−0.07	−0.07	0.29	0.25

[a]For description of domains, see table 1.

a control). We also included education (EDU) in these models, which was nested separately within the 3 main sample groups (SZ/SZA, relative, control).

Details of the DNA analysis have been described in detail elsewhere.[18] Briefly, genotyping of the Illumina Linkage Panel, consisting of 6008 Single Nucleotide Polymorphisms (SNPs) having an average genetic distance between SNPs of 0.62 cM, was performed by the Center for Inherited Disease Research (http://www.cidr.jhmi.edu/). After quality control edits, 5631 SNPs remained for linkage analysis, of which 4905 independent SNPs ($r^2 < .10$) were selected using Hclust software.[19]

We explored evidence for linkage for 3 PCH with substantial heritability as well as individual domains. Using estimated degree of shared identity-by-descent (IBD) at specific loci, the algorithm decomposes the total genetic variance into a component proportional to the estimated sharing IBD at that locus and the remainder of the genetic variance. The relative value of these 2 components gages the evidence linking a genetic variant with a cosegregating trait. We used the software package MERLIN[20] to determine the IBD values, which were then used within SOLAR software[21] to produce the linkage traces.

Results

The sample included 3536 individuals from 749 families. Of these, 2288 individuals from 745 families completed the Penn CNB. Heritability estimates for individual cognitive domains, (defined in table 1), ranged from 16% (±3%) for ATTN to 54% (±3%) for SPA, with SEs at approximately 3%. Estimated phenotypic correlations among the neurocognitive domains were all positive and ranged from a high of 0.55 (±0.01) between

Table 3. Analysis of Principal Components of Heritability in Relation to Key Variables

	PCH1		PCH2		PCH3	
	Beta Coefficient (SE)	P Value	Beta Coefficient (SE)	P Value	Beta Coefficient (SE)	P Value
Overall mean	0.91 (0.08)		−0.46 (0.07)		−0.09 (0.06)	
Heritability	0.55 (0.05)	9.12×10^{-32}	0.43 (0.05)	1.52×10^{-20}	0.31 (0.05)	9.20×10^{-13}
Covariates						
Diagnostic categories						
Schizophrenia[a]	−1.14 (0.10)	2.51×10^{-31}	−0.25 (0.08)	1.82×10^{-3}	0.02 (0.07)	8.19×10^{-1}
Nonpsychotic relatives	−0.48 (0.09)	2.85×10^{-7}	−0.16 (0.08)	3.93×10^{-2}	0.11 (0.07)	1.24×10^{-1}
Mood disorders[b]	0.13 (0.08)	1.32×10^{-1}	0.01 (0.07)	8.50×10^{-1}	−0.09 (0.07)	1.48×10^{-1}
Substance related disorders[c]	0.16 (0.07)	2.66×10^{-2}	−0.05 (0.06)	4.17×10^{-1}	0.02 (0.06)	7.18×10^{-1}
Nested education variables						
EDU|schizophrenia	0.20 (0.02)	1.94×10^{-18}	0.05 (0.02)	1.58×10^{-2}	0.00 (0.02)	9.49×10^{-1}
EDU|nonpsychotic relative	0.20 (0.02)	1.16×10^{-32}	0.05 (0.01)	1.52×10^{-3}	0.02 (0.01)	1.27×10^{-1}
EDU|control	0.25 (0.03)	3.44×10^{-17}	0.09 (0.02)	3.64×10^{-4}	−0.02 (0.02)	3.34×10^{-1}

[a]Includes schizophrenia and schizoaffective disorder.
[b]Major depressive disorder, other nonpsychotic mood related disorders, and a small number of bipolar disorder 1 cases.
[c]Alcohol or illicit substance abuse or dependence.

VMEM andFMEM to a low of 0.16 (±0.01) between ATTN and LANG.

Estimated genetic correlations among the traits (ie, for 2 traits, how much of their heritability is affected by the same genetic variation) were in general higher than the corresponding estimates of the phenotypic correlations. Estimated genetic correlations ranged from 0.30 (±0.08) for ATTN and SPA to 0.80 (±0.04) for SPA and EMOD, with 27 of the 36 genetic correlation estimates greater than 0.50 (see online supplementary material for table 5).

The genetic and phenotypic correlations between PCH1–PCH3 and individual neurocognitive domains are listed in table2. While a total of 9 PCH were generated, PCH1, PCH2, and PCH3 accounted for 72% of the total variation in the cognitive domains on the canonical scale. Heritability estimates for the first 3 PCH were 68%, 45%, and 33%, respectively (unadjusted for diagnostic status and education.)

Weights to calculate the PCH from the cognitive domains are given in online supplementary table 2. PCH1 is essentially an average of 8 of the 9 neurocognitive domains, with relatively low contribution from ATTN. ATTN makes a more substantial contribution to PCH2, where VMEM, FMEM, SMEM, WMEM, and LANG also show strong representation. ABST, SPA, and EMOD do not contribute substantially to PCH2. Finally, the variation in ATTN, VMEM, FMEM, and SMEM contribute to PCH3.

For PCH1, the mean neurocognitive performance of control individuals was significantly higher (estimated by the overall mean in the model, 0.91; table3) than individuals diagnosed with SZ/SZA (estimated effect $b = -1.14$, $P = 1.09 \times 10^{-31}$) or nonpsychotic relatives ($b = -0.44$, $P = 2.85 \times 10^{-7}$). Mood disorders had no significant predictive value, while individuals using illicit substances had slightly higher mean PCH1 (table 3.) As anticipated, education was a highly significant predictor of PCH1 over all diagnostic groups. Results for PCH2 and PCH3 were less easily interpreted. For PCH2, controls had higher mean values than SZ/SZA and relatives, who did not differ significantly in their mean values. For PCH3, none of these 3 diagnostic classes differed significantly in their means. Consistent with results for PCH1, education had a positive impact on the mean PCH2 for all diagnostic groups. All other predictors for PCH2 and PCH3 were nonsignificant.

For exploratory linkage analysis, we analyzed data from 888 individuals in 212 families. No significant or suggestive linkages were detected for any of the 3 PCH (see online supplementary material for table 6). A log of odds of 3.3 is a standard threshold for linkage on a quantitative trait. It translates to a P value threshold of approximately 0.0001. For 3 PCH, after Bonferroni correction, the threshold would be 0.00003. Correcting for additional multiple testing yields a P value threshold of approximately 0.000003. Neither the PCH linkage traces nor the linkage analysis of individual traits meet these criteria. This result probably is attributable to the limited power of the sample. In addition, while PCH maximize heritability, they do not necessarily maximize power to detect a particular quantitative trait locus or QTL. Indeed, PCH analysis could have less power than analysis of an individual QTL, if the QTL were more directly related to an individual neurocognitive feature. After all, while quantitative genetic models assume a large number of loci, each with small effect on a trait or traits, the reality is that some loci have a major impact on the variability of one or more traits. How this balance is realized—whether the locus has a large effect on an individual trait or on a linear combination of traits—will determine whether linkage analysis of individual traits or PCH is more powerful.[12] Exploratory analysis using individual domains yields some linkage signals of interest (see online supplementary material for table 6), but none of the results could be viewed as significant because of multiple testing.

Discussion

The etiology of SZ remains enigmatic. Genetic factors apparently underlie a substantial portion of risk, yet only a small fraction of these factors have been identified. New paradigms for understanding the etiology of SZ could prove valuable. One potentially useful observation is that individuals diagnosed with SZ, on average, show diminished neurocognitive performance when compared with controls samples, and a similar but more moderate pattern occurs in their close relatives. In addition, evidence from at risk children of SZ patients and prospective studies indicate that these patterns exist prior to the prodromal period.[22–26] These patterns are also observed for individual dimensions of cognition. As we show here, they also emerge from a linear combination of these dimensions that maximize heritability and especially the PCH1. This pattern of diminished average neurocognitive performance is consistent with genetic variation affecting PCH1 trait values and liability to schizophrenia, a phenomenon referred to as genetic correlation or pleiotropy.

To obtain an estimate of the genetic correlation between SZ and PCH1, we can use evolutionary theory that defines the correlated response to selection.[11] The rationale for the calculation is straightforward. Family members in our study were selected based on SZ status of the proband. That close relatives of the proband are at higher liability to SZ is well known[27] and therefore, selection for SZ liability occurs by sampling families through affected probands. Estimates of the heritability of SZ range from 40% to 80%.[27] The nominal rate of SZ in the population is roughly 1%, while the rate in family members of probands ranges from 4% to 8%.[27] This difference supplies the selection differential for the trait under selection. Furthermore, it is reasonable to assume the

phenotypic SD of SZ on the liability (or threshold) scale is 1. We can estimate genetic correlation by using these assumptions, as well as the formula for correlated response to selection (see Falconer, equation 11.2),[11] the estimated heritability of PCH1 from our study, h^2 = 0.55, SD = 1.56 (after adjustment for diagnosis and education), and the fact that population controls scored 0.48 units higher, on average, than nonpsychotic family members. Based on these observations, the estimated genetic correlation between SZ liability and PCH1 is −0.32 or −0.45, depending on whether we assume the heritability of SZ is 0.4 or 0.8, respectively, and by assuming the probability of a family member of an SZ proband is also affected is 0.068.

Toulopoulou and colleagues[4] also estimated the genetic correlation between SZ and neurocognitive function. To do so, they compiled data sets from the UK and the US, with the UK data set containing both monozygotic and dizygotic twin pairs. All of the subjects from families, as well as the control subjects, were assessed by various measures of neurocognitive function, which were standardized across studies. Using sophisticated multivariate path models, they were able to partition the variation in liability to SZ and variation in neurocognitive function into genetic, common environment, and residual components, as well as estimate genetic correlations. Using assumptions similar to our own, yet for different populations and modeling approaches, they obtained similar point estimates in terms of heritability of neurocognitive function (range 0.48–0.66) and genetic correlation between liability to SZ and neurocognitive function (−0.34 to −0.50). Thus, Toulopoulou et al's calculations, as well as our own, underscore an important message emanating from all such family studies[3,4,7,9]—that there is substantial genetic overlap between liability to SZ and dimensions of normal neurocognitive function.

Quantitative genetic calculations, while theoretically appealing, lack the concreteness inherent in a mapping between specific genetic variants and their impact on both SZ liability and neurocognitive function. Indeed, the basis for most quantitative genetic theory is the infinitesimal model, which assumes a very large number of independent loci, each with very small effect. The reality for most human phenotypes is a mix of loci with small, modest, and larger effects. At this time, 6 copy number variant or CNV loci are known to affect both liability to SZ and neurocognitive function. They fall at chromosomal locations 1q21.1,[28] 3q29,[29] 15q11,[28,30] 15q13.3,[28,30] 16p11.2,[31] and 22q11.2.[32]

The most thoroughly studied of these CNVs occurs in the 22q11.2 region, specifically the 22q11.2 deletion syndrome.[32] Individuals carrying these deletions are at risk for the velo-cardio-facial syndrome, schizophrenia, other psychotic disorders, and diminished neurocognitive performance. This deletion produces roughly 25-fold increased risk for SZ over population prevalence. With respect to neurocognitive performance, learning disabilities are common and intellect ranges from just below average to mild intellectual disability.[32] Because all but 10% of the 22q11.2 deletions are de novo events and the phenotype is severe, the deletion itself is a poor candidate to be a major contributor to the subtle variation in neurocognitive performance reported here. Still, inherited genetic variation altering the function or expression of one or more key 22q11.2 genes could produce subtler effects.

Of the other CNVs listed previously, only 3q29 deletions[29] have an impact on liability to SZ and neurocognitive function similar to 22q11.2 deletions. All others have substantially less impact on liability[33] and their impact on neurocognitive function ranges from typically severe (1q21.1) to modest (15q11). Of these CNVs, 15q11 deletions appear to increase liability to SZ the least[33] with an estimated 2- to 3-fold increased risk. These deletions also have a modest impact on cognitive function[34,35] epilepsy[36] and behavior.

Regarding recent discoveries for more common variants, their impact on cognitive function is undoubtedly more subtle. For example, a single nucleotide polymorphism in gene ZNF804A, namely rs1344706, is associated with risk for SZ. It impacts certain cognitive functions according to recent studies but the functions vary by study as does the population (case or control) in which it acts: episodic and working memory in subjects with SZ but not controls[37]; executive control of attention in a control population[38]; working memory, mediated by decoupling of functional connectivity, in a control sample[39]; and visual memory in SZ subjects but not controls.[40]

By definition PCH2 and PCH3 are less heritable than PCH1. The mean value for PCH2 does not differ significantly between SZ and their relatives, although both their means are smaller than controls (table3). The correlations of individual cognitive domains for PCH2 are quite distinct from those for PCH1 (table2), partly because PCH1 and PCH2 must be orthogonal. Assessed as the absolute value of these correlations, however, spatial processing and emotion recognition are most strongly associated with PCH1, followed by verbal memory and attention, whereas working memory is most strongly correlated with PCH2, followed by face and verbal memory (table2). For PCH3, means for all 3 diagnostic groups are statistically indistinguishable. It apparently represents a heritable aspect of neurocognition that is unrelated to SZ.

Using PCH, we identified 3 principal components that have substantial heritability. PCH1 encompasses variability across all domains, but it is most heavily weighted by abstraction, spatial processing, and emotion processing. PCH1 represents general cognitive ability. PCH2 is related to more specific cognitive domains including working memory. No individual domains are outstanding for PCH3. For PCH1, our results are consistent with pleiotropic inheritance relevant to SZ, namely that there

are shared genetic loci that determine the cognitive variation inherent in PCH1 as well as risk for SZ. Other studies have generated data supporting this argument on the basis of individual cognitive domains; we evaluate linear combinations of domains that maximize heritability and find that the conclusions remain unchanged. Hence, while analysis of PCH derived from neurocognitive domains cannot be guaranteed to be a more powerful means of identifying risk loci for SZ, it does hold the promise of making the effects of discovered loci more easily interpretable.

Supplementary Material

Supplementary material is available at http://schizophrenia bulletin.oxfordjournals.org.

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References

1. Saykin AJ, Gur RC, Gur RE, et al. Neuropsychological function in schizophrenia. Selective impairment in memory and learning. *Arch Gen Psychiatry*. 1991;48:618–624.

2. Saykin AJ, Shtasel DL, Gur RE, et al. Neuropsychological deficits in neuroleptic naive, first episode schizophrenic patients. *Arch Gen Psychiatry*. 1994;51:124–131.

3. Calkins ME, Tepper P, Gur RC, et al. Project among African-Americans to explore risks for schizophrenia (PAARTNERS): evidence for impairment and heritability of neurocognitive functioning in families of schizophrenia patients. *Am J Psychiatry*. 2010;167:459–472.

4. Toulopoulou T, Goldberg TE, Mesa IR, et al. Impaired intellect and memory: a missing link between genetic risk and schizophrenia? *Arch Gen Psychiatry*. 2010;67:905–913.

5. Gur RC, Ragland JD, Moberg PJ, et al. Computerized neurocognitive scanning: I. Methodology and validation in healthy people. *Neuropsychopharmacology*. 2001;25:766–776.

6. Gur RC, Richard J, Hughett P, et al. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. *J Neurosci Methods*. 2010;187:254–262.

7. Gur RE, Nimgaonkar VL, Almasy L, et al. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *Am J Psychiatry*. 2007;164:813–819.

8. Aliyu MH, Calkins ME, Swanson CL, Jr, et al. Project among African-Americans to explore risks for schizophrenia (PAARTNERS): recruitment and assessment methods. *Schizophr Res*. 2006;87:32–44.

9. Greenwood TA, Braff DL, Light GA, et al. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Arch Gen Psychiatry*. 2007;64:1242–1250.

10. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12:426–445.

11. Falconer DS. *Introduction to Quantitative Genetics*. 3rd ed. Burnt Mill, Harlow, Essex, England 1989.

12. Klei L, Luca D, Devlin B, Roeder K. Pleiotropy and principal components of heritability combine to increase power for association analysis. *Genet Epidemiol*. 2008;32:9–19.

13. Klei L, Pollak EJ, Quaas RL. Genetic and environmental parameters associated with linearized type appraisal scores. *J Dairy Sci*. 1988;71:2744–2752.

14. Ott J, Rabinowitz D. A principal-components approach based on heritability for combining phenotype information. *Hum Hered*. 1999;49:106–111.

15. Gur RC, Ragland JD, Moberg PJ, et al. Computerized neuro-cognitive scanning: II. The profile of schizophrenia. *Neuropsychopharmacology*. 2001;25:777–788.

16. Box GEP, Cox DR. An analysis of transformations. *J R Stat Soc Series B Stat Methodol*. 1964;26:211–252.

17. Misztal I. Reliable computing in estimation of variance components. *J Anim Breed Genet*. 2008;125:363–370.

18. Wiener HW, Klei L, Irvin MD, et al. Linkage analysis of schizophrenia in African-American families. *Schizophr Res*. 2009;109:70–79.

19. Rinaldo A, Bacanu SA, Devlin B, Sonpar V, Wasserman L, Roeder K. Characterization of multilocus linkage disequilibrium. *Genet Epidemiol*. 2005;28:193–206.

20. Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin–rapid analysis of dense genetic maps using sparse gene flow trees. *Nat Genet*. 2002;30:97–101.

21. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet*. 1998;62:1198–1211.

22. Cannon M, Caspi A, Moffitt TE, et al. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry*. 2002;59:449–456.

23. Cannon TD, Bearden CE, Hollister JM, Rosso IM, Sanchez LE, Hadley T. Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull*. 2000;26:379–393.

24. Niendam TA, Bearden CE, Rosso IM, et al. A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am J Psychiatry*. 2003;160:2060–2062.

25. Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *Am J Psychiatry*. 2000;157:1416–1422. 1411: Docherty NM et al. A twin study of communication.[PMID: 10919696]Related Articles, Links.

26. Woodberry KA, Giuliano AJ, Seidman LJ. Premorbid IQ in schizophrenia: a meta-analytic review. *Am J Psychiatry*. 2008;165:579–587.

27. Gottesman I. *Schizophrenia Genesis: The Origins of Madness.* New York, NY: WH Freeman; 1991.

28. Consortium TIS. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*. 2008;455:237–241.

29. Mulle JG, Dodd AF, McGrath JA, et al. Microdeletions of 3q29 confer high risk for schizophrenia. *Am J Hum Genet*. 2010;87:229–236.

30. Stefansson H, Rujescu D, Cichon S, et al. Large recurrent microdeletions associated with schizophrenia. *Nature*. 2008;455:232–236.

31. McCarthy SE, Makarov V, Kirov G, et al. Microduplications of 16p11.2 are associated with schizophrenia. *Nat Genet*. 2009;41:1223–1227.

32. Bassett AS, Chow EW, Husted J, et al. Clinical features of 78 adults with 22q11 deletion syndrome. *Am J Med Genet A*. 2005;138:307–313.

33. Vassos E, Collier DA, Holden S, et al. Penetrance for copy number variants associated with schizophrenia. *Hum Mol Genet*. 2010;19:3477–3481.

34. Bittel DC, Kibiryeva N, Butler MG. Expression of 4 genes between chromosome 15 breakpoints 1 and 2 and behavioral outcomes in Prader-Willi syndrome. *Pediatrics*. 2006;118:e1276–e1283.

35. de Kovel CG, Trucks H, Helbig I, et al. Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain*. 2010;133(pt 1):23–32.

36. Doornbos M, Sikkema-Raddatz B, Ruijvenkamp CA, et al. Nine patients with a microdeletion 15q11.2 between breakpoints 1 and 2 of the Prader-Willi critical region, possibly associated with behavioural disturbances. *Eur J Med Genet*. 2009;52:108–115.

37. Walters JT, Corvin A, Owen MJ, et al. Psychosis susceptibility gene ZNF804A and cognitive performance in schizophrenia. *Arch Gen Psychiatry*. 2010;67:692–700.

38. Balog Z, Kiss I, Keri S. ZNF804A may be associated with executive control of attention. *Genes Brain Behav*. 2011;10:223–227.

39. Esslinger C, Kirsch P, Haddad L, et al. Cognitive state and connectivity effects of the genome-wide significant psychosis variant in ZNF804A. *Neuroimage*. 2011;54:2514–2523.

40. Hashimoto R, Ohi K, Yasuda Y, et al. The impact of a genome-wide supported psychosis variant in the ZNF804A gene on memory function in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B:1459–1464.