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Heritability Estimates for Cognitive Factors and Brain White Matter Integrity as Markers of Schizophrenia

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Abstract

Recent genetics research focusing on schizophrenia has led to candidate cognitive and neuroimaging variables as intermediate phenotypes or "endophenotype" markers for the illness. Among other stringent criteria, to be an endophenotype, a marker must demonstrate heritability. In an effort to explore the validity of a selection of cognitive and neuroimaging endophenotypes, the present study was designed to determine estimates of their heritability. One hundred fourteen subjects, including 27 with schizophrenia and 39 unaffected relatives from 23 multiplex schizophrenia families, participated in a comprehensive neuropsychological test battery and structural brain imaging with diffusion tensor imaging (DTI). Variables were selected if they previously have been demonstrated to show differences between people with schizophrenia and normal controls. Significant evidence of heritability was confirmed for overall cognitive function ("g"), as well as expressive and receptive language, verbal and visual memory, processing speed and cognitive inhibition. In addition, significant heritability estimates were determined for specific regions in the frontal, central, parietal, and occipital areas. These results suggest that the variables chosen may be useful endophenotypes for genetic and early detection studies, although further work with larger cohorts should be conducted to show that deficits in these functions and structures also segregate with schizophrenia within families and thus fully satisfy the definition of an endophenotype. In addition, other cognitive and neuroimaging variables that were not studied here may be candidates for schizophrenia endophenotypes.

Keywords

genetic; cognition; neuroimaging; DTI

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INTRODUCTION

The use of cognitive and brain imaging markers as endophenotypes for a range of psychiatric and neurological illnesses has become a popular concept in the recent literature, particularly with diagnoses determined to have a strong familial component, but no clear Mendelian inheritance. According to the definition offered by Gottesman and Gould [2003], in order to be considered a valid endophenotype, a variable must (1) be associated with illness in the population, (2) demonstrate heritability, (3) be state-independent (manifest whether or not an illness is active), (4) co-segregate with illness within families, and (5) be found in unaffected family members at a higher rate than the general population for complex illnesses. The latter is because expression of illness may not be complete in some family members, but also some unaffected relatives may still be at risk age-wise to develop a full blown illness. Estimating the heritability of candidate markers already shown to be associated with illness within populations is then the next step in determining their usefulness for future large scale genetic association studies and may also give clues to the biology of the disorder.

It is often difficult to determine the heritability of a trait due to the influence of environmental factors as well as the interaction between genes and environment. Despite this, twin and adoption studies have provided substantial evidence for the heritability of general cognitive function (“g”), particularly in healthy adults [McGue and Bouchard, 1998; Plomin and Craig, 2001]. Heritability estimates for specific cognitive skills are more variable, but there is evidence to support familial correlations for functions such as memory and language [Lee, 2003]. Likewise, structural imaging studies with healthy samples have generally concluded that “some genes [may therefore] have a general effect on the brain, while other genes may affect specific volumes [Glahn et al., 2007].” In addition, there is empirical support for the heritability of whole brain volume, corpus callosumsize, and gray and white matter volume in normal controls [Glahn et al., 2007].

The literature on heritability of white matter integrity, as measured using diffusion tensor imaging (DTI) is far more limited. Pfefferbaum et al. [2001] conducted a small DTI twin study in healthy elderly. They found that in the corpus callosum, the ratio of genetic to environmental effects ranged was up to 5:1 for the total corpus callosum, but varied from 3:1 in the splenium of the corpus callosum to 1:1 in the genu of the corpus callosum. In a recent twin study, Chiang et al. [2009] found high heritability of white matter integrity in bilateral frontal, bilateral parietal, and left occipital regions in a healthy sample. Moreover, white matter integrity was correlated with measures of IQ in multiple regions, suggesting a common mechanism for both domains in this sample.

Heritability has been demonstrated in attention-deficit hyperactivity disorder (ADHD), dementia, and autism, three clinical disorders that are defined strictly by cognitive and structural anomalies. These evidenced-based models offer a framework by which to study schizophrenia, a diagnosis that is defined by complex psychiatric, neuropsychological, and brain structural changes. Twin and family studies on ADHD, for instance, have indicated a strong genetic component to the disorder, with response inhibition proposed as a potential cognitive endophenotype [Aron and Poldrack, 2005; Banerjee et al., 2007]. Further associations have been made between several alleles on the DRD4 gene and other cognitive and personality traits that are characteristics of the disorder, including novelty seeking, in those with either the diagnosis or with the genotype for ADHD [Greenwood and Parasuraman, 2003]. Similarly, studies with Alzheimer’s disease (AD) patients have linked at least one allele on the APOE gene with both increased risk of developing AD and cognitive impairment even in adults who do not later develop the diagnosis. Although the research in this area has been limited, one study of adults with a specific APOE allele linked

the genotype to reduced performance on tasks of learning, memory, and attention span, which are hallmark features of the AD diagnosis [Greenwood and Parasuraman, 2003]. Finally, while research to identify biological markers for autism is still underway, it is known that the illness has a heritability of about 90% and is defined according to three core domains, including deficits in language development and reduced ability to empathize [Santangelo and Tsatsanis, 2005]. Family studies of autism have suggested similar cognitive deficits in unaffected first-degree relatives [Baron-Cohen, 2004].

In all three of the disorders described above (ADHD, AD, and autism), neuroimaging studies have revealed structural abnormalities in areas including the frontal and temporal lobes, the cerebellum, and in the hippocampus/limbic system in those with the phenotype and frequently in unaffected relatives [Glahn et al., 2007]. Based on familial patterns observed in both affected and unaffected relatives, a recent EEG study also supports the use of EEG anomalies as possible endophenotypes for ADHD[Loo and Smalle, 2008].

The search for endophenotypes becomes more intricate with a multifaceted neuropsychiatric illness such as schizophrenia. The process is complicated in this specific disorder by the fact that schizophrenia is a genetically complex illness, with patterns of incidence and inheritance that are better explained when an oligogenic (10 or less genes) or multifactorial (~100 genes)model is assumed, in which multiple genes interact with environmental stressors. A series of methodological issues, such as the study of different types of relatives (i.e., comparing siblings to parent-offspring dyads or larger multiplex families may cause greater variability in gene expression, age effects, etc.) and the interaction of environmental and genetic factors on psychopathology further complicate the process [Heydebrand, 2006]. A genetic predisposition for the illness has been established in the literature, and some candidate genes exist, although their replication is generally weak [e.g., dysbindin, DTNP1, neuregulin, NRG1, disrupted in schizophrenia, DISC1; reviewed in Owen et al., 2005]. While cognitive deficits are a known feature of the disorder, many studies have shown that these impairments also occur in unaffected relatives of people with schizophrenia [Hoff et al., 2005] and certainly cannot be specific for the illness. A recent meta-analysis documents that to date, candidate neuropsychological endophenotypes for schizophrenia include working memory, verbal memory, executive function, and attention [Heydebrand, 2006]. In addition, research suggests that deficits in backward visual span, delayed story recall, semantic verbal fluency, cognitive inhibition, and perceptual motor speed are more pronounced in multiplex schizophrenia families with a stronger familial influence of schizophrenia as compared to simplex family members [Heydebrand, 2006]. A recent genetics study also found that sensorimotor skill, verbal fluency, and spatial working memory demonstrate moderate familial correlations in multiplex schizophrenia families [Aukes et al., 2008]. Attention, verbal memory and working memory have been identified by the Consortium on the Genetics of Schizophrenia (COGS) as domains that both meet established criteria for endophenotypes and can provide clues to the underlying neurobiology of schizophrenia [Gur et al., 2007a].

For over two decades, increasingly sophisticated brain imaging techniques have supported that several brain structural anomalies are present in people with chronic schizophrenia in areas such as the lateral ventricles and frontal and medial temporal regions and there is some evidence that the variation in these structures is heritable [Reveley et al., 1982; DeLisi et al., 1986; van Haren et al., 2008]. In a twin study [Styner et al., 2005], found that the shape of the anterior and posterior lateral ventricles was under genetic influence in both patients with schizophrenia and healthy controls, suggesting that such influences are stronger for morphometry than for diseaserelated effects. Cannon et al. [2006] used a probabilistic atlas-based approach to examine heritability in twins and found genetic influences on gray matter density in patients with schizophrenia and in healthy controls. Finally, in a large twin study

on resting state functional connectivity, Smit et al. [2008] found that local and global regional interconnectedness, as well as “small-world” organization [Strogatz, 2001] (preponderance of short-distance with some long-distance connections)were heritable. These small-world networks are disrupted in schizophrenia [Liu et al., 2008]. A more comprehensive presentation of seminal studies investigating the heritability of neuroimaging and cognitive phenotypes across healthy and clinical samples is presented in Table I.

Within the cohort described in the current article, both individuals with schizophrenia and their unaffected relatives demonstrated abnormal white matter integrity in areas such as the left inferior frontal gyrus and left middle and superior temporal gyri, as well as the angular gyrus bilaterally [Hoptman et al., 2008]. Similarly, individuals with schizophrenia in the present cohort demonstrated impairment in verbal working memory and unaffected relatives had reductions in delayed visual memory [Bertisch et al., 2008]. Though there is cumulative evidence to support the existence of familial neuroimaging and cognitive patterns that can differentiate between patients, unaffected relatives, and controls, there is also a need to understand the extent of their heritability to determine the utility of these variables as proxies for schizophrenia in genetic studies, rather than the more heterogeneous clinical diagnosis itself. The aim of the present study was therefore to calculate heritability for cognitive factors and brain white matter integrity, variables already shown to differentiate people with schizophrenia from controls in both our current cohort and in other samples.

METHODS

Subjects

Families with members diagnosed with schizophrenia were recruited from a national registry as described elsewhere [detailed in DeLisi et al., 2006]. Any family member from age 12 through adulthood was eligible for participation (with parental/ guardian consent, as needed) and younger subjects were followed longitudinally as part of a parallel study of individuals at high genetic risk for developing the schizophrenia phenotype. Control sibling pairs ages 18 and over with no personal or family history of schizophrenia were also recruited. A total of 114 subjects from 47 families (including 23 multiplex schizophrenia families) ranging in age from 13 to 56 constituted the complete cohort. All subjects provided written informed consent and/or assent, completed the Diagnostic Interview for Genetics Studies [Nurnberger et al., 1994] and DTI scans and/or neuropsychological assessments. Table II provides a description of the pedigree structures and population distributions used for the final heritability analyses. Information from medical records from current or prior psychiatric treatments was used to assist in obtaining final diagnoses. Consensus diagnoses were established between two trained doctoral-level raters. Of the total N, 27 had a primary diagnosis of schizophrenia or schizoaffective disorder, 39 were family members without the phenotype and the remainder were healthy controls. Of the unaffected members from the schizophrenia families, 11 had diagnoses of a past or present mood disorder only, 1 had a diagnosis of a substance abuse disorder, 1 met full criteria for an Axis II Personality Disorder (Antisocial Personality Disorder), and 7 met criteria for a combination of these diagnoses. Any lifetime history of psychosis or brief intermittent psychotic symptoms would disqualify a family member from the “unaffected” group. One family member did not complete the diagnostic interview and was unavailable for follow-up. Five of the 27 participants with schizophrenia were on neuroleptic medications only at the time of the evaluation, 21 were taking other psychotropicmedications (i.e., antidepressants) either in addition to or instead of neuroleptics at the time of evaluation and none were on anticholinergic medication. Subjects from the complete cohort were included in the final heritability analyses if they had available cognitive test scores and/or DTI indices within each designated variable. This project received Institutional Review Board approval at both

New York University School of Medicine and at the Nathan Kline Institute for Psychiatric Research (NKI).

Assessments

Cognitive assessment

- *Wechsler Adult Intelligence Scale, Third Edition* [*WAIS-III*; Wechsler, 1997a]: Digit Span, Letter-Number Sequencing, Vocabulary, Similarities, Information, Block Design, and Matrix Reasoning subtests were selected based on the literature to capture a variety of attentional, verbal and visual cognitive skills in adult participants.
- *Wechsler Intelligence Scale for Children, Fourth Edition* [*WMS-IV*; Wechsler, 2003]: Parallel subtests from theWAIS-III were used to measure comparable skills in participants under age 16.
- *Wechsler Memory Scale, Third Edition* [*WMS-III*; Wechsler, 1997b]: Immediate and delayed recall indices from the Verbal Paired Associates and Visual Recognition subtests were used to measure verbal and visual-spatial memory in adult participants.
- *Children's Memory Scale* [*CMS*; Cohen, 1997]: Immediate and delayed recall indices from theWordPairs and Dots subtests were selected to measure comparable verbal and visual memory skills in participants under age 16.
- *The Wide Range Achievement Test, Third Edition* [*WRAT-III*; Wilkinson, 1993]: Scores from Reading, Arithmetic, and Spelling subtests reflect academic achievement in these areas.
- *California Verbal Learning Tests* [*CVLT*; DeLis et al., 1987, 1994]: Indices of short and long delayed free and cued recall, recognition, perseverative errors, and intrusions capture verbal memory on adult and child versions of these tests.
- *Boston Naming Test, Second Edition* [*BNT*; Kaplan et al., 1983]: A measure of expressive language in which participants are required to name a series of pictures of increasing difficulty.
- *Peabody Picture Vocabulary Test, Third Edition* [*PPVT*; Dunn and Dunn, 1997]: An index of receptive language in which subjects are identify a picture that best describes a word or concept spoken by the examiner.
- *Controlled Oral Word Association Test* [*COWA*; Spreen and Strauss, 1991]: A measure of verbal fluency in which participants are timed as they list words that begin with C, F, and L.
- *Stroop Color and Word Test* [Golden, 1978a,b]: A measure of executive function in which participants are asked to read a list of colors, words and then inhibit their responses to the text of the stimulus and respond only to the color. Interference scores are calculated based on the final response condition.
- *Trail Making Test* [Spreen and Strauss, 1991]: An index of mental flexibility, visual scanning, and motor speed in which participants are timed as they connect a series of numbers (part A) and then alternate between numbers and letters (part B).
- *Finger Tapping Test* [Reitan, 1969]: A measure of motor speed and dexterity. Subjects are timed as they tap a manual finger tapper on multiple trials per hand and average scores are calculated.

- *Purdue Pegboard Test* [Tiffin, 1968]: A measure of motor speed and dexterity in which participants are timed as they insert pegs into a pegboard using their dominant hand, non-dominant hand, both hands, and then construct assemblies. A laterality index was then calculated from the final scores.

Due to the large number of subtests within this extensive testing battery, a principal component analysis with varimax rotation was conducted in an effort to reduce the cognitive dataset into more condensed skill areas for supplementary heritability analysis. Eight independent factors reflecting (1) General IQ/"g," (2) Verbal Memory, (3) Attention/ Working Memory, (4) Visual Memory, (5) Motor Speed/Dexterity, (6) Inhibition (executive), (7) Laterality, and (8) Visual Motor skill were defined in this data set and incorporated into the heritability analysis.

Brain imaging

Image acquisition and processing: The DTI data reported herein are a subset of those in [Hoptman et al., 2008] to which the reader is referred for additional details. Briefly, image sequences acquired included: magnetization-prepared rapid gradient echo (MPRAGE) (TR/ TE=11.6/4.9 msec, flip angle=8°, 172 slices, 1.20mm slice thickness, 307mm FOV, 256 × 256 matrix, pixel size=1.20 × 1.20mm^2), dual spin echo (TR=5,000msec, TE=22/90msec, 24 slices, 5mm slice thickness, no gap, NEX=1, 256×256 matrix, flip angle=180°, 224mm FOV, pixel size=0.88 × 0.88mm^2), and diffusion-weighted images (TR=6,000msec, TE=100msec, 128 × 128 matrix, 320mm FOV, b-value=1,000 sec/mm^2, eight non-collinear gradient orientations, NEX=7, 19 slices, 5mm slice thickness, no gap, pixel size=2.5 × 2.5mm^2).

The b=0 images were corrected for susceptibility induced distortion and were transformed into Talairach space using methods described elsewhere [Ardekani et al., 2003]. MPRAGE images were registered to the b=0 images using the Automated Registration Toolbox (ART) [Ardekani et al., 1995]. The MPRAGE images were skull stripped using Freesurfer [Ségonne et al., 2004]. The MPRAGE was also registered to the dual echo images using ART. This transformation was applied to the skull stripped binary mask, which was then used to skull strip the dual echo images. The MPRAGE images were then registered to a template brain that had already been placed into Talairach space using ART. Next, the b=0 images were matched to the rawT2 weighted images and were corrected for distortion using ART. Finally, the distortion-corrected b=0 images were transformed into Talairach space. The same transformations were applied to the FA maps. Images had a final voxel size of 1 × 1 × 1 mm^3.

Following transformation into Talairach space, images were masked such that only voxels with data present for all participants were included in the analyses. This ensured that missing data, which would have zero values, would not drive voxelwise statistics. We created a white matter mask based on the average map computed from the normalized FA. This map was thresholded using a non-parametric histogram-based segmentation algorithm [Otsu, 1979]. The obtained white matter threshold was applied to the mean FA image, and the resulting white matter mask was used in the analysis of FA data. Only the voxels that were within this mask were analyzed.

Thresholding was done as described in [Hoptman et al., 2008], based the approach of Baudewig et al. [2003]. Briefly, clusters of 100 contiguous voxelwise were identified, each significant at $P<0.05$, with the further constraint that at least one voxel was significant at $P<0.001$. Thus, the variables used here were mean FA of white matter within each significant cluster identified in that article.

Statistical Analysis

The data used in the heritability analyses included individual subjects with schizophrenia, relatives without schizophrenia, and control sibling pairs. Table I shows the structure and the distribution of the cohort used in the analysis.

As a first step in data analysis, we performed preliminary analysis to obtain summary statistics and to check for outliers and distribution properties of the measured traits, examining the range (minimum–maximum), means, and standard deviations of the measured variables. The data were checked for errors, missing information, outliers, and distribution properties. Basic descriptive statistics were calculated to assess the baseline characteristics of the traits under study. The analyses were performed using the SAS statistical package [Version 8.2; SAS Institute, Inc., 2001]. Tables III and V provide summaries of the basic statistics for all variables included in the analysis. The tables present the number of individuals (N), range calculated as the minimum(min) and maximum (max) for the cognitive variables, and the mean and standard deviations (std) of individual traits/measured variables.

Heritability estimates were calculated using the maximum-likelihood variance components analysis implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) version 4.0.2 software package [Almasy and Blangero, 1998]. The program uses the pedigree covariance matrix to take into account all family relationships. Thus, in this analysis the pedigree matrix included information on affected and unaffected family members. The model decomposes the phenotypic variance into the genetic variance and the environmental variance, while accounting for the population and pedigree structure as follows;

$\mathbf{\Omega}=2\mathbf{\Phi}\sigma_g^2+\mathbf{I}\sigma_e^2$, where Ω is the covariance matrix derived from the family pedigree, Φ is the matrix of kinship values, σ_g^2 represents the additive genetic variance I is the identity matrix, and σ_e^2 is the random environmental variance [Almasy and Blangero, 1998]. Because this model allows for complex pedigree data beyond parent-offspring pairs (i.e., includes all family information from Table I), the resulting heritability estimates are more accurate than those obtained using only nuclear family members. For analysis, each variable was entered into a separate univariate model, so the covariance term represents the covariance between individuals in the sample, not between image traits. Heritability was estimated as the ratio of genetic variance to total phenotypic variance via a maximum likelihood method. All individuals in the sample were entered into the variance components models, although only those individuals belonging to pedigrees contributed to the calculation of the heritability. All variables were treated as continuous variables assuming a normal distribution or normal distribution approximation a critical assumption in use of maximum likelihood estimation [Cheverud et al., 1979; Konigsberg et al., 1993]. Estimates of heritability were adjusted for the effects of gender, age, and multiplicative adjustments the interaction of age and gender to account for any extreme differences in age, and were considered significant at $P<0.10$ level. The point-wise P values were corrected for multiple testing using the Benjamini and Hochberg [1995] False Discovery Rate (FDR). For each trait two analyses were performed, first with all covariates, if the covariate was not significant it was dropped from the model, then the polygenic model was maximized again to determine the variance caused by all remaining covariates. As stated earlier, uninformative data, such as missing information, incomplete pedigree on the measured variables could bias the results, and therefore were excluded from the analyses.

RESULTS

Table III provides the descriptive statistics for the cognitive data and Tables IV and V present the descriptive statistics for the imaging data and the maximum-likelihood heritability estimates and associated standard errors, respectively, for the cognitive and neuroimaging variables resulting from the variance components model. Heritabilities for the cognitive traits ranged from h^2=0.000 (no genetic component) to h^2=1.000 (complete genetic control of the trait). From the analysis, no variables showed a significant effect of age and only one variable showed a significant effect of sex (P<0.5) (Tables IV and V). Many traits showed high heritability, whereas other showed low to mediumestimates of heritability. Twenty-nine of the 67 total variables analyzed exhibited heritable variation. The standard errors (Std) of heritability were high, in some cases larger than estimates themselves, presumably reflecting the small sample size.

The heritable cognitive variables detected at the P≤0.05 level were Wechsler Vocabulary, Information, Similarities, Block Design, Digit Symbol, WRAT Reading, WRAT Arithmetic, CVLT Immediate Recall, CVLT Delayed Recall, Wechsler Verbal Pairs Immediate, Visual Memory Immediate, Visual Memory Delayed, Boston Naming, PPVT, Stroop Interference, Pegboard right hand raw score, Pegboard right hand percentile, Pegboard left hand raw score, Pegboard assemblies raw score, and Factors General Intelligence (“g”), Verbal Memory, Visual Memory, and Inhibition. With the exception of Pegboard right hand raw score where sex was also significant, age and gender did not account for a significant proportion of the variance for these variables.

Of the selected DTI white matter variables, FA in the left subgenual anterior cingulate, left cingulate gyrus, left lingual gyrus, right pericaudate region, and bilateral perilentiform regions demonstrated significant heritability.

DISCUSSION

In this study we provide maximum-likelihood heritability estimates for candidate cognitive and human brain white matter integrity. In addition, we have examined the effect of age and sex on estimates of heritability for the variables under study. Some of the variables have heritability values that differ significantly from a model of h^2=0, though several variables show heritability of 0.000. The high level of additive genetic variation for many of the selected variables in these data indicates that these traits could potentially be useful in the study of schizophrenia, because such research relies on the assumption that these traits are at least partially heritable. Our findings strongly support the heritability of overall cognitive function (“g”), as well as specific abilities such as expressive and receptive language, verbal and visual memory, perceptual motor skill, processing speed and cognitive inhibition in families with schizophrenia. These factors have been documented in previous studies, including from the present cohort, to discriminate between members of schizophrenia families and controls [McGue and Bouchard, 1998; Plomin and Craig, 2001; Heydebrand, 2006; Bertisch et al., 2008]. As heritability is integral to the definition of endophenotype, the present study also provides direct support for the use of these variables as endophenotypes for schizophrenia.

We have specifically focused the brain imaging markers in this study on white matter integrity. It has recently been recognized by several investigators that the integrity of white matter in several brain regions is reduced in people with chronic schizophrenia [Kubicki et al., 2005; Kanaan et al., 2006; Ellison-Wright and Bullmore, 2009]. FA was heritable in left frontal, parietal, and occipital regions, and bilateral central regions. Our results are therefore generally consistent with those of Chiang et al. [2009] in showing heritability of white

matter integrity. White matter pathways that are distributed between frontal and temporal cortex have been particularly of interest to many investigators as possible regions for abnormalities during development that could make individuals more vulnerable to schizophrenia. Despite the limitations of a relatively small number of families studied and the potential effect medication may have had on themeasurements that could mask baseline heritability, the present study and our past analyses [Hoptman et al., 2008] in people at high genetic risk for schizophrenia and within the age of risk are consistent with this notion. We thus conclude that white matter integrity, at least as detected by DTI, may provide a good quantitative marker for the genetic basis of schizophrenia. This does not rule out that other measurements of white matter pathway organization or other brain measurements from MRI may also reflect valid schizophrenia endophenotypes. Moreover, a voxelwise analysis of heritability, as was done by Chiang et al. [2009] might be useful. Nevertheless, the finding of genetic influences on FA in the current set of regions of interest again provide support for the use of these variables as endophenotypes for schizophrenia.

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TABLE I

Major Heritability Studies on Neuroimaging and Cognitive Phenotypes

Author and Year	N	Conclusions
Neuroimaging		
Goldman et al. [2009]	503	Risch-lambda analysis revealed widespread evidence for heritability of cortical thickness reduction throughout the brain in a schizophrenia sample
Chiang et al. [2009]	92	White matter integrity significantly heritable in bilateral frontal, bilateral parietal and left occipital lo be in a study of healthy identical and fraternal twins
Goldman et al. [2008]	573	Risch-lambda analysis detected significant evidence of heritability of reduced cortical volume and moderate evidence for hippocampal volume in schizophrenia families
Lenroot et al. [2007]	600	Statistically significant genetic effects in areas including the frontal pole, dorsolateral and orbital prefrontal cortices, prefrontal gyrus, angular and superior temporal gyri and the superior parietal region in healthy twins, twin siblings and singletons
Baare et al. [2001]	258	Structural equation modeling in twin pairs and singleton siblings revealed a statistically significant proportion of genetic variance in whole brain and gray and white matter volume
Cognitive		
Aukes et al. [2008]	180	Heritability detected in sensorimotor gating, openness, verbal fluency, early visual perception and spatial working memory in 25 multiplex schizophrenia families
Giubilei et al. [2008]	186	Moderate to high heritability estimates in fluency, verbal memory and attention as well as genetic contribution of attention and praxic abilities in senior healthy twin pairs
Rommelse et al. [2008]	826	Significant correlations between ADHD and control sibling sets revealed that neuropsychological tests of motor inhibition, cognitive flexibility, time reproduction, and motor timing are heritable
Antila et al. [2007]	110	Significant additive heritabilities detected in verbal function, processing speed and executive functioning in families with bipolar disorder
Greenwood et al. [2007]	—	Significant heritability detected for domains including abstraction/flexibility, memory, spatial processing, dexterity, recognition and attention in 183 nuclear families with a schizophrenia proband.
Gur et al. [2007b]	503	Significant heritability estimates obtained for memory, spatial processing, emotional processing, abstraction/flexibility, attention and sensorimotor processing in multiplex schizophrenia families and healthy controls
Kremen et al. [2007]	690	Detected significant genetic variance for word recognition, working memory and reading span in a sample of 345 healthy male twin pairs

While studies differ in terms of methods used to calculate heritable effects, significance is generally defined as $P<0.05$.

TABLE II

Population Distribution and Pedigree Structure Used for Estimates of Heritability

Demographic	**N**
(A) Population distribution	
Male	53
Female	61
Founder	1
Non-founder	113
Total	114
Pair	**N**
(B) Pedigree structure	
Parent-offspring	15
Siblings	67
Grandparent-grandchild	4
Uncle/niece-nephew	14
Half-siblings	1
1st cousins	4

TABLE III

Summary of Basic Statistics for Cognitive Data (Number of Observations, Means, Range, Standard Deviations) for Variables Used in Estimating Heritability

Traits	N	Mean	Lower	Upper	SD
Vocabulary	85	12.2286	3	18	3.5157
Similarities	85	11.2522	4	17	3.1088
Information	85	11.4024	3	17	2.9406
Block Design	69	11.3733	4	17	2.8653
Matrix Reasoning	86	11.8980	4	17	2.9468
Digits Forward	85	7.1420	4	17	1.6878
Digits Back	85	5.3882	3	8	1.5973
Digit Span	85	11.1059	2	19	3.3573
LN Sequencing	84	11.0598	2	19	3.3642
Digit Symbol	72	9.4246	3	18	3.1353
WRAT Spell	86	100.6674	11	127	15.9253
WRAT Arithmetic	86	98.0516	60	129	14.4246
WRAT Reading	85	105.1743	72	122	11.3159
CVLT lists 1–5 Total	86	40.6794	5	69	17.7256
CVLT Immediate	86	−0.8439	−5	2	1.7609
CVLT Delayed	86	−1.0161	−5	2	1.6937
CVLT Recognition	86	−1.6002	−5	1	1.6851
Verbal Pairs Immediate	84	10.2687	2	16	3.1652
Verbal Pairs Delayed	84	10.3353	2	17	3.0401
Visual Memory Immediate	83	64.6177	1	99	33.2708
Visual Memory Delayed	82	60.6501	1	99	35.6279
Boston Naming	83	54.5596	26	62	6.8462
PPVT	85	103.4735	7	147	17.5183
COWA Total	84	41.2784	21	70	11.0855
Stroop Interference	80	49.4343	20	80	10.9628
Trails A Raw	85	33.4127	15	76	11.7666
Trails A Percentile	59	44.2373	1	95	26.2763
Trails B Raw	81	77.8950	31	279	39.4744

Traits	N	Mean	Lower	Upper	SD
Trails B Percentile	53	45.1346	1	99	28.1921
Tapping Dominant Raw	82	44.0870	18.8	59.4	7.9763
Tapping Dominant Percentile	69	23.4898	0	93	25.2260
Tapping Non-Dominant Raw	79	40.8338	19.8	58	7.6318
Tapping Non-Dominant Percentile	69	31.2148	1	95	27.9688
Pegboard Right Raw	89	13.5976	9.33	20	1.9869
Pegboard Right Percentile	75	5.3034	1	70	13.0094
Pegboard left raw	90	13.2429	5.66	19.33	2.1865
Pegboard both Raw	89	11.3410	3.67	20	2.3659
Pegboard both Percentile	73	8.9888	1	76	13.5467
Pegboard Assemblies Raw	87	6.1305	−3	43	12.7476
Laterality Index	87	0.0275	−0.16	0.36	0.0671
Factor 1: “g”	48	0.0921	−2.33137	1.62945	0.9324
Factor 2: Verbal Memory	48	0.0663	−2.6121	1.98963	1.0003
Factor 3: WM	48	−0.0271	−2.34527	1.79213	0.9525
Factor 4: Visual Memory	48	0.0175	−4.22581	1.5986	0.9990
Factor 5: Speed	48	−0.0631	−2.79028	2.65622	1.0152
Factor 6: Inhibition	48	−0.3517	−2.02255	1.6558	0.8491
Factor 7: Laterality	48	−0.0707	−1.83839	3.78296	0.9203
Factor 8: Motor	48	0.0888	−1.45331	3.69351	0.9400

TABLE IV

Heritability Estimates for Cognitive Data

Traits	N	Heritability estimate	Std. error	*P*	Age	Sex	Age × sex
Vocabulary	85	0.7827	0.258	0.016*	0.983	0.864	0.987
Similarities	85	0.8969	0.2215	0.012*	0.983	0.761	0.958
Information	85	0.9367	0.2553	0.012*	0.999	0.628	0.987
Block Design	69	0.7314	0.3039	0.035*	0.983	0.478	0.888
Matrix Reasoning	86	0.1531	0.3487	0.470	0.999	0.864	0.888
Digits Forward	85	0	—	0.500	0.983	0.628	0.888
Digits Back	85	0	—	0.500	0.921	0.817	0.888
Digit Span	85	0	—	0.500	0.999	0.864	0.981
LN Sequencing	84	0.0073	0.3224	0.500	0.983	0.817	0.888
Digit Symbol	72	0.8749	0.2442	0.012*	0.999	0.874	0.958
WRAT Reading	85	0.5879	0.2571	0.035*	0.999	0.864	0.888
WRAT Spelling	86	0.6056	0.4786	0.230	0.282	0.478	0.888
WRAT Arithmetic	86	0.7924	0.3071	0.035*	0.999	0.864	0.958
CVLT 1–5 Total	86	0.3542	0.2482	0.124	0.999	0.864	0.992
CVLT Immediate	86	0.4971	0.2541	0.043*	0.999	0.817	0.968
CVLT Delayed	86	0.7301	0.2653	0.019*	0.999	0.668	0.888
CVLT Recognition	86	0.2465	0.2849	0.296	0.999	0.478	0.968
Verbal Pairs Immediate	84	0.6171	0.2728	0.031*	0.999	0.864	0.958
Verbal Pairs Delayed	84	0.3830	0.2475	0.104	0.983	0.801	0.968
Visual Memory Immediate	83	0.7402	0.2671	0.019*	0.999	0.817	0.888
Visual Memory Delayed	82	0.5877	0.2652	0.035*	0.983	0.973	0.888
Boston Naming	83	0.7900	0.2760	0.019*	0.983	0.864	0.888
PPVT	85	0.8299	0.2661	0.016*	0.999	0.628	0.958
COWA Total	84	0.1734	0.2773	0.391	0.983	0.864	0.888
Stroop Interference	81	0.7453	0.3003	0.035*	0.983	0.618	0.888
Trails A Raw	85	0.3732	0.2710	0.130	0.983	0.864	0.987

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Traits	N	Heritability estimate	Std. error	*P*	Age	Sex	Age × sex
Trails A Percentile	59	0	0.3437	0.500	0.999	0.550	0.958
Trails B Raw	81	0	—	0.500	0.983	0.864	0.958
Trails B Percentile	53	0.2335	0.4915	0.466	0.999	0.864	0.981
Tapping Dominant Raw	82	0.0662	0.1954	0.470	0.282	0.628	0.888
Tapping Dominant Percentile	69	0	—	0.500	0.517	0.511	0.888
Tapping Non-Dominant Raw	79	0.0142	0.1905	0.500	0.999	0.550	0.888
Tapping Non-Dominant Percentile	69	0.0162	0.2819	0.500	0.983	0.817	0.888
Pegboard Right Raw	89	0.7349	0.2704	0.019*	0.983	0.047*	0.968
Pegboard Right Percentile	75	0.7260	0.2617	0.026*	0.983	0.118	0.987
Pegboard Left Raw	90	0.4721	0.2397	0.043*	0.983	0.478	0.958
Pegboard both Raw	89	0.3473	0.2578	0.131	0.999	0.603	0.888
Pegboard Assemblies Raw	87	1	—	0.012*	0.999	0.864	0.888
Laterality	87	0	—	0.500	0.999	0.674	0.888
Factor 1: “g”	48	0.9826	0.3642	0.035*	0.999	0.723	0.888
Factor 2: Verbal Memory	48	0.8085	0.3439	0.035*	0.999	0.817	0.888
Factor 3: WM	48	0.1364	0.3662	0.470	0.999	0.864	0.888
Factor 4: Visual Memory	48	1	—	0.035*	0.999	0.864	0.888
Factor 5: Speed	48	0.1025	0.295	0.470	0.983	0.894	0.888
Factor 6: Inhibition	48	1	—	0.040*	0.999	0.511	0.888
Factor 7: Laterality	48	0	—	0.500	0.501	0.663	0.888
Factor 8: Motor	48	0.3401	0.3739	0.274	0.983	0.577	0.958

*$P<0.05$.

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TABLE V

Summary of Basic Statistics (Means, Standard Deviations) and Heritability Estimates for Neuroimaging Data

Anatomical region	Mean FA (SD)	Heritability	Std. error	*P*	Age	Sex	Age × sex
Frontal							
L subgenual anterior cingulate	0.51 (0.07)	0.71	0.31	0.040*	0.300	0.754	0.896
R deep frontal white matter	0.33 (0.04)	0.34	0.33	0.172	0.611	0.842	0.892
R middle/superior gyrus	0.30 (0.04)	0.00	—	0.500	0.611	0.352	0.892
L inferior frontal gyrus	0.37 (0.07)	0.58	0.32	0.068	0.611	0.842	0.892
Temporal							
L middle temporal gyrus	0.34 (0.04)	0.60	0.31	0.064	0.300	0.352	0.892
L BA 13/22/superior temporal gyrus	0.36 (0.06)	0.85	0.36	0.058	0.871	0.808	0.892
Parietal							
L posterior cingulate/precuneus	0.36 (0.05)	0.73	0.33	0.051	0.300	0.808	0.800
L angular gyrus	0.36 (0.08)	0.50	0.30	0.064	0.300	0.655	0.896
R precuneus/angular gyrus	0.32 (0.09)	0.54	0.36	0.096	0.984	0.363	0.896
L cingulate gyrus	0.37 (0.05)	1.00	—	0.010*	0.472	0.465	0.896
L cingulate gyrus/BA 31	0.46 (0.04)	0.32	0.40	0.240	0.983	0.352	0.892
Occipital							
L middle occcipital gyrus/ILF	0.38 (0.06)	0.59	0.33	0.074	0.611	0.842	0.896
L lingual gyrus	0.30 (0.08)	0.86	0.27	0.010*	0.871	0.352	0.892
Central							
R pericaudate region	0.39 (0.05)	0.84	0.30	0.025*	0.871	0.372	0.892
L insula/BA 13	0.33 (0.05)	0.78	0.35	0.064	0.611	0.363	0.896
L PLIC	0.58 (0.04)	0.00	—	0.500	0.871	0.372	0.892
L perilentiform region	0.47 (0.04)	0.82	0.31	0.040*	0.567	0.808	0.896
R perilentiform region	0.40 (0.04)	0.85	0.29	0.013*	0.611	0.352	0.892
R anterior commissure	0.30 (0.04)	0.37	0.28	0.100	0.611	0.372	0.896
Brainstem							
B dorsal pontine tegmentum	0.46 (0.04)	0.52	0.45	0.172	0.611	0.577	0.896

Location is centroid of cluster, L, left; R, right; B, bilateral; BA, Brodmann area; h2r, heritability estimate; ILF, inferior longitudinal fasciculus; PLIC, posterior limb of internal capsule.