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Heritability of Neurocognitive Traits in Familial Schizophrenia

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Abstract

Neurocognitive deficits are considered promising endophenotypes for gene discovery in schizophrenia. Understanding the heritability and genetic inter-relationships of neurocognitive traits could support their use as alternatives to diagnosis. Participants were 85 adults from 17 multiplex Canadian families with familial schizophrenia linked to 1q23 who had neurocognitive testing results available. Heritability of 13 standard measures assessing motor skills, processing speed, verbal, and visuospatial memory, attention/working memory, executive functioning, and IQ was estimated using variance component models and SOLAR software. We then investigated bivariate relationships between those variables found to be heritable. IQ showed the highest heritability ($h^2 = 0.64\text{--}0.74$) and seven other neurocognitive measures, reflecting immediate and delayed verbal memory, attention/working memory, delayed visual memory, processing speed and motor skills, showed significant heritability ($h^2 = 0.31\text{--}0.62$) under one or more of the models assessed. A schizophrenia diagnostic covariate was significant ($P < 0.0001$) for all heritable variables. Bivariate analyses suggested that memory-IQ and visuomotor-processing speed formed two groups of heritable traits. The results provide further evidence of the heritability of selected neurocognitive measures, and their relationship to schizophrenia and underlying genetic architecture. Composite measures of memory or processing speed may be heritable phenotypes useful for studies of neurocognition.

Keywords

heritability; schizophrenia; genetics; chromosome 1q23; memory; visuospatial; processing speed

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INTRODUCTION

Schizophrenia is a complex disorder characterized by both clinical and genetic heterogeneity. Researchers have employed various strategies to attempt to minimize this heterogeneity. One such approach for gene discovery proposes using quantitative neurobiological traits as intermediate phenotypes (“endophenotypes”) instead of the diagnosis of schizophrenia. This strategy has the potential to reduce clinical and genetic heterogeneity by identifying alternative phenotypes that better reflect underlying genetic vulnerability than does diagnostic categorization [Egan et al., 2001; Gottesman and Gould, 2003].

One promising neurobiological phenotype for genetic studies is neurocognitive dysfunction, long considered a core component of schizophrenia [Heinrichs and Zakzanis, 1998; Chow et al., 2002; Gur et al., 2007a]. There is substantial evidence [Posthuma et al., 2002; Polderman et al., 2006] suggesting that most cognitive abilities have a genetic basis. Twin studies have shown that performance on selected cognitive tasks was more strongly correlated within monozygotic than within dizygotic twin pairs, in both control and schizophrenic twin samples [Cannon et al., 1990; Goldberg et al., 1990]. Also, some family studies have found higher rates of cognitive impairment in unaffected biological relatives of individuals with schizophrenia than in the general population [Snitz et al., 2006].

Several neurocognitive endophenotypes have been proposed, but to have utility for genetic analysis, these must be heritable traits [Greenwood et al., 2007]. Six studies have provided formal heritability estimates for neurocognitive endophenotypes, using heterogeneous samples of schizophrenia and various candidate measures [Tuulio-Henriksson et al., 2002; Glahn et al., 2007; Greenwood et al., 2007; Gur et al., 2007a,b; Touloupoulou et al., 2007]. The results suggest that elevated familial risk for schizophrenia is accompanied by greater impairments in verbal memory, attention, working memory, and perceptual-motor speed [Hoff et al., 2005; Gur et al., 2007a,b]. The most recent study [Greenwood et al., 2007] also reported on the genetic inter-relationships between neurocognitive tests, observing significant genetic correlations between many of the measures used. Based on the observation that the candidate endophenotypes were not 100% coheritable, the authors suggested there may be genetic subtypes of schizophrenia with different endophenotypic profiles [Greenwood et al., 2007]. Schork et al. [2007] also noted that a key issue in the analysis of multiple endophenotypes involves pleiotropy and the detection of sets of endophenotypes that are likely influenced by the same sets of genetic abnormalities.

The primary aim of this study was to characterize the heritable neurocognitive profile in an inherited form of schizophrenia shown to have enhanced etiologic homogeneity. The sample comprised of members of multiply affected families, demonstrating highly significant linkage of narrowly defined schizophrenia (schizophrenia or chronic schizoaffective disorder) to a 1q22–q23 locus and significant association to the NOS1AP gene [Brzustowicz et al., 2000, 2004]. We estimated the heritabilities of neurocognitive traits previously shown to be associated with genetic liability in schizophrenia: motor skills, processing speed, learning and memory, attention and working memory, and executive tasks of abstraction, and mental flexibility [Cannon et al., 1994; Faraone et al., 2000; Asarnow et al., 2002; Brewer et

al., 2003; Hoff et al., 2005; Gur et al., 2007a]. We then conducted an exploratory investigation of the genetic inter-relationships between the individual tests that were found to be significantly heritable.

METHODS

Participants

Subjects were adults from 17 to 25 Canadian families ascertained as part of an ongoing study of familial schizophrenia and demonstrating highly significant evidence for genetic linkage of narrowly defined schizophrenia (schizophrenia or chronic schizoaffective disorder) to a locus on chromosome 1q22–q23 and association to the NOS1AP gene [Brzustowicz et al., 2000, 2004]. Subject ascertainment and assessment methods are detailed elsewhere [Bassett et al., 1994; Brzustowicz et al., 2000, 2004]. Briefly, pedigrees were recruited if schizophrenia appeared to be segregating in an autosomal dominant-like manner and selected if multiple affected and unaffected relatives would participate. Participating subjects were assessed by a psychiatrist using the Structured Clinical Interview for DSM-III-R (SCID-I). Collateral information, including extensive family history and medical records where available, was also collected. After a review of all available information, lifetime DSM-III-R diagnoses were assigned. Ethics approval was granted by the University of Toronto and Centre for Addiction and Mental Health Ethics Review Board, and subjects provided written informed consent to participate in the study.

For the current study, we excluded family members with IQ <65 or with a history of dementia, stroke or severe head injury, and those aged >65 years. We included 85 participants for whom neurocognitive data were available and who were affected with narrowly defined schizophrenia or were first-degree relatives of affected subjects. First-degree relatives were siblings (n =48), offspring (n =2), or parents (n =1) of affected individuals from 25 siblines, including four 2-generation siblines, of 17 families. We studied 34 subjects with narrowly defined schizophrenia and 44 subjects with broadly defined schizophrenia, comprising those with narrowly defined schizophrenia (n =34) and those with schizophrenia-spectrum disorders (i.e., non-affective psychotic disorder, schizotypal or paranoid personality disorder) (n =10) [Brzustowicz et al., 2000, 2004]. The unaffected group (n =41) comprised subjects who met neither narrow nor broad criteria for schizophrenia. There were 28 siblings of affected subjects who met inclusion criteria for the current study, but for whom neurocognitive data were unavailable. Of the 28, 17 (10 males and 7 females) were unaffected; 7 (2 males and 5 females) had narrowly defined schizophrenia and 4 males had schizophrenia spectrum disorder. Data were unavailable mainly due to logistical reasons (e.g., geographical distance), clinical instability or refusal to participate in the study. There was no difference in mean age at the time of neurocognitive assessment between study participants and their non-participating siblings. However, unaffected non-participants were more likely to be male (59%) than unaffected participants (37%).

Neuropsychological Measures

Affected and unaffected family members were assessed by trained psychometrists using standardized tests to obtain Wechsler Adult Intelligence Scale, third edition (WAIS-III) full-scale IQ [Wechsler, 1997a] and 12 other measures chosen based on prior studies indicating their association with familial loading or genetic liability in schizophrenia [Cannon et al., 1994; Faraone et al., 2000; Asarnow et al., 2002; Brewer et al., 2003; Hoff et al., 2005; Gur et al., 2007a]. The measures were assigned to one of the following five groups: (1) motor skills (bilateral Purdue Pegboard) [Tiffin, 1968]; (2) processing speed (Digit Symbol [Wechsler, 1997a], Trails A and B [Reitan, 1955]); (3) learning and memory (Rey Auditory Verbal Learning Test (RAVLT) 5-trial total recall [Rey, 1958], Wechsler Memory Scale, third edition (WMS-III) Logical Memory I (immediate) and II (delayed) recall [Wechsler, 1997b], WMS-III Visual Reproduction I (immediate) and II (delayed) recall [Wechsler, 1997b]), (4) attention and working memory (Digit Span [Wechsler, 1997a]), and (5) executive tasks of abstraction and mental flexibility (Wisconsin Card Sorting Test (WCST) abstraction and preservative error scores [Heaton et al., 1993]). At the time of testing affected participants with psychotic illness were clinically stable on standard antipsychotic medications.

Analyses

Descriptive statistics were used to both characterize the study sample and describe distribution properties of neurocognitive measures. Comparisons of neurocognitive profile between affected and unaffected groups used generalized estimating equation (GEE) models to account for familial clustering [Horton and Lipsitz, 1999; Hanley et al., 2003]. For the neurocognitive test variables, raw scores were converted to *Z*-scores using available age, sex, and education level adjusted published norms [Heaton et al., 1991; Wechsler, 1997a,b; Spreen and Strauss, 1998]. We used *Z*-score standardization, which maintains the shape of the distribution of the data, to facilitate interpretation of the results and comparison of the neurocognitive profiles with those of normative samples and other samples including general population schizophrenia [Heaton et al., 1991; Chow et al., 2006].

To estimate heritability of the neurocognitive measures, we used Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package. Heritability (h^2) was estimated as the ratio of the variance of the individual measure explained by additive polygenic effects to the total variance for the individual measure. Neurocognitive measures with stronger covariance between genetically more similar individuals than between genetically less similar individuals have higher heritability estimates [Glahn et al., 2007]. In the univariate heritability analyses, each neurocognitive test *Z*-score was used as a single dependent variable in the SOLAR models. Several covariates were considered for inclusion in these models. Using demographic variables already accounted for in *Z*-scores as covariates in the heritability analyses could have resulted in over-correction and decreased power. Since all test *Z*-scores were adjusted for age, it was unnecessary to fit age as a covariate in the SOLAR models. Sex was used as a covariate in all univariate SOLAR models, with the exception of those for Purdue Pegboard and Trails A and B where test *Z*-scores adjusted for both sex and age. Univariate heritability estimates were computed for three models (Table

III). Model 1 included a single covariate, sex; model 2 included narrow diagnosis of schizophrenia and sex; and model 3 included WAIS-III full-scale IQ and sex as covariates.

Model 2 allowed us to identify neurocognitive measures that showed significant heritability (h^2) after accounting for the effects of a narrow diagnosis of schizophrenia. Such measures will be those most relevant to the genetic susceptibility component of the schizophrenia vulnerability within the families. For this model, we assumed that the diagnosis of schizophrenia shifted the values of the neurocognitive scores upwards or downwards, but did not substantially alter their distribution. To test this assumption, we examined the variances among affected individuals (both narrow and broad definitions of schizophrenia) and among unaffected relatives. Overall, the schizophrenia group tended to have a somewhat greater variance for the individual measures than the unaffected group, but the observed differences were in general not statistically different. We were therefore sufficiently confident that the diagnosis of schizophrenia did not affect the distribution of neurocognitive measures enough to invalidate the assumptions of the random effect SOLAR models. Model 3 allowed us to examine heritability of the 12-neurocognitive measures, while controlling for general cognitive ability.

The univariate heritability analyses did not correct for multiple testing. Others have argued that the appropriate correction for multiple testing is unknown and may be unnecessary [Greenwood et al., 2007]. Because there are no heritability estimates for neurocognitive measures in a sample of this kind and size, we felt that preliminary data need to be presented in full without censoring results due to any multiple comparisons.

The univariate heritability analyses were followed by exploratory bivariate analyses among the subset of neurocognitive variables that demonstrated significant heritability in at least one univariate model. This is similar to the approach taken by Greenwood et al. [2007]. Two neurocognitive measures were fitted together as bivariate dependent variables in the bivariate SOLAR models. Our primary aim of these exploratory analyses was to further characterize this inherited form of schizophrenia. Thus, all bivariate models used narrow schizophrenia diagnosis and sex (where applicable) as covariates. We were primarily interested in estimating the correlations (and their standard errors) between the variance components of heritability for each pair of neurocognitive variables. This would allow us to assess whether two traits tended to be co-inherited. We attempted multivariate models but opted for bivariate analyses due to computational constraints. Also, bivariate analyses reduce the difficulty of obtaining adequate sample sizes with complete data as the number of measures increases. We present the standard errors for these exploratory bivariate analyses of inheritance patterns. *P*-values are estimated but should be interpreted cautiously due to the limited sample size.

RESULTS

Sample Characteristics

Table I shows the demographic and clinical characteristics for the study sample by diagnostic group. Overall, the sample was through the peak period of risk for schizophrenia. In the narrowly defined schizophrenia group, the mean age at onset was 24.1 (SD =6.7)

years and mean illness duration was 28.0 (SD =9.8) years. As expected, subjects in the narrowly defined schizophrenia group on average had less formal education and lower IQ than those in the unaffected group. A similar pattern of findings was observed between the broadly defined schizophrenia group and unaffected group.

Neurocognitive Performance

The distribution of individual neurocognitive test Z -scores by diagnostic group is presented in Table II. The narrowly defined schizophrenia group showed significant impairment on measures of motor skills, processing speed, and learning and memory. Performance on attention/working memory and executive tasks was better preserved. Results were similar for the broadly defined schizophrenia group, except performance on learning and memory tests was less impaired. In the unaffected group, Z -scores indicated sub-average motor skills but performance on remaining test variables was relatively intact.

Performance was significantly poorer in the narrowly defined schizophrenia group than the unaffected group on all tests, with the exception that there was no statistically significant difference on WCST categories between the two groups. The results of the comparison between the broadly defined schizophrenia and unaffected groups were similar; however, neither WCST categories nor perseverative errors significantly differed between the two groups (data not shown).

Univariate Heritability Estimates for Neurocognitive Variables

Table III shows univariate heritability estimates for the 12-neuro-cognitive test Z -scores measures and for WAIS-III full-scale IQ. In model 1, sex was entered as covariate in each univariate SOLAR analyses, with the exception of models for Purdue Pegboard, Trails A and B, where Z -scores were adjusted for both age and sex. The heritability estimate was substantial for WAIS-III full-scale IQ ($h^2 = 0.735$; $P = 0.0001$), moderate for Purdue Pegboard, Digit Span and WMS-III Logical Memory I ($h^2 = 0.385$ – 0.487 ; $P < 0.05$), and at the trend level for WMS-III Logical Memory II and WMS-III Visual Reproduction I and II. The remaining four measures were not significantly heritable under all three models in this sample.

In model 2, where h^2 was adjusted for the presence of narrowly defined schizophrenia and sex, the results were similar to those for model 1. The effect of the diagnostic covariate was highly significant ($P < 0.0001$) in all univariate SOLAR analyses for variables that provided evidence of heritability (data not shown), indicating that even though the diagnosis of narrowly defined schizophrenia strongly influenced the scores, heritability was still detectable. We repeated these analyses adjusting for the presence of broadly defined schizophrenia (data not shown). The results were similar; with the exception that the heritability estimate of WMS-III Visual Reproduction I increased ($h^2 = 0.275$), coming into the significant range ($P = 0.045$).

The results for model 3 were notably different from those in models 1 and 2. Heritability estimates adjusted for full-scale IQ and sex showed increases for Purdue Pegboard, Digit Symbol, WMS-III Visual Reproduction II and Trails B ($h^2 = 0.493$ – 0.621). On the other hand, h^2 decreased for Digit Span and WMS-III Logical Memory I and II.

Bivariate Heritability Estimates

The exploratory bivariate SOLAR analyses used the 8-neurocognitive variables that demonstrated significant heritability in one of the three-univariate models, including IQ. All bivariate models included sex and narrow diagnosis of schizophrenia as covariates. Table IV shows the genetic correlations between each pair of variables, and Figure 1 presents a summary diagram of only those bivariate correlations that exceeded the value of their standard error. Purdue Pegboard, Digit Symbol, and Trails B formed one correlated group of measures. This group was negatively correlated with immediate and delayed verbal learning and memory (WMS-III Logical Memory I and II), which in turn were positively correlated with WAIS-III full scale IQ and Digit Span, thus forming a second group of traits. The genetic correlations between IQ and WMS-III Logical Memory tests I and II and Digit Span were extremely high (0.84–1.00). This helped to explain why h^2 estimates for Digit Span and WMS-III Logical Memory I and II decreased in model 3 of the univariate analyses where IQ was included as a covariate.

Measures of immediate and delayed visual learning and memory (WMS-III Visual Reproduction I and II, respectively) were positively correlated with each other and with measures in both the first and second group. The pattern of results suggests that memory-IQ and visuomotor-processing speed form two groups of heritable traits. The higher standard errors of bivariate results for Digit Symbol and Visual Reproduction II (see Table IV) indicate these measures may be less important components of the visuomotor processing speed group. In general, the results for bivariate SOLAR models with broadly defined schizophrenia were similar to those based on the narrow diagnosis.

DISCUSSION

To our knowledge this is the first study to characterize the heritable neurocognitive profile in a known inherited form of familial schizophrenia [Brzustowicz et al., 2000, 2004]. The use of standard neurocognitive tests along with the computation of Z -scores based on published norms allow us to compare our sample's neurocognitive profile with that observed in general population schizophrenia. The cognitive functions showing the greatest differences between the affected and unaffected family members were among those most consistently reported for general population schizophrenia [Heinrichs and Zakzanis, 1998; Hoff and Kremen, 2003]: motor skill, processing speed, and learning and memory.

We estimated heritability for 12-neurocognitive measures and found significant heritability for five measures reflecting immediate and delayed verbal memory, attention/working memory and motor skills, and to a lesser degree delayed visual memory. The magnitude of these heritability estimates was moderate, with estimates ranging from 0.308 to 0.480. All five measures that demonstrated significant heritability were also linked to the expression of schizophrenia, as indicated by the highly significant effects of the diagnostic covariate in the SOLAR models. This supports their utility as potential markers of genetic liability to the illness segregating in these families.

Comparison of the heritability results with those in the literature revealed both similarities and differences. Using extended pedigrees with at least two siblings with schizophrenia or

schizoaffective disorder, Glahn et al. [2007] estimated heritability for 18-neurocognitive measures. Consistent with our results, measures reflecting working memory, and speed of processing were found to be moderately to strongly heritable ($h^2 = 0.34\text{--}0.75$) and to model genetic liability for schizophrenia. By contrast, Glahn et al. [2007] reported significant heritability for both verbal learning (California Verbal Learning Test, a similar test to RAVLT) and Trails A while we found no evidence of significant heritability for these measures. Tuulio-Henriksson et al. [2002] investigated the heritability of working and verbal memory and both verbal and visual ability in a sample of patients with schizophrenia and their family members from an isolated region in Finland. They reported significant heritability estimates ($h^2 = 0.28\text{--}0.66$) for traits reflecting encoding in verbal learning, verbal working memory, and visuospatial ability. Gur et al. [2007b] reported heritability estimates in a sample of 349 European Americans from 35 multiplex multigenerational families, using a novel computerized battery of neurocognitive measures that assessed accuracy and speed on a range of cognitive domains. Significant heritability estimates were obtained for accuracy of verbal, facial and spatial memory, and spatial and emotional processing. Estimates of heritability were also significant for speed of abstraction/mental flexibility, attention, facial memory and spatial, and sensorimotor processing. Heritability estimates for these variables were weak to moderate ($h^2 = 0.25\text{--}0.66$). Using monozygotic and dizygotic twin data and accounting for effects of shared and unique environment, Touloupoulou et al. [2007] have reported estimates for working memory, processing speed, verbal comprehension, perceptual organization, and IQ. Estimates were moderate for all measures ($h^2 = 0.43\text{--}0.65$), with the exception of highly heritable IQ ($h^2 = 0.70$).

Similar to Touloupoulou et al. [2007], we found significant additive heritability for IQ ($h^2 = 0.636\text{--}0.735$). This finding is consistent with previous reports of comparably high heritability for IQ in adults in the general population [Plomin et al., 2001]. Since IQ reflects general cognitive abilities, we estimated heritability of the 12-neurocognitive measures studied adjusting for IQ. As shown in Table III, there were noteworthy differences between the results of SOLAR models that include IQ as a covariate (model 3) from those that did not (models 1 and 2). In the former analyses only the heritability estimate for motor skills (Purdue Pegboard) remained significant; whereas, consistent with the findings of Glahn et al. [2007] and Gur et al. [2007b], heritability estimates for two measures of processing speed (Digit Symbol and Trails B) became significant and substantial. These differences in heritability estimates between SOLAR models with and without IQ as a covariate could, in part, be explained by results of the bivariate heritability correlations (Table IV and Fig. 1). The bivariate heritability correlations for IQ and WMS-III Logical Memory tests I and II and Digit Span were particularly high, ranging from 0.84 to 1.00. In the presence of such strong co-inheritance, the univariate heritability estimates for WMS-III logical memory tests I and II and Digit Span would be expected to show substantial dependence upon whether or not highly heritable IQ was (model 3) or was not (models 1 and 2) included as a covariate in the SOLAR analysis. In contrast, the bivariate heritability correlations between IQ and Digit Symbol and between IQ and Trails B were negative (see Table IV). In the case of each of these variables, the inclusion of IQ as a covariate would be expected to lead to a larger proportion of the residual variance for these variables being explained by additive polygenic effects, in other words, stronger heritability estimates (model 3, Table III).

Figure 1 highlights the salient inter-relationships between the neurocognitive variables that demonstrated significant heritability in univariate models, including IQ. The results suggest there are two relatively separate inheritance domains. One domain comprises visuomotor and processing speed measures (Digit symbol, Trails B, Purdue Pegboard, Visual Reproduction II). The other domain shows correlated heritability involving general intelligence and measures from several memory dimensions (working, auditory, and verbal memory). The results further suggest that while heritability of visual memory is more closely related to that of the visuomotor and processing speed domain, it may also in part be related to heritability of IQ, as is likely to a greater or lesser extent for all cognitive measures. Overall, the results of the bivariate heritability analyses suggested that in the sample studied, where schizophrenia is associated with the NOS1AP locus on chromosome 1, the memory-IQ domain and the processing speed domain, may be possible endophenotypes for schizophrenia. In the only previous report on genetic correlations between neurocognitive tests [Greenwood et al., 2007], there was evidence of modest correlations (0.34–0.38) between standard measures of working memory, attention, and verbal declarative memory. However, the specific results are difficult to compare with ours because different neurocognitive tests, covariates, methods, and sampling strategy were used. Consistent with results for another genetic subtype of schizophrenia [Chow et al., 2006], our results do not support the theory that genetic subtypes of schizophrenia have different endophenotypic profiles.

We found no evidence of heritability for the tasks used to assess abstraction and mental flexibility (i.e., categories and preservative error scores of the WCST). This is consistent with a recent study reporting that WCST performance showed no significant heritability in the largest adult twin study to date [Kremen et al., 2007]. However, the literature in this area is limited and the results are mixed [Faraone et al., 2000; Kremen et al., 2004].

Future investigations will need to address the limitations of the current study. The sample size restricted the number of covariates included in the SOLAR models. As in other comparable studies [Tuulio-Henriksson et al., 2002; Glahn et al., 2007; Gur et al., 2007b], we adjusted for age, sex, and general ability level (IQ). Other potentially important covariates may be medication status and illness duration, although there is evidence that medication effects alone do not account for the observed neurocognitive deficits in schizophrenia and that deficits have been observed in all stages of illness [Gur et al., 2007a; Touloupoulou et al., 2007]. Another methodological limitation is that not all areas of neurocognitive functioning (or different aspects of an area) were assessed. This limits our findings on the co-inheritance of neurocognitive measures in the sample studied. In addition, there are no healthy controls. However, the use of standard neurocognitive tests allowed us to compute Z-scores, using published norms from large general population samples. This permits comparison of the neurocognitive profile in our study sample with normal samples and general population schizophrenia. Also, our findings that demonstrate significant heritability of selected neurocognitive measures are consistent with past studies that have examined heritability of schizophrenia and normal cognitive performance [Hoff et al., 2005; Greenwood et al., 2007; Gur et al., 2007a,b]. Another limitation is that 28 eligible family members did not participate in this study. It is also possible that the observed heritability estimates may be inflated due to shared environment influences, since of the sample

comprised mostly affected and unaffected siblings. Finally, while we have identified traits that tend to be co-inherited, this does not necessarily mean that these traits share the same genetic (or non-genetic) causes. Traits could be co-inherited simply because they are correlated, regardless of whether they share the same cause or not.

CONCLUSION

In summary, the results provide evidence of the heritability of neurocognitive measures reflecting immediate and delayed verbal memory, attention/working memory and motor skills, and to a lesser degree delayed visual memory in a familial form of schizophrenia that is associated with the NOS1AP gene on chromosome 1. We found that these measures were highly related to the diagnosis of schizophrenia within our familial sample. The heritability of neurocognitive phenotypes, apart from IQ, was only moderate in magnitude however, despite using a sample shown to have enhanced etiologic homogeneity. The results of bivariate SOLAR analyses examining of inter-relationships between neurocognitive traits found to be heritable suggest that composite measures of processing speed on the one hand and memory on the other may represent possible endophenotypes for schizophrenia. We plan to investigate this in comprehensive association studies of the NOS1AP gene, stratifying the sample based on the two heritable cognitive domains identified.

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References

- Asarnow RF, Nuechterlein KH, Subotnik KL, Fogelson DL, Torquato RD, Payne DL, Asamen J, Mintz J, Guthrie D. Neurocognitive impairments in nonpsychotic parents of children with schizophrenia and attention-deficit/hyperactivity disorder: The University of California, Los Angeles Family Study. *Arch Gen Psychiatry*. 2002; 59:1053–1060. [PubMed: 12418939]
- Bassett AS, Bury A, Honer WG. Testing Liddle's three syndrome model in families with schizophrenia. *Schizophr Res*. 1994; 12:213–221. [PubMed: 8054313]
- Brewer WJ, Wood SJ, McGorry PD, Phillips LJ, Yung AR, Anderson V, Copolov DL, Singh B, Velakoulis D, Pantelis C. Impairment of olfactory identification ability in individuals at ultra-high risk for psychosis who later develop schizophrenia. *Am J Psychiatry*. 2003; 160:1790–1794. [PubMed: 14514492]
- Brzustowicz LM, Hodgkinson KA, Chow EWC, Honer WG, Bassett AS. Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21–q22. *Science*. 2000; 288:678–682. [PubMed: 10784452]
- Brzustowicz LM, Simone J, Mohseni P, Hayter JE, Hodgkinson KA, Chow EW, Bassett AS. Linkage disequilibrium mapping of schizophrenia susceptibility to the CAPON region of chromosome 1q22. *Am J Hum Genet*. 2004; 74:1057–1063. [PubMed: 15065015]

- Cannon TD, Mednick SA, Parnas J. Antecedents of predominantly negative- and predominantly positive-symptom schizophrenia in a high-risk population. *Arch Gen Psychiatry*. 1990; 47:622–632. [PubMed: 2360856]
- Cannon TD, Zorrilla LE, Shtasel D, Gur RE, Gur RC, Marco EJ, Moberg P, Price RA. Neuropsychological functioning in siblings discordant for schizophrenia and healthy volunteers. *Arch Gen Psychiatry*. 1994; 51:651–661. [PubMed: 8042914]
- Chow EWC, Zipursky RB, Mikulis DJ, Bassett AS. Structural brain abnormalities in patients with schizophrenia and 22q11 deletion syndrome. *Biol Psychiatry*. 2002; 51:208–215. [PubMed: 11839363]
- Chow EWC, Watson M, Young DA, Bassett AS. Neurocognitive profile in 22q11 deletion syndrome and schizophrenia. *Schizophr Res*. 2006; 87:270–278. [PubMed: 16753283]
- Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, Bigelow L, Weinberger DR. Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biol Psychiatry*. 2001; 50:98–107. [PubMed: 11527000]
- Faraone SV, Seidman LJ, Kremen WS, Toomey R, Pepple JR, Tsuang MT. Neuropsychological functioning among the nonpsychotic relatives of schizophrenia patients: The effect of genetic loading. *Biol Psychiatry*. 2000; 48:120–126. [PubMed: 10903408]
- Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, Meyenberg N, Castro MP, Barrett J, Nicolini H, et al. Adjudicating neurocognitive endophenotypes for schizophrenia. *Am J Med Genet Part B*. 2007; 144B:242–249. [PubMed: 17034022]
- Goldberg TE, Ragland JD, Torrey EF, Gold JM, Bigelow LB, Weinberger DR. Neuropsychological assessment of monozygotic twins discordant for schizophrenia. *Arch Gen Psychiatry*. 1990; 47:1066–1072. [PubMed: 2241508]
- Gottesman I, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *Am J Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, et al. Initial heritability analyses of endophenotypic measures for schizophrenia: The consortium on the genetics of schizophrenia. *Arch Gen Psychiatry*. 2007; 64:1242–1250. [PubMed: 17984393]
- Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, Stone WS. The consortium on the genetics of schizophrenia: Neurocognitive endophenotypes. *Schizophr Bull*. 2007a; 33:49–68. [PubMed: 17101692]
- Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, Kanes S, Blangero J, Gur RC. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *Am J Psychiatry*. 2007b; 164:813–819. [PubMed: 17475741]
- Hanley JA, Negassa A, Edwardes MD, Forrester JE. Statistical analysis of correlated data using generalized estimating equations: An orientation. *Am J Epidemiol*. 2003; 157:364–375. [PubMed: 12578807]
- Heaton, RK., Grant, I., Matthews, CG. Comprehensive norms for an expanded Halstead-Reitan Battery: Demographic corrections research findings, and clinical applications. Odessa: Psychological Assessment Resources; 1991.
- Heaton, RK., Chelune, GJ., Talley, J., Kay, GG., Curtiss, G. Wisconsin card sorting test manual, revised and expanded. Odessa: Psychological Assessment Resources; 1993.
- Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*. 1998; 12:426–445. [PubMed: 9673998]
- Hoff A, Kremen W. Neuropsychology in schizophrenia: An update. *Curr Opin Psychiatry*. 2003; 16:149–155.
- Hoff AL, Svetina C, Maurizio AM, Crow TJ, Spokes K, DeLisi LE. Familial cognitive deficits in schizophrenia. *Am J Med Genet Part B*. 2005; 133B:43–49. [PubMed: 15635688]
- Horton NJ, Lipsitz SR. Review of software to fit generalized estimating equation regression models. *Am Statistician*. 1999; 59:160–169.
- Kremen WS, Seidman LJ, Faraone SV, Toomey R, Tsuang MT. Heterogeneity of schizophrenia: A study of individual neuropsychological profiles. *Schizophr Res*. 2004; 71:307–321. [PubMed: 15474901]

- Kremen WS, Eisen SA, Tsuang MT, Lyons MJ. Is the Wisconsin Card sorting test a useful neurocognitive endophenotype? *Am J Med Genet Part B*. 2007; 144B:403–406. [PubMed: 17492770]
- Plomin, R., DeFries, JC., McClearn, GE., McGuffin, P. Behavioural genetics. New York: Worth Publishers; 2001.
- Polderman TJ, Gonso MF, Posthuma D, Van Beijsterveldt TC, Heutink P, Verhulst FC, Boomsma DI. A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. *Acta Neurol Belg*. 2006; 106:191–207. [PubMed: 17323837]
- Posthuma D, Mulder EJ, Boomsma DI, de Geus EJ. Genetic analysis of IQ, processing speed and stimulus-response incongruency effects. *Biol Psychol*. 2002; 61:157–182. [PubMed: 12385674]
- Reitan R. The relation of trail making to organic brain damage. *J Consult Psychol*. 1955; 19:393–394. [PubMed: 13263471]
- Rey, A. L'examen clinique en psychologie. Paris, France: Presse Universitaire de France; 1958.
- Schork NJ, Greenwood TA, Braff DL. Statistical genetics concepts and approaches in schizophrenia and related neuropsychiatric research. *Schizophr Bull*. 2007; 33:95–104. [PubMed: 17035359]
- Snitz BE, Macdonald AW, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: A meta-analytic review of putative endophenotypes. *Schizophr Bull*. 2006; 32:179–194. [PubMed: 16166612]
- Spreen, O., Strauss, E. A compendium of neuropsychological tests. New York: Oxford University Press; 1998.
- Tiffin, J. Purdue Pegboard examiner manual. Chicago: Science Research Associates; 1968.
- Toulopoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, Murray R. Substantial genetic overlap between neurocognition and schizophrenia: Genetic modeling in twin samples. *Arch Gen Psychiatry*. 2007; 64:1348–1355. [PubMed: 18056542]
- Tuulio-Henriksson A, Haukka J, Partonen T, Varilo T, Paunio T, Ekelund J, Cannon TD, Meyer JM, Lonnqvist J. Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *Am J Med Genet Part B*. 2002; 114B:438–490.
- Wechsler, D. Wechsler adult intelligence scale. 3. San Antonio, TX: The Psychological Corporation; 1997a.
- Wechsler, D. Wechsler memory scale. 3. San Antonio, TX: The Psychological Corporation; 1997b.

FIG. 1.

Diagram of exploratory bivariate heritability results showing the inter-relationship between pairs of 8-neurocognitive variables with significant heritability (see Table III) in familial schizophrenia. The width of connecting lines between the neurocognitive variables indicates the relative strength of positive (green solid lines) and negative (red dotted lines) heritability correlations that exceeded standard error, adjusted for age, sex, and narrowly defined schizophrenia (see Table IV).

TABLE I

Demographic and Clinical Characteristics of the Sample (n =85)

	Subject groups		
	Narrow schizophrenia (n =34)	Broad schizophrenia ^a (n =44)	Unaffected (UA) (n =41)
Sex			
Men, n (%)	16 (47)	21 (48)	15 (37)
Mean age in years (SD)	52.1 (9.6)	51.8 (9.5)	49.1 (10.5)
Mean education in years (SD)	12.0 (3.1)	13.0 (3.6)	13.7 (3.0)
Full scale IQ (SD)	87.9 (15.1)	92.2 (15.6)	101.5 (13.1)

^aNarrow schizophrenia (n =34) plus those with schizophrenia-spectrum disorders (n =10).

TABLE II

Neurocognitive Test Z-Scores for the Sample (n = 85) by Diagnostic Group

Neurocognitive variables	Z-scores					
	Narrow schizophrenia (n = 34)		Broad schizophrenia (n = 44)		Unaffected (n = 41)	
	Mean	SD	Mean	SD	Mean	SD
Motor skills						
Purdue Pegboard ^a	-2.99	1.32	-2.51	1.54	-0.96	1.15
Processing speed						
Trails A ^b	-1.36	1.02	-1.18	1.04	-0.35	1.09
Trails B ^b	-1.34	1.26	-1.11	1.23	-0.18	0.78
Digit symbol ^c	-1.24	0.87	-1.01	0.97	-0.26	0.76
Learning and memory						
Visual reproduction I ^c	-1.46	1.30	-0.91	1.55	-0.06	1.25
Visual reproduction II ^c	-0.89	0.88	-0.63	0.95	0.24	1.02
Logical memory I ^c	-1.31	1.20	-0.99	1.23	-0.26	1.08
Logical memory II ^c	-1.12	1.30	-0.76	1.35	0.06	1.03
RAVLT ^c	-1.70	1.60	-1.30	1.64	-0.10	1.06
Attention and working memory						
Digit span ^c	-0.32	0.65	-0.23	0.70	0.12	0.80
Abstraction and mental flexibility						
WCST-categories ^d	-0.73	1.01	-0.59	0.98	-0.28	0.74
WCST-perseverative errors ^d	-0.76	0.94	-0.68	0.93	-0.42	0.78

^aCorrected for age and sex.^bCorrected for age, sex, and educational level.^cCorrected for age.^dCorrected for age and educational level.

TABLE III
Results of Univariate Heritability Analyses of Neurocognitive Test -Scores* in Familial Schizophrenia

	n ^a	Heritability					
		Model 1			Model 2		
		h ² (±SE)	P	Covariate(s)*	h ² (±SE)	P	Covariate(s)*
Motor							
Purdue Pegboard	81	0.39 (0.26)	0.038	NA	0.48 (0.20)	0.006	Dx
Speed of processing							
Trails A	82	0.17 (0.18)	0.14	NA	0.09 (0.17)	0.28	Dx
Trails B	82	0.10 (0.23)	0.32	NA	0.28 (0.21)	0.07	Dx
Digit symbol	80	0.23 (0.24)	0.13	Sex	0.24 (0.24)	0.13	Dx, Sex
Learning and memory							
WMS-III visual reproduction I	80	0.25 (0.21)	0.06	Sex	0.16 (0.19)	0.14	Dx, sex
WMS-III visual reproduction II	80	0.27 (0.25)	0.09	Sex	0.29 (0.25)	0.09	Dx, sex
WMS-III logical memory I	80	0.49 (0.26)	0.010	Sex	0.40 (0.28)	0.013	Dx, sex
WMS-III logical memory II	80	0.34 (0.26)	0.05	Sex	0.31 (0.21)	0.041	Dx, sex
RAVLT-recall	80	0.05 (0.19)	0.40	Sex	0.06 (0.18)	0.37	Dx, sex
Attention/working memory							
Digit span	82	0.48 (0.27)	0.011	Sex	0.50 (0.26)	0.010	Dx, sex
Executive functioning							
WCST-categories	81	0.14 (0.18)	0.18	Sex	0.09 (0.18)	0.27	Dx, sex
WCST-perseverative errors	81	0.28 (0.28)	0.11	Sex	0.32 (0.30)	0.09	Dx, sex
Full scale IQ	83	0.74 (0.21)	0.0001	Sex	0.64 (0.19)	0.0001	Dx, sex

NA, non applicable (test Z-scores already adjusted for sex); IQ, WAIS full scale IQ; Dx, narrow diagnosis of schizophrenia; SE, standard error; significant heritability results ($P < 0.05$) are bolded.

* All neurocognitive test Z-scores were adjusted for age, thus age was not included as a covariate in SOLAR analyses.

^aNumber of subjects varies due to missing data.

TABLE IV
Results of Bivariate Heritability Analyses: Genetic Correlations Between Neurocognitive Measures^a

	Polygenic correlation (SE)						
	Purdue Pegboard	Trails B	Digit symbol	WMS-III visual reproduction I	WMS-III visual reproduction II	WMS-III logical memory I	WMS-III logical memory II
Purdue Pegboard	1.00	0.84 (0.32)^b	1.00 (NA)	-0.21 (0.76)	0.54 (0.32)	-0.52 (0.47)	-0.91 (0.67)^b
Trails B		1.00	1.00 (NA)	-0.49 (1.22)	0.84 (0.30)	-1.00 (NA) ^c	-1.00 (NA) ^c
Digit symbol			1.00	0.62 (0.62)	0.88 (0.73)	-0.70 (0.47)	-0.61 (0.74)
WMS-III visual reproduction I				1.00	0.62 (0.39)	0.55 (0.53)	0.04 (0.64)
WMS-III visual reproduction II						-0.17 (0.49)	-0.54 (0.45)
WMS-III logical memory I						1.00	1.00 (NA)^c
WMS-III logical memory II							1.00
Digit span							0.51 (0.39)
Full scale IQ							0.81 (0.20)^d

NA, not applicable; results where correlation exceeds standard error are bolded.

^a All bivariate SOLAR models included diagnosis of narrowly defined schizophrenia and sex (where applicable) as covariates.

^b Correlations with $P < 0.10$ and > 0.05 .

^c Correlations with $P < 0.05$ and > 0.01 .

^d Correlations with $P < 0.01$.