Published in final edited form as:

Biol Psychiatry. 2013 May 15; 73(10): 976–984. doi:10.1016/j.biopsych.2012.12.021.

Sex Differences in Familiality Effects on Neurocognitive Performance in Schizophrenia

Monica E. Calkins^{1,*}, Amrita Ray², Ruben C. Gur¹, Robert Freedman³, Michael F. Green^{4,13}, Tiffany A. Greenwood⁵, Gregory A. Light⁵, Keith H. Nuechterlein⁴, Ann Olincy³, Allen D. Radant^{6,7}, Larry J. Seidman^{8,9}, Larry J. Siever^{10,11}, Jeremy M. Silverman^{10,11}, William S. Stone^{8,9}, Catherine Sugar¹³, Neal R. Swerdlow⁵, Debby W. Tsuang², Ming T. Tsuang⁵, Bruce I. Turetsky¹, David L. Braff^{5,**}, Laura C. Lazzeroni², and Raquel E. Gur¹

¹Department of Psychiatry, University of Pennsylvania, Philadelphia, Pennsylvania

²Departments of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California

³Department of Psychiatry, University of Colorado Health Sciences Center, Denver, Colorado

⁴Department of Psychiatry and Biobehavioral Sciences, Geffen School of Medicine at University of California Los Angeles, Los Angeles, California

⁵Department of Psychiatry, University of California San Diego, La Jolla, California and VA San Diego Healthcare System; VISN-22 Mental Illness Research, Education, and Clinical Center

⁶Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington

⁷The Department of Veteran Affairs VISN-20 Mental Illness Research, Education, and Clinical Center; Seattle, Washington

⁸Harvard Institute of Psychiatric Epidemiology and Genetics, Boston, Massachusetts

⁹Massachusetts Mental Health Center Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Harvard Medical School Department of Psychiatry, Boston, Massachusetts

¹⁰Medical Genetics Research Program and Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY

¹¹Department of Psychiatry, The Mount Sinai School of Medicine, New York, New York

© 2013 Society of Biological Psychiatry. Published by Elsevier Inc. All rights reserved.

*Corresponding Author. mcalkins@upenn.edu. Current postal address: University of Pennsylvania School of Medicine, Department of Psychiatry, 9 Maloney, 3600 Spruce Street, Philadelphia, PA 19104.15. Tel.: 215.615.3183; fax: 215.662.7903.

**For general inquiries regarding the Consortium on the Genetics of Schizophrenia (COGS). dbraff@ucsd.edu.

All other authors report no biomedical financial interests or potential conflicts of interest.

Financial Disclosures.

Dr. Michael F. Green reports having received consulting fees from Abbott Laboratories, Amgen, Cypress, Lundbeck, and Teva. He has received speaking fees from Otsuka and Sunovion.

Dr. Gregory A. Light has received compensation for one-time participation in a scientific advisory board meeting for Astellas Inc.

Dr. Keith H. Nuechterlein reports research grant funding from Janssen Scientific Affairs and Genentech and consulting fees from Genentech and Otsuka.

Dr. Neal R. Swerdlow was a consultant to Neurocrine, Inc.

Dr. Bruce I. Turetsky reports unrelated research grant support from AstraZeneca and Pfizer Pharmaceuticals and consulting fees from La Roche and Bristol-Myers.

Dr. Laura C. Lazzeroni is named as an inventor on a pharmacogenetic patent application that is being pursued by Stanford University.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

¹²James J. Peters VA & VISN3 Mental Illness Research, Education and Clinical Center, Bronx, New York

¹³The Department of Veteran Affairs VISN-22 Mental Illness Research, Education, and Clinical Center; Los Angeles, CA

Abstract

Background—Numerous studies have documented that patients with schizophrenia show neurocognitive impairments, which are also heritable in schizophrenia families. In view of these findings, the current investigation tested the hypothesis that neurocognitive performance of schizophrenia probands can predict the neurocognitive performance of their unaffected family members.

Methods—Participants (n=1,967; schizophrenia=369; first-degree relatives=1,072; community comparison subjects=526) in the Consortium on the Genetics of Schizophrenia (COGS) were administered the Penn Computerized Neurocognitive Battery (CNB).

Results—Consistent with prior work, probands showed significant neurocognitive impairment, and neurocognitive ability was significantly heritable, across domains. On average, unaffected relatives did not differ from community comparison subjects in their neurocognitive performance. However, in 6 of 7 domains, probands' score predicted the performance of their unaffected siblings. Male, but not female, probands' performance was predictive of their unaffected relatives (siblings and mothers) performance, most consistently in face memory and spatial processing.

Conclusions—Using a novel approach in which individual probands are paired with their respective unaffected relatives within each family, we found that male probands' performance predicted both sister and brother performance, an effect that was most powerfully observed for face memory and spatial processing. Results suggest that the familial transmission of sexually dimorphic neurocognitive domains, in which a particular sex tends to show a performance advantage over the other, may not itself be sex specific in schizophrenia families.

Keywords

Schizophrenia; neurocognition; endophenotype; heritability; genetics; sex differences

Introduction

Building on well-established neurocognitive deficits in schizophrenia (1), genetic strategies have examined quantitative neuropsychological measures in a family study design. Heritability of measures of several neurocognitive domains has been reported in families of schizophrenia patients using traditional neuropsychological tests (2–10) and a computerized neurocognitive battery that provides performance measures of accuracy and speed (11). We used the Penn Computerized Neurocognitive Battery (CNB), which was previously validated against traditional neuropsychological tests in healthy people (12) and patients with schizophrenia (13), in three large-scale genetic family studies. In the Multiplex Multigenerational Investigation of Caucasian families ((MGI 14)), we reported significant heritability estimates for accuracy of verbal, facial, and spatial memory and spatial and emotion processing. For speed, estimates of heritability were significant for abstraction and mental flexibility, attention, face memory, and spatial and sensorimotor processing. The Project Among African-Americans to Explore Risks for Schizophrenia (PAARTNERS) also showed significant heritabilities for most neurocognitive domains, with the highest for accuracy of abstraction and flexibility, verbal memory, face memory, spatial processing, and emotion processing, and for speed of attention (15). The Consortium on the Genetics of

Schizophrenia (COGS) included the CNB, among other endophenotypic measures, and reported initially on a subsample where all CNB measures were significantly heritable (16).

Heritability of quantitative neurocognitive performance deficits in schizophrenia families supports their use as endophenotypes by suggesting that they reflect familial effects, which could be used to dissect the genetics of schizophrenia (17). Other family studies have also supported this family-based strategy by showing that unaffected family members exhibit neurocognitive performance that is intermediate in mean level between proband-related deficits and healthy control “normal” scores (18, 19). Such findings do not, however, directly address familial aggregation of neurocognitive abilities, and few studies have examined within-family prediction of performance based on proband performance. Evaluation of the similarity of probands and parents, compared to probands and siblings can add to our understanding of genetic (G) and environmental (E) separable and interactive contributions to cognitive deficits in schizophrenia.

Previous studies examining relationship of neurocognitive functioning within families of schizophrenia have been informative. For example, whereas siblings and offspring of schizophrenia probands in one sample tended to perform poorly across multiple neurocognitive domains, parents showed deficits only in verbal memory, indicating that parents, on average, were less impaired than siblings (3, 20). Complementing this finding, another investigation showed a high sibling-sibling correlation but moderate parent-offspring correlation for an abstraction task (10). In an earlier evaluation of familial prediction, Egan and colleagues reported that siblings of schizophrenia patients with impairments in executive function, verbal memory (21) or attention (22) had moderate to high relative risk of similar impairments, supporting the familiarity of these neurocognitive domains. Importantly, none of these prior investigations evaluated whether sex differences in neurocognition may moderate the transmission of neurocognitive abilities. In the general population, sex differences in neurocognition are robust, with males tending to show relative strengths in tests of spatial ability, and females tending to show relative strengths in verbal and emotion processing (23). These sex-related dimorphic results in schizophrenia patients are not entirely isomorphic (24), with some investigations reporting male and female advantages mirroring those in the general population ((e.g., 13)) and others failing to find expected male advantages (24, 25). Because sex differences in neurocognitive abilities in schizophrenia may reflect differences in neurodevelopmental processes, understanding sexual dimorphism has contributed to the elucidation of the neurobiology of schizophrenia (26).

To evaluate familiarity of a comprehensive set of neurocognitive abilities, we examined CNB data from the entire COGS sample. The family design (i.e., families identified via an affected proband with at least one unaffected sibling and parents available for testing) and large sample size of the COGS study enables comparison of the predictions for hierarchical family relationships among first-degree relatives of schizophrenia probands including siblings and parents. We hypothesized that the neurocognitive abilities of probands would predict neurocognitive performance of unaffected first-degree family members, particularly for same sex relatives.

Methods and Materials

Participants

Participants were recruited through the Consortium on the Genetics of Schizophrenia (COGS), a 7-site, NIMH funded, linked R01 project investigating the genetics of quantitative endophenotypes that show replicable deficits in schizophrenia patients. The sample included schizophrenia probands (n=369), their first-degree biological relatives

(n=1242), among which 1072 are unaffected *with schizophrenia or schizoaffective disorder*, and healthy community comparison subjects (CCS, n=526). Participants were recruited and assessed according to standardized procedures detailed previously (27). Briefly, all participants were between the ages of 18–65 and able to understand and provide informed consent in English. Eligible families fulfilled the following criteria: (1) a proband meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia or schizoaffective disorder (depressed type) as determined by a Best Estimate Final Diagnosis (BEFD) procedure(27), (2) both biological parents available for at least genotyping (and endophenotyping if possible), and, (3) at least one full sibling unaffected with schizophrenia available for endophenotyping and genotyping. First-degree biological relatives included parents and siblings of the proband. This family configuration was selected to optimize the study of quantitative phenotypic variation, in which contrasts between individuals with high and low phenotypic values generate greater power. Probands having only one available parent but 2 or more available full siblings (with at least one unaffected by schizophrenia) were also included, as were probands having no available parents but 3 or more available full siblings (with at least one unaffected by schizophrenia). For the current analyses, data from all available family members were used, including from enrolled families that did not meet final COGS familial structure inclusion criteria (n of families= 369; mean number of relatives per family = 3.41, range=2–13). *Families did not meet COGS familial structure criteria if only 1 parent and 1 full sibling participated, or if no parents and fewer than 3 full siblings participated.* Potential participants were excluded if they did not fulfill the eligibility criteria, which included: being adopted, physically unable to participate in testing of at least one endophenotype, severe systemic illness interfering with ability to be tested, previous endophenotyping in the last month, previous neuropsychological testing in the last 3 months, and testing positive for illicit drug use or alcohol screen at the time of testing. These and additional exclusion criteria specific to participant group are detailed elsewhere (27).

Computerized Neurocognitive Battery

The Penn Computerized Neurocognitive Battery (CNB) (12) was administered in the COGS along with 6 core candidate endophenotypes. The CNB was originally included as a secondary measure to characterize neurocognitive performance and potentially generate additional endophenotypes, and was abbreviated to reduce redundancy with core endophenotypes. The CNB was administered on Macintosh computers in a fixed order and included brief standardized rest periods, for a total administration time of about 60 minutes. Eight neurocognitive domains were assessed (11–13): (1) Abstraction and Mental Flexibility (ABF; Penn Conditional Exclusion Test); (2) Working Memory (WM; Letter-n-Back, 1-back and 2-back conditions); (3) Face Memory (FME; Penn Face Memory Test); (4) Spatial Memory (SME; Visual Object Learning Test); (5) Spatial Processing (SPA; Computerized Judgment of Line Orientation); (6) Sensori-Motor dexterity (S-M; Motor Praxis test); (7) Motor (Finger Tapping test); (8) Emotion Processing (EMO; Penn Emotion Recognition Test). Additionally, participants in the second phase of the study (n=459) were administered a Verbal Memory Test (VME; Penn Word Memory Test). For six of the domains, two summary functions were calculated: (1) Accuracy, which reflects the number of correct responses; (2) Speed, the median response time for correct answers. These parameters were combined by calculating an “Efficiency” index defined as number of correct responses per unit time (accuracy/log of speed). For the Sensori-Motor and Motor domains, only speed measures were used. Scoring of the battery is automated and validated, and produces scaled scores for each neurocognitive domain. Data from CCS were used to obtain z-scores for each domain.

Statistical Analyses

Probands, their unaffected first-degree relatives and community comparison subjects (CCS) were included in the statistical analysis. Individuals with missing CNB values were excluded from the corresponding analysis. Some individuals were identified with trait values lower than 3 standard deviations from the trait mean (range =0–1.73% of participants). Trait values for these individuals were set to a floor value of *−4 standard deviations, which we have previously applied to reduce undue influence of extreme scores that reflect very little meaningful variation in performance at that level* (11–13).

The accuracy and speed scores on the CNB domains were first age corrected *using linear regressions where score was predicted from age, and since these were z-scores (with a mean of 0), the residuals served as the dependent measures. These age adjusted scores were then* entered as the dependent measures in Mixed Model analysis. Grouping factors were diagnostic group (Group, 4 levels: Community Comparison Subjects, Probands, Parents, Siblings) and sex, and domain (separate analyses on the 7 efficiency and accuracy and 9 speed domains) was a repeated measures factor. The model incorporated clustering by family. Mixed Model analysis was used because the verbal memory test was introduced approximately two-thirds of the way through data collection and the number of individuals available for this task was almost one third compared to other variables.

Although we have previously reported heritability estimates for the COGS sample (28), we aimed here to maximize the number of available participants with CNB data for the regression analyses and thus included additional families not meeting family structure inclusion criteria for the prior heritability analyses. Therefore, we performed heritability analyses on this slightly larger sample so that both heritability and regression analyses were conducted with the same individuals. Heritability analyses were performed on the efficiency scores only (accuracy/log RT) to reduce the number of variables (16), and the Motor domain was not included. Heritabilities were calculated using the variance component method in Sequential Oligogenic Linkage Analysis Routines (SOLAR) v4 (29), using age, sex and site as covariates. In COGS, families were recruited through the identification of a proband with schizophrenia and thus the sample is not representative of the general population. Hence we pre-specified the probands in the pedigree input file to implement the correction for ascertainment bias. Non-significant covariates ($p>0.05$) for each CNB variable were dropped from final heritability analyses.

The predictive ability of the probands' efficiency score on relatives' performance was evaluated using linear regression for each relationship type. Separate analyses for each type of unaffected first-degree relative (full sib, mother, father) relied on linear regression of the relatives' efficiency scores on the probands' efficiency scores, with age, sex and maximum parental education as covariates. All tests were two-sided and utilized a 0.05 significance level. We also tested the predictive ability of probands' performance on the same sex and opposite sex relatives' performance. The sex specific analysis examines the predictive pattern of male proband on the unaffected brother and father, and that of female proband on the unaffected sister and mother.

Heritability analyses were conducted in SOLAR, and the mixed model analysis in SAS. All other analyses were conducted in Stata.

Results

A total of 1,967 individuals comprising 369 probands, 1,072 unaffected first-degree relatives, and 526 CCS with valid CNB data were included in the statistical analysis. Demographic characteristics are given in Table 1. The proband group was

disproportionately male (76%) compared to CCS and unaffected siblings, as is common in many schizophrenia research studies (24).

Group Differences

The Mixed Model analysis on the efficiency scores showed a main effect of group, $F(3,1683) = 5.89$, $p = 0.0005$, no effect of sex, $F(1,1683) = 1.73$, $p = 0.1880$, and a significant main effect of Domain, $F(6,1683) = 10.78$, $p < .0001$. Both Group*Domain and Sex*Domain interactions were significant, $F(18,1683) = 6.98$, $p < .0001$ and $F(6,1683) = 3.49$, $p = 0.0019$, respectively, while the Group*Sex interaction was not, $F(3,1683) = 0.28$, $p = 0.8376$. Notably, the Group*Sex*Domain interaction was also significant, $F(18,1683) = 2.01$, $p = 0.0073$. *The same analysis applied to the accuracy and speed measures separately yielded the same results with the exception that the Group*Sex*Domain interaction for speed was not significant either when all 9 speed measures were entered, $F(24,1663) = 1.28$, $p = 0.1650$, or when entering only the 7 domains that were obtained from the same tests as the accuracy scores, $F(18,1683) = 1.36$, $p = 0.1427$. Neurocognitive profiles for males and females are presented in Figure 1. Targeted pairwise follow-up tests revealed that probands had significantly reduced accuracy and speed compared to all other groups (all p 's < 0.001). In contrast, siblings and parents showed few significant differences from CCS for most comparisons. Exceptions included that, compared to CCS, fathers showed reduced accuracy in abstraction/flexibility ($p=0.0336$) and emotion processing ($p=0.0002$). Although mothers had lower face memory accuracy than female CCS ($p=0.0261$), their performance fell within the normal range for the entire CCS sample.*

Figure 2 presents the standardized mean difference (95% confidence interval) of efficiency variables between probands and relatives. On average, siblings showed greater neurocognitive efficiency than probands for all neurocognitive measures. Mothers but not fathers performed better than probands in face memory and emotion processing, whereas fathers but not mothers showed greater spatial processing efficiency. Overall, sex differences were attenuated in probands and siblings compared to CCS. In spatial memory, there was a significant sex bias among probands, siblings and CCS, with males performing significantly better than females. Conversely, females performed better in emotion processing.

Heritability

Heritability estimates from SOLAR were significantly different from zero for all measures (see Table 2): abstraction/flexibility $h^2=0.26$ ($SE=0.06$), face memory $h^2=0.30$ (0.05), spatial memory $h^2=0.33$ (0.06), spatial processing $h^2=0.51$ (0.06), sensorimotor $h^2=0.35$ (0.05), emotion processing $h^2=0.19$ (0.05), and verbal memory $h^2=0.18$ (0.08). Age was a significant covariate for all variables.

Prediction of Performance of Family Members

As the variability of all the CNB measures is partly influenced by genetic factors inherited within a family, we tested the hypothesis that neurocognitive abilities of probands predict neurocognitive performance of unaffected family members through linear regression models among the different relative groups. Table 3 presents the number of pairs included in the regression analysis, the estimate of the proband effect on the corresponding relative, 95% confidence interval of the estimate, the significant covariates (p -value) with the direction (+ or -) of the covariate effect in the model. On a family basis, the proband efficiency scores on abstraction/flexibility, face memory, spatial memory, spatial processing, sensorimotor, and emotion processing were significantly (two sided p -value < 0.05) associated with the efficiency score of their unaffected sibling. Likewise, proband efficiencies significantly predicted face memory, spatial processing and sensorimotor efficiency scores of their

mothers. Conversely, proband performance was not predictive of their fathers' performance in any domain.

Table 4 presents estimates of proband effect on unaffected relatives of the same sex. *Male probands' performance significantly predicted their brother's performance in face memory (0.174), spatial memory (0.161), spatial processing (0.245) and emotion processing (0.223). For these same abilities, female proband effects in respective domains were smaller than those observed in male probands; they did not significantly predict their sister's (face memory=0.110, spatial memory=0.074, spatial processing=0.166, emotion processing=0.182) or parent's performance (range=-0.053 to 0.143), and all 95% confidence intervals overlapped with 0.* Table 5 gives estimates of proband effects on unaffected relatives of the opposite sex. Male probands' performance significantly predicted both their mothers' and sisters' face memory (sister=0.178; mother=0.175) and spatial processing (sister=0.433; mother=0.335) performance, as well as their mothers' spatial memory performance (0.215). Again, female proband's performance in these same domains did not predict opposite sex performance (range=-0.131 to 0.092), the corresponding 95% confidence intervals overlapped with 0, and no other opposite sex proband effects were observed.

Discussion

The key novel finding of our family study is that proband performance predicted sibling performance in all Computerized Neurocognitive Battery (CNB) domains, except verbal memory. In addition, in this large study, a typical pattern of schizophrenia deficits across multiple domains was noted (14, 15). Analysis of male and female probands' performance separately revealed that male, but not female, probands' performance was predictive of their same as well as opposite sex siblings' performance, most prominently in face memory and spatial processing.

These findings are noteworthy because: 1) Our study confirmed the well-documented neurocognitive deficits in patients with schizophrenia, with a similar performance pattern obtained in previous independent samples with the CNB (14, 15); 2) Despite this replication, siblings of probands in the current investigation did not differ in performance from community comparison subjects. Notably, although there was no group effect, male probands' performance predicted both sister and brother performance, an effect that was most powerfully observed for spatial processing and face memory. Proband performance also selectively predicted mothers' performance in these two domains, as well as in sensorimotor processing. Analysis by proband sex revealed that, as for siblings, only male proband performance was predictive of mothers' performance in spatial processing and face memory. The performance of fathers was not predicted by proband performance in any domain. Thus, spatial processing and face memory performance of male probands with schizophrenia predicted their male and female siblings and mothers, but not fathers, performance. We detected these relationships using a novel approach in which individual probands are paired with their respective unaffected relatives within each family, which appears more powerful than comparing mean scores across proband and relative groups.

Although spatial memory has been widely investigated in schizophrenia, spatial processing has not previously been implicated as an endophenotype in schizophrenia. However, in the current investigation and in our previous studies using the same task, spatial processing was found to show the highest heritability among measures (14, 15). Moreover, it has shown suggestive linkage with candidate genes associated with schizophrenia (28). This pattern of results could occur if spatial processing is simply a highly heritable ability that is not specifically associated with liability to schizophrenia. Alternatively, our current findings that

male probands performance predicts neurocognitive performance of unaffected siblings and mothers indicates that further evaluation of the endophenotypic candidacy of spatial processing is warranted.

Like spatial processing, face memory has consistently shown significant heritability across samples, including in the current investigation, but has not been widely examined as a candidate endophenotype of schizophrenia (30). Unlike spatial processing, memory for faces has typically exhibited a female advantage in healthy populations. Inconsistent with our initial hypothesis, these two neurocognitive domains that are usually strongly sexually dimorphic in the general population nonetheless behaved similarly in prediction from male proband performance. This may suggest that familial transmission of neurocognitive domains is not itself sexually dimorphic. *In other words, even neurocognitive domains with well-established sex advantages may be genetically informative in schizophrenia families. This suggestion is supported by our previous report of significant associations between these neurocognitive domains and single nucleotide polymorphisms (SNPs) on genes implicated in schizophrenia (28). However, given that spatial processing and face memory appear particularly predictive in families of male probands, future large-scale family studies could evaluate the genetic significance of this finding by, for example, analyzing the associations between schizophrenia implicated SNPs and neurocognitive domains in families of male compared to female probands.*

The current study replicates and extends prior work supporting genetic influences on multiple domains of neurocognitive function within families. All domains examined in the current study were significantly heritable, with the highest heritabilities observed for spatial processing, as described, and for spatial memory, sensorimotor, face memory, and abstraction/flexibility. Differences between heritability estimates obtained here and from previous COGS analyses are slight, and can be attributed to the inclusion of all COGS participants with available CNB data regardless of available genotype data. As in our prior analyses, heritabilities of individual cognitive domains are lower than the reported heritability of schizophrenia, which may reflect a “parsing” of schizophrenia into additive heritable components (16). The lack of significant impairment in siblings of schizophrenia probands differs from reports where performance of siblings was, on average, intermediate to that of probands and controls (18, 19). *We have previously reported deficits in particular neurocognitive domains in relatives of schizophrenia families using neurocognitive tasks employed in this investigation (14, 15), so it does not appear that lack of overall impairment in relatives in this sample is attributable to a general lack of sensitivity of the CNB.* In the COGS sample, we have found reduced relative-control differences in some aspects of verbal declarative memory (31) and verbal working memory (32), *but other measures have not shown expected impairments (31, 32).* Possible explanations for the low levels of deficits in relatives include the ascertainment strategy of the COGS, where most participants were from intact families with relative high functioning (32), and inclusion of community comparison subjects with some non-psychotic clinical disorders (32).

There are some limitations of our investigation. As for all family studies of first-degree relatives, we can't exclude environmental, including socio-economic, effects that may contribute to familial performance similarity. *Also, because our sample only included families of schizophrenia patients, it is possible that the observed effects are not specific to schizophrenia, more generally reflecting transmission of neurocognitive abilities in families. This possibility can be investigated by future studies employing comparable statistical methods but ascertaining families of probands who are healthy or have non-schizophrenia psychiatric diagnoses. In addition, relatively fewer female probands and fathers than other participant types in the COGS sample may have affected our ability to detect significant effects in these groups.* Moreover, a longstanding potential problem in schizophrenia sex

differences research is the disproportionate number of males typically presenting for research studies, which may affect representativeness (24). Potential sex differences in associated abnormal brain processes, symptomatology, function or other clinical features may also contribute (33). Furthermore, because comparatively few parents, especially fathers, participated in the COGS study, ability to detect significant father effects may have been weakened. Finally, the late introduction into the study of the verbal memory task, leading to relatively small sample sizes in this domain, may have decreased power in verbal memory analyses.

In conclusion, the current results from the large COGS cohort provide further support for familial influence on neurocognitive deficits in schizophrenia families, even when pronounced deficits in unaffected family members are not observed.

Acknowledgments

This study was supported by NIMH grants R01 MH086135, R01 MH65571, R01 MH42228, R01 MH65588, R01 MH65562, R01 MH65707, R01 MH65554, R01 MH65578, R01 MH65558, K08 MH79364, a Neuropsychiatry Post-doctoral traineeship (MH19112), and a Scottish Rite Schizophrenia Research Fellowship. We thank the families who participated in this study for their invaluable time and effort.

References

1. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology*. 1998; 12:426–445. [PubMed: 9673998]
2. Husted JA, Lim S, Chow EW, Greenwood C, Bassett AS. Heritability of neurocognitive traits in familial schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2009; 150B:845–853. [PubMed: 19180565]
3. Wang Q, Vassos E, Deng W, Ma X, Hu X, Murray RM, et al. Factor structures of the neurocognitive assessments and familial analysis in first-episode schizophrenia patients, their relatives and controls. *Aust N Z J Psychiatry*. 2010; 44:109–119. [PubMed: 20113299]
4. Touloupoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, et al. Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Arch Gen Psychiatry*. 2007; 64:1348–1355. [PubMed: 18056542]
5. Chen LS, Rice TK, Thompson PA, Barch DM, Csernansky JG. Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia. *Schizophr Res*. 2009; 111:159–166. [PubMed: 19398304]
6. Tuulio-Henriksson A, Haukka J, Partonen T, Varilo T, Paunio T, Ekelund J, et al. Heritability and number of quantitative trait loci of neurocognitive functions in families with schizophrenia. *Am J Med Genet*. 2002; 114:483–490. [PubMed: 12116181]
7. Owens SF, Rijdsdijk F, Picchioni MM, Stahl D, Nenadic I, Murray RM, et al. Genetic overlap between schizophrenia and selective components of executive function. *Schizophr Res*. 2011; 127:181–187. [PubMed: 21056927]
8. Glahn DC, Almasy L, Blangero J, Burk GM, Estrada J, Peralta JM, et al. Adjudicating neurocognitive endophenotypes for schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B:242–249. [PubMed: 17034022]
9. Bertisch H, Li D, Hoptman MJ, Delisi LE. Heritability estimates for cognitive factors and brain white matter integrity as markers of schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153B:885–894. [PubMed: 20052692]
10. Aukes MF, Alizadeh BZ, Sitskoorn MM, Selten JP, Sinke RJ, Kemner C, et al. Finding suitable phenotypes for genetic studies of schizophrenia: heritability and segregation analysis. *Biol Psychiatry*. 2008; 64:128–136. [PubMed: 18295748]
11. Gur RC, Richard J, Hughett P, Calkins ME, Macy L, Bilker WB, 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. [PubMed: 19945485]

12. Gur R, Ragland J, Moberg P, Turner T, Bilker W, Kohler C, et al. Computerized neurocognitive scanning: I. Methodology and validation in healthy people. *Neuropsychopharmacology*. 2001; 25:766–788. [PubMed: 11682260]
13. Gur RC, Ragland JD, Moberg PJ, Bilker WB, Kohler C, Siegel SJ, et al. Computerized neurocognitive scanning: II. The profile of schizophrenia. *Neuropsychopharmacology*. 2001; 25:777–788. [PubMed: 11682261]
14. Gur RE, Nimgaonkar VL, Almasy L, Calkins ME, Ragland JD, Pogue-Geile MF, et al. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. *Am J Psychiatry*. 2007; 164:1–7. [PubMed: 17202533]
15. Calkins ME, Tepper P, Gur RC, Ragland JD, Klei L, Wiener HW, 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. [PubMed: 20194479]
16. Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, 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]
17. Gottesman II, Gould TD. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
18. Snitz BE, Macdonald AW 3rd, 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]
19. Sitskoorn MM, Aleman A, Ebisch SJ, Appels MC, Kahn RS. Cognitive deficits in relatives of patients with schizophrenia: a meta-analysis. *Schizophr Res*. 2004; 71:285–295. [PubMed: 15474899]
20. Ma X, Wang Q, Sham PC, Liu X, Rabe-Hesketh S, Sun X, et al. Neurocognitive deficits in first-episode schizophrenic patients and their first-degree relatives. *Am J Med Genet B Neuropsychiatr Genet*. 2007; 144B:407–416. [PubMed: 17440937]
21. Egan MF, Goldberg TE, Gscheidle T, Weirich M, Rawlings R, Hyde TM, et al. Relative risk for cognitive impairments in siblings of patients with schizophrenia. *Biol Psychiatry*. 2001; 50:98–107. [PubMed: 11527000]
22. Egan MF, Goldberg TE, Gscheidle T, Weirich M, Bigelow LB, Weinberger DR. Relative risk of attention deficits in siblings of patients with schizophrenia. *Am J Psychiatry*. 2000; 157:1309–1316. [PubMed: 10910796]
23. Halpern DF, Benbow CP, Geary DC, Gur RC, Hyde JS, Gernsbacher MA. The science of sex differences in science and mathematics. *Psychological Science in the Public Interest*. 2007; 8:1351.
24. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand Suppl*. 2000; 401:3–38. [PubMed: 10887978]
25. Jimenez JA, Mancini-Marie A, Lakis N, Rinaldi M, Mendrek A. Disturbed sexual dimorphism of brain activation during mental rotation in schizophrenia. *Schizophr Res*. 2010; 122:53–62. [PubMed: 20385471]
26. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. *Int Rev Psychiatry*. 2010; 22:417–428. [PubMed: 21047156]
27. Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, et al. The Consortium on the Genetics of Endophenotypes in Schizophrenia: model recruitment, assessment, and endophenotyping methods for a multisite collaboration. *Schizophr Bull*. 2007; 33:33–48. [PubMed: 17035358]
28. Greenwood TA, Lazzeroni LC, Murray SS, Cadenhead KS, Calkins ME, Dobie DJ, et al. Analysis of 94 candidate genes and 12 endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia. *Am J Psychiatry*. 2011; 168:930–946. [PubMed: 21498463]
29. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet*. 1998; 62:1198–1211. [PubMed: 9545414]

30. Gur RE, Calkins ME, Gur RC, Horan WP, Nuechterlein KH, Seidman LJ, et al. The Consortium on the Genetics of Schizophrenia: neurocognitive endophenotypes. *Schizophr Bull.* 2007; 33:49–68. [PubMed: 17101692]
31. Stone WS, Giuliano AJ, Tsuang MT, Braff DL, Cadenhead KS, Calkins ME, et al. Group and site differences on the California Verbal Learning Test in persons with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia (COGS). *Schizophr Res.* 2011; 128:102–110. [PubMed: 21288694]
32. Horan WP, Braff DL, Nuechterlein KH, Sugar CA, Cadenhead KS, Calkins ME, et al. Verbal working memory impairments in individuals with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia. *Schizophr Res.* 2008; 103:218–228. [PubMed: 18406578]
33. Vaskinn A, Sundet K, Simonsen C, Hellvin T, Melle I, Andreassen OA. Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder. *Neuropsychology.* 2011; 25:499–510. [PubMed: 21463042]

Figure 1.

Neurocognitive Profiles of Community Comparison Subjects (CCS), Fathers (FA), Brothers (BR), Male Probands (PR M), Mothers (M), Sisters (SIS) and Female Probands (PR F). Domain scores were standardized to z-scores using CCS mean and standard deviation *and age adjusted using linear regression*. Verbal memory n's: CCS=304; Proband=177; Sibling=221; Mother=55; Father=37.

Figure 2.

Standardized mean difference (SMD) and 95% confidence intervals by neurocognitive profile, when compared to proband. Domains are presented in alphabetical order. Values greater than 0 indicate relatives' ability is higher than probands' performance. SMD represents the difference between group means standardized by pooled standard deviation.

Table 1
Demographic Characteristics of Probands, Relatives and Community Comparison Subjects

Group	n	Age		Sex M/F% (<i>p value</i>) ^b		Education	
		Mean years (<i>p value</i>) ^b	sd	Mean years (<i>p value</i>) ^b	sd	Mean years (<i>p value</i>) ^b	sd
Proband	369	34.86 (0.129)	11.04	76/24 (0.000)		13.44 (0.000)	2.08
Sibling ^a	480	36.78 (0.377)	11.57	44/56 (0.776)		15.29 (0.800)	2.45
Brother ^a	214	35.28 (0.403)	10.48	100/0		15.23 (0.630)	2.58
Sister ^a	266	37.89 (0.048)	12.18	0/100		15.34 (0.957)	2.34
Father ^a	276	64.35 (0.000)	11.03	100/0		15.34 (0.951)	3.22
Mother ^a	316	62.34 (0.000)	10.50	0/100		14.93 (0.055)	2.89
Community Comparison Subject	526	36.10	12.67	43/57		15.33	2.36

^a All family members are unaffected by schizophrenia/schizoaffective disorder.

^b Group compared with Community Comparison Subject. Mean levels compared using unpaired t-test, and proportions compared using binomial proportion test.

Table 2

Heritability Estimates of the Neurocognitive Domains

Domain	n	H ² ±SE	95% CI	P Value	Age	Sex	Covariate P Value ^a	Variance explained by covariates
ABF ^b	939	0.26±0.06	0.14 to 0.38	<0.001	<0.001	0.46		0.14
WM ^b	919	0.22±0.07	0.08 to 0.30	0.01	0.02	0.32		0.11
VME ^b	459	0.18±0.08	0.02 to 0.34	0.01	0.04	0.19		0.01
FME ^b	963	0.29±0.05	0.20 to 0.39	<0.001	<0.001	0.01		0.12
SME ^b	951	0.33±0.06	0.21 to 0.45	<0.001	<0.001	0.95		0.10
SPA ^b	887	0.51±0.06	0.39 to 0.63	<0.001	<0.001	<0.001		0.19
EMO ^b	947	0.19±0.05	0.09 to 0.29	<0.001	<0.001	0.00		0.17
S-M ^b	950	0.35±0.05	0.25 to 0.45	<0.001	<0.001	0.14		0.16

Abbreviations: ABF= Abstraction and Mental Flexibility; WM=Working Memory; VME= Verbal Memory; FME=Face Memory; SME=Spatial Memory; SPA=Spatial Processing; EMO=Emotion Processing; S-M=Sensorimotor Dexterity; CI=confidence interval.

^a Only significant covariates included in heritability analysis of each domain

^b Significantly heritable domains (p<0.05)

Table 3

Estimates of Proband Effect on Each Unaffected Relative as Estimated from the Linear Regression Model

Relationship	Domain	N of pairs	Proband Effect	P Value	95% CI	Significant Covariates
Sibling	ABF	349	0.104	0.009	0.03 to 0.18	(-) Sib age*** (+) Ed Yrs*
	WM	327	0.047	0.150	-0.02 to 0.11	(-) Sib age*** (-) Sib sex* (+) Ed Yrs***
	VME	165	0.039	0.527	-0.08 to 0.16	
	FME	373	0.144	0.000	0.07 to 0.22	(+) Ed Yrs*
	SME	366	0.214	0.000	0.13 to 0.30	(-) Sib age**
	SPA	326	0.310	0.000	0.23 to 0.39	(-) Sib sex***
	EMO	366	0.092	0.010	0.02 to 0.16	(-) Sib sex*
	S-M	363	0.099	0.002	0.04 to 0.16	(-) Sib age***
	ABF	90	0.126	0.214	-0.07 to 0.33	(-) Father age* (+) Ed Yrs*
	WM	79	0.083	0.287	-0.07 to 0.24	
	VME	27	0.012	0.936	-0.29 to 0.31	
	FME	93	0.009	0.916	-0.16 to 0.18	(-) Father age** (+) Ed Yrs*
	SME	89	0.028	0.778	-0.17 to 0.22	
Mother	SPA	82	0.110	0.229	-0.07 to 0.29	(+) Ed Yrs**
	EMO	89	0.098	0.311	-0.09 to 0.29	
	S-M	90	-0.004	0.962	-0.18 to 0.17	(+) Proband sex*
	ABF	128	0.111	0.128	-0.03 to 0.25	(+) Proband sex* (+) Ed Yrs*
	WM	120	0.078	0.164	-0.03 to 0.19	
	VME	44	0.105	0.324	-0.11 to 0.32	
	FME	134	0.219	0.004	0.07 to 0.37	
	SME	132	0.086	0.258	-0.06 to 0.24	

Relationship	Domain	N of pairs	Proband Effect	P Value	95% CI	Significant Covariates
	SPA	117	0.226	0.010	0.05 to 0.40	
	EMO	130	0.021	0.763	-0.12 to 0.16	
	S-M	130	0.181	0.014	0.04 to 0.33	(-) Mother age*

Abbreviations: ABF= Abstraction and Mental Flexibility; WM=Working Memory; VME= Verbal Memory; FME=Face Memory; SME=Spatial Memory; SPA=Spatial Processing; EMO=Emotion Processing; SM=Sensorimotor Dexterity; CI=confidence interval; Ed Yrs=years of education.

* p<0.05,
** p<0.01,
*** p<0.001

Table 4

Estimates (95% CI) of proband effect on each unaffected relative of SAME SEX as estimated from the linear regression model.

Relationship	Domain	N of pairs	Proband Effect	P Value	95% CI	Significant Covariates
Brother	ABF	121	0.113	0.137	-0.04 to 0.26	
	WM	113	0.049	0.281	-0.04 to 0.14	
	VME	42	0.391	0.359	-0.39 to 0.15	
	FME	127	0.174	0.005	0.05 to 0.29	
	SME	93	0.161	0.026	0.02 to 0.30	
	SPA	78	0.245	0.004	0.08 to 0.41	
	EMO	89	0.223	0.005	0.07 to 0.38	(-) Sib age *
	S-M	88	0.139	0.142	-0.05 to 0.33	
Sister	ABF	45	0.035	0.764	-0.20 to 0.27	
	WM	43	0.124	0.390	-0.17 to 0.41	
	VME	20	0.179	0.448	-0.31 to 0.67	
	FME	49	0.110	0.419	-0.16 to 0.38	
	SME	46	0.074	0.608	-0.22 to 0.37	
	SPA	43	0.166	0.154	-0.07 to 0.40	
	EMO	47	0.182	0.877	-0.18 to 0.16	
	S-M	47	0.010	0.450	-0.13 to 0.15	
Father	ABF	67	0.085	0.469	-0.15 to 0.32	(+) Ed Yrs * (-) Father age *
	WM	58	0.047	0.577	-0.12 to 0.22	
	VME	10	-0.104	0.723	-0.82 to 0.61	
	FME	70	0.022	0.812	-0.16 to 0.21	(+) Ed Yrs *
	SME	54	0.021	0.825	-0.17 to 0.21	(+) Edu * (-) Father age *
	SPA	46	0.006	0.954	-0.22 to 0.23	(+) Ed Yrs (p=0.05)
	EMO	50	0.143	0.267	-0.11 to 0.40	(-) Proband age *
	S-M	51	-0.040	0.790	-0.34 to 0.26	
	ABF	27	0.021	0.887	-0.29 to 0.33	
Mother	ABF	27	0.021	0.887	-0.29 to 0.33	

Relationship	Domain	N of pairs	Proband Effect	P Value	95% CI	Significant Covariates
	WM	29	0.051	0.702	−0.22 to 0.32	
	VME	9	0.541	0.348	−0.88 to 1.96	
	FME	31	−0.015	0.936	−0.38 to 0.35	
	SME	27	−0.053	0.798	−0.48 to 0.37	
	SPA	23	0.016	0.959	−0.62 to 0.66	
	EMO	27	0.022	0.852	−0.22 to 0.26	
	S-M	28	0.162	0.172	−0.08 to 0.41	

Abbreviations: ABF= Abstraction and Mental Flexibility; WM=Working Memory; VME= Verbal Memory; FME=Face Memory; SME=Spatial Memory; SPA=Spatial Processing; EMO=Emotion Processing; SM=Sensorimotor Dexterity; CI=confidence interval; Ed Yrs= years of education.

* p<0.05

Table 5

Estimates (95% CI) of proband effect on each unaffected relative of the OPPOSITE SEX as estimated from the linear regression model.

Relationship	Domain	N of pairs	Proband Effect	P Value	95% CI	Significant Covariates
Brother	ABF	37	-0.003	0.983	-0.26 to 0.26	
	WM	36	-0.149	0.222	-0.39 to 0.09	
	VME	14	0.060	0.854	-0.66 to 0.78	
	FME	41	-0.038	0.752	-0.28 to 0.20	
	SME	41	-0.032	0.618	-0.27 to 0.20	
	SPA	34	-0.147	0.358	-0.47 to 0.18	(+) Ed Yrs *
						(-) Sib age **
Sister	EMO	39	-0.074	0.555	-0.32 to 0.18	
	S-M	41	0.029	0.698	-0.12 to 0.18	
	ABF	99	0.104	0.147	-0.04 to 0.25	
	WM	107	0.091	0.105	-0.02 to 0.20	(+) Ed Yrs ***
	VME	47	0.149	0.216	-0.09 to 0.39	
	FME	147	0.178	0.008	0.05 to 0.31	
	SME	108	0.092	0.278	-0.08 to 0.26	
	SPA	88	0.433	0.000	0.23 to 0.63	
	EMO	106	0.066	0.307	-0.06 to 0.19	
	S-M	101	0.082	0.885	0.00 to 0.15	
Father	ABF	23	0.349	0.139	-0.12 to 0.82	(-) Father age *
	WM	21	0.216	0.386	-0.29 to 0.73	
	VME	10	0.399	0.378	-0.66 to 1.46	
	FME	23	-0.075	0.732	-0.53 to 0.38	(-) Father age *
	SME	23	-0.068	0.527	-0.50 to 0.31	
	SPA	20	-0.131	0.609	-0.66 to 0.40	
	EMO	23	0.017	0.949	-0.52 to 0.55	
	S-M	24	-0.110	0.268	-0.31 to 0.09	
Mother	ABF	65	0.057	0.623	-0.17 to 0.29	
	WM	70	0.055	0.479	-0.09 to 0.21	

Relationship	Domain	N of pairs	Proband Effect	P Value	95% CI	Significant Covariates
	VME	21	−0.066	0.756	−0.51 to 0.37	
	FME	94	0.175	0.046	0.00 to 0.35	
	SME	70	0.215	0.034	0.02 to 0.41	
	SPA	57	0.335	0.022	0.05 to 0.62	
	EMO	66	0.024	0.821	−0.19 to 0.24	
	S-M	93	0.172	0.187	−0.10 to 0.35	

Abbreviations: ABF= Abstraction and Mental Flexibility; WM= Working Memory; VME= Verbal Memory; FME=Face Memory; SME= Spatial Memory; SPA= Spatial Processing; EMO=Emotion Processing; S-M=Sensorimotor Dexterity; CI=confidence interval; Ed Yrs= years of education.

* p<0.05