Schizophrenia Research xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia

Li-Shiun Chen [a,*], Treva K. Rice [a,b], Paul A. Thompson [b], Deanna M. Barch [a,c], John G. Csernansky [a,d]

[a] Department of Psychiatry, Washington University School of Medicine, United States
[b] Division of Biostatistics, Washington University, St. Louis, MO, United States
[c] Department of Psychology, Washington University, St. Louis, MO, United States
[d] Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

ARTICLE INFO

Article history:
Received 26 November 2008
Received in revised form 19 March 2009
Accepted 20 March 2009
Available online xxxx

Keywords:
Schizophrenia
Familial aggregation
Neurocognition
Siblings

ABSTRACT

Objective: Neurocognitive impairment was found to be heritable in individuals with schizophrenia and their relatives. However, the heritability of neurocognitive measures in families with and without schizophrenia has not been directly compared. In this study, we examined the genetic structure of clinical and neurocognitive measures in sibling pairs with and without schizophrenia to test the hypothesis that the familial aggregation of such measures may be altered by having schizophrenia.
Method: A total of 278 subjects including patients with schizophrenia and their non-psychotic full siblings, healthy controls, and their full siblings were recruited. Heritability was estimated for working memory, episodic memory, executive function and attention, as well as clinical features, such as positive, negative and disorganization symptoms.
Results: Many clinical and cognitive domains were impaired in subjects with schizophrenia and their non psychotic siblings. Negative symptoms, working memory, episodic memory and executive function, but not positive, disorganization symptoms and attention, were found to be significantly heritable in all sibling pairs. However, the heritability of working memory function was significantly ($\chi^2_{(d.f.=6)} = 13.9, p = .031$) decreased in proband sibling pairs ($h^2 = .38$) as compared to control sibling pairs ($h^2 = .95$). Significant genetic correlations were observed between negative symptoms and the cluster of working memory, episodic memory and executive function.
Conclusions: Several neurocognitive measures were heritable in sibling pairs with and without schizophrenia. However, schizophrenia reduced the heritability of working memory, perhaps due to disease-related environmental or genetic factors. Evidence for potential pleiotropy will inform future phenotypic studies.

1. Introduction

Cognitive impairment has been suggested as a schizophrenia-related endophenotype (Mohamed et al., 1999; Gottesman and Gould, 2003; Greenwood et al., 2007). Prior research suggests that neurocognitive measures may qualify as schizophrenia-related endophenotypes (Goldberg et al., 1990; Dollfus et al., 2002; Toulopoulou et al., 2007; Wedenoja et al., 2008). For example, impairments in working memory, episodic memory, and executive function are present in patients with schizophrenia across all phases of illness, and have been observed in the unaffected relatives of patients with schizophrenia (e.g., Toulopoulou et al., 2003; Snitz et al., 2006). Furthermore, variation in quantifiable traits such as working memory, have been associated with specific allelic variants (Wedenoja et al., 2008).

* Corresponding author. Department of Psychiatry (Box 8134), Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110, United States. Tel.: +1 314 747 2160; fax: +1 314 747 2182.
E-mail addresses: chenli@psychiatry.wustl.edu (L.-S. Chen), rice@wubios.wustl.edu (T.K. Rice), paul@wubios.wustl.edu (P.A. Thompson), dbarch@artsci.wustl.edu (D.M. Barch), jgc@northwestern.edu (J.G. Csernansky).

0920-9964/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.schres.2009.03.030

Heritability in the general population is an important criterion for a disease-related endophenotype, and there is much evidence to support the heritability of neurocognition. Heritability for working memory has been estimated to be 33–64% (Ando et al., 2001; Wright et al., 2001; Glahn et al., 2007; Greenwood et al., 2007; Kremen et al., 2007). Genetic studies on episodic memory and executive function have shown a wide range of heritability from near 0 to 49% (Johansson et al., 1999; Cannon et al., 2000; Polderman et al., 2006; Greenwood et al., 2007; Taylor 2007). Recent results from a multi-site study of neurocognition, the Consortium on the Genetics of Schizophrenia, have added support to the hypothesis that neurocognition is a schizophrenia-related endophenotype (Gur et al., 2007), but suggest that both genetic and environmental factors can influence neurocognitive performance in patients with schizophrenia and their relatives (Greenwood et al., 2007).

Very few studies have directly compared the heritability of neurocognitive measures in sibling pairs with and without schizophrenia. This comparison is important, as environmental factors associated with the disease process of schizophrenia could reduce the heritability of potential phenotypes, while genetic influences on the illness might actually increase heritability of such characteristics. In a recent study of the relatives of patients with schizophrenia, the heritability of neurocognitive measures was estimated in the full sample and in a subsample that excluded affected individuals with schizophrenia (Glahn et al., 2007). The results suggested that heritability estimates were increased or decreased by the inclusion of affected individuals, depending on the measure examined. However, this study did not allow the comparison of heritability in families with and without schizophrenia. Cannon and colleagues used a neuropsychological battery to examine disease versus liability predictors in twin pairs discordant for schizophrenia and control twin pairs (Cannon et al., 2000). For the disease predictors among MZ twins, they reported numerically lower familiality\Intra-Class Correlations (ICCs) in proband twin pairs than in control twin pairs, suggesting that the disease process of schizophrenia could alter the ICC of some measures such as episodic memory.

In the current study, we characterized the heritability structure of clinical and neurocognitive measures in sibling pairs with and without schizophrenia and tested the hypothesis that the familial aggregation of these domains was influenced by the presence of the disorder. We first determined which neurocognitive deficits were present in the siblings of subjects with schizophrenia as compared to the siblings of controls (Delawalla et al., 2006). Next, we examined the familiality of these measures by estimating their heritability in all sibling pairs, control sibling pairs and proband sibling pairs with schizophrenia. The availability of sibling pairs with and without schizophrenia provided an unique opportunity to both estimate the heritability of neurocognitive measures in the non-diseased population and to determine how this heritability might be altered by schizophrenia. Such alterations might be due to the presence of shared disease vulnerability, the development of the disease in one sibling, or non-shared environmental factors associated with treatment for the disease. We also tested the hypothesis that pleiotropy (evidence of shared genes for multiple traits)

Table 1
Descriptive statistics for the clinical and neurocognitive domains across four subject groups.

Demographic variable	Affected proband (PRO)		Proband siblings (PRO-SIB)		Healthy controls (CON)		Control siblings (CON-SIB)				
	n	Mean(SE)	*n*	Mean(SE)	*n*	Mean(SE)	*n*	Mean(SE)	F or χ^2	*p*	Effect size
Age	56	22.7(.44)	65	22.0(.53)	77	20.6 (.46)	80	19.7 (.50)	7.07	<.001	.58
Education (years)	56	11.5(.26)	65	12.6(.36)	77	12.7 (.35)	80	12.0 (.41)	6.14	<.001	−.44
Parental education (years)	51	15.2(.40)	61	15.0(.35)	75	14.8(.23)	79	14.7(.23)	0.58	.63	
Gender (%male)	56	76.8%	65	41.5%	77	53.2%	80	33.8%	34.1	<.0001	
Race (%Caucasian)	56	57.1%	65	61.5%	77	66.2%	80	67.5%	6.58	.086	
Clinical domains											
Z_postive symptoms	56	1.21(.14)	65	−.21(.047)	77	−.39(.034)	80	−.28(.045)	43.8	<.0001	2.06
Z_negative symptoms	56	1.18(.097)	65	−.13(.062)	77	−.36(.034)	80	−.36(.039)	75.2	<.0001	2.76
Z_disorganization	56	1.12(.15)	65	−.11(.057)	77	−.32(.028)	80	−.26(.042)	37.4	<.0001	1.01
Neurocognitive domains											
Z_Working memory	53	−.66(.11)	60	.033(.096)	70	.24(.080)	75	.17(.077)	14.9	<.0001	−1.21
Z_Episodic memory	52	−.84(.11)	60	.043(.072)	70	.30(.078)	75	.32(.076)	30.3	<.0001	−1.56
Z_Executive function	53	−.64(.12)	60	.10(.057)	70	.25(.064)	75	.20(.068)	15.8	<.0001	−1.26
Z_attention	36	−.71(.17)	34	.25(.083)	51	.15(.11)	53	.23(.11)	9.50	<.0001	−.94

The working memory domain ($\alpha = 0.82$) (Harms et al., 2007) consisted of subtests from the Wechsler Memory Scale — Third Edition (scaled scores on letter-number sequencing, digit span, and spatial span) (Wechsler, 1997), percentage correct on the 2-back version of the N-back task (Braver et al., 1997), 4-item d' score from the Continuous Performance Task (CPT). The episodic memory domain ($\alpha = 0.77$) consisted of scaled scored on immediate recall on family pictures and logical memory (also subtests of Wechsler Memory Scale — Third Edition), and the free recall score for trials 1-5 on the California Verbal Learning Test (Delis et al., 1983). The executive function domain ($\alpha = 0.73$) included time to completion on Trails B (Reitan and Wolfson, 1985), number of novel words generated on the category and verbal fluency tasks (Benton et al., 1976), scaled scores on the matrix reasoning subtest from the WAIS-III and the score for perseverative errors (reversed in sign) from the Wisconsin Card Sort (Berg and Grant, 2003). The attention domain ($\alpha = 0.73$) consisted of 2 different versions of the CPT — AX and Degraded.

The age distribution of our sample is from 9 to 31 with mean = 21.1, standard error 0.26, standard deviation 4.25. The lowest to highest quartile are 19 and 24 years of age.

All models used *z*-scored endophenotype measures, adjusted for covariates (age, gender).

There was no statistical difference in parental years of education and racial distribution across the groups. However, there were group differences in age ($F_{3, 128} = 7.07$, $p < .001$) and gender (χ^2 (3) = 26.7, $p < .001$). As expected, there was also a group difference in years of education ($F_{3, 128} = 6.14$, $p < .001$) with PRO having fewer years of education.

Please cite this article as: Chen, L.-S., et al., Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.03.030

could link clinical and neurocognitive features in all sibling pairs.

2. Methods

2.1. Subjects

The subjects for this study were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University School of Medicine in St. Louis, and included: (1) probands with DSM-IV schizophrenia (PRO) ($n=56$); (2) their full non-psychotic siblings (PRO-SIB) ($n=65$); (3) healthy control participants (CON) ($n=77$); and (4) their siblings (CON-SIB) ($n=80$). All subjects gave written informed consent for participation following a complete description of the risks and benefits of participating in the study.

All subjects were diagnosed using DSM-IV criteria on the basis of a consensus between a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 2001). Participants (in any group) were excluded if they: (a) met DSM-IV criteria for substance dependence or severe/moderate abuse during the 6 months preceding assessment; (b) had a clinically unstable or severe medical disorder, or a medical disorder that confounded the assessment of psychiatric diagnosis or rendered research participation dangerous; (c) had a history of head injury with documented neurological sequelae or loss of consciousness; or (d) met DSM-IV criteria for mental retardation (mild or greater in severity).

Probands were recruited from local inpatient and outpatient facilities, and were stabilized on antipsychotic medication for at least two weeks before participating in the study. Controls were recruited using local advertisements in the same community, and were required to have no lifetime history of Axis I psychotic or major mood disorders and no first-degree relatives with a psychotic disorder. CON-SIB subjects were enrolled in an identical manner to PRO-SIB subjects, and met the same general and specific inclusion and exclusion criteria. However, potential proband siblings were excluded if they had a lifetime history of any DSM-IV Axis I psychotic disorder, but not other DSM-IV Axis I disorders.

2.2. Clinical and cognitive assessments

Psychopathology and cognitive function were assessed in a manner as described in Delawalla et al. (2006). Please see Table 1 (footnote) for detailed description of individual tests. Briefly, psychopathology was assessed using the Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen et al., 1995), the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 1999), and the Chapman Psychosis Proneness Scales (Chapman et al., 1995). Neurocognition was assessed using a battery of neuropsychological tests. The raw scores from the individual neuropsychological tests were first standardized by *z*-scores using the means and standard deviations computed across all subjects who have participated in research studies at the CCNMD at Washington University, and selected clusters of standardized *z*-scores were then averaged to yield four cognitive domains — working memory, episodic memory, executive function, attention (individual tests in Table 1). The reliability estimates for domain scores and individual tests are shown in Supplemental Table 1.

2.3. Data analysis

We compared age, gender, race, and years of education across four subject groups using a mixed-model analysis of variance (i.e., PROC MIXED in SAS 9.1; SAS Institute Inc., Cary, NC) to account for the familial correlations of siblings within the same family, since siblings members are not independent observations. F statistics or Pearson χ^2 were used to examine the differences among all four subject groups. We modeled the associations of each cognitive domain with covariates (age, gender, indicator for having schizophrenia, indicator for having sibling with schizophrenia) using random effects regression models.

We estimated heritability (h^2) using a variance components analysis as implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software program (version 4.0)

Table 2
Random effects regression models of clinical and neurocognitive domains: Proband (PRO) and proband siblings (PRO-SIB) compared to control and control siblings.

Dependent variable	Covariates/predictor variable			
	Male gender	Age	PRO	PRO-SIB
	β (se)	β (se)	β (se)	β (se)
Clinical domains				
Z_postive symptoms	−.027(.072)	−.014(.0084)	1.60(.095)***	.15(.086)
Z_negative symptoms	.098(.058)	−.012(.0071)	1.55(.080)***	.27(.074)***
Z_disorganization	.027(.073)	−.0084(.0086)	1.42(.098)***	.20(.088)*
Neurocognitive domains				
Z_Working memory	.21(.085)*	.047(.011)***	−1.04(.12)***	−.25(.11)*
Z_Episodic memory	−.16(.081)*	.021(.010)*	−1.15(.12)***	−.33(.11)**
Z_Executive function	−.026(.075)	.038(.0092)***	−.96(.10)***	−.20(.097)*
Z_ Attention	−.21(.13)	.033(.018)	−.87(.17)***	.024(.16)

PRO: proband with schizophrenia, PRO-SIB: sibling of the proband.
Covariates in the model include indicator for being a proband, indicator for being a proband sibling, age and gender.
Random Effects Model is used to estimate the regression coefficients.
*: $p<.05$, **: $p<.01$, ***: $p<.001$.

Please cite this article as: Chen, L.-S., et al., Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.03.030

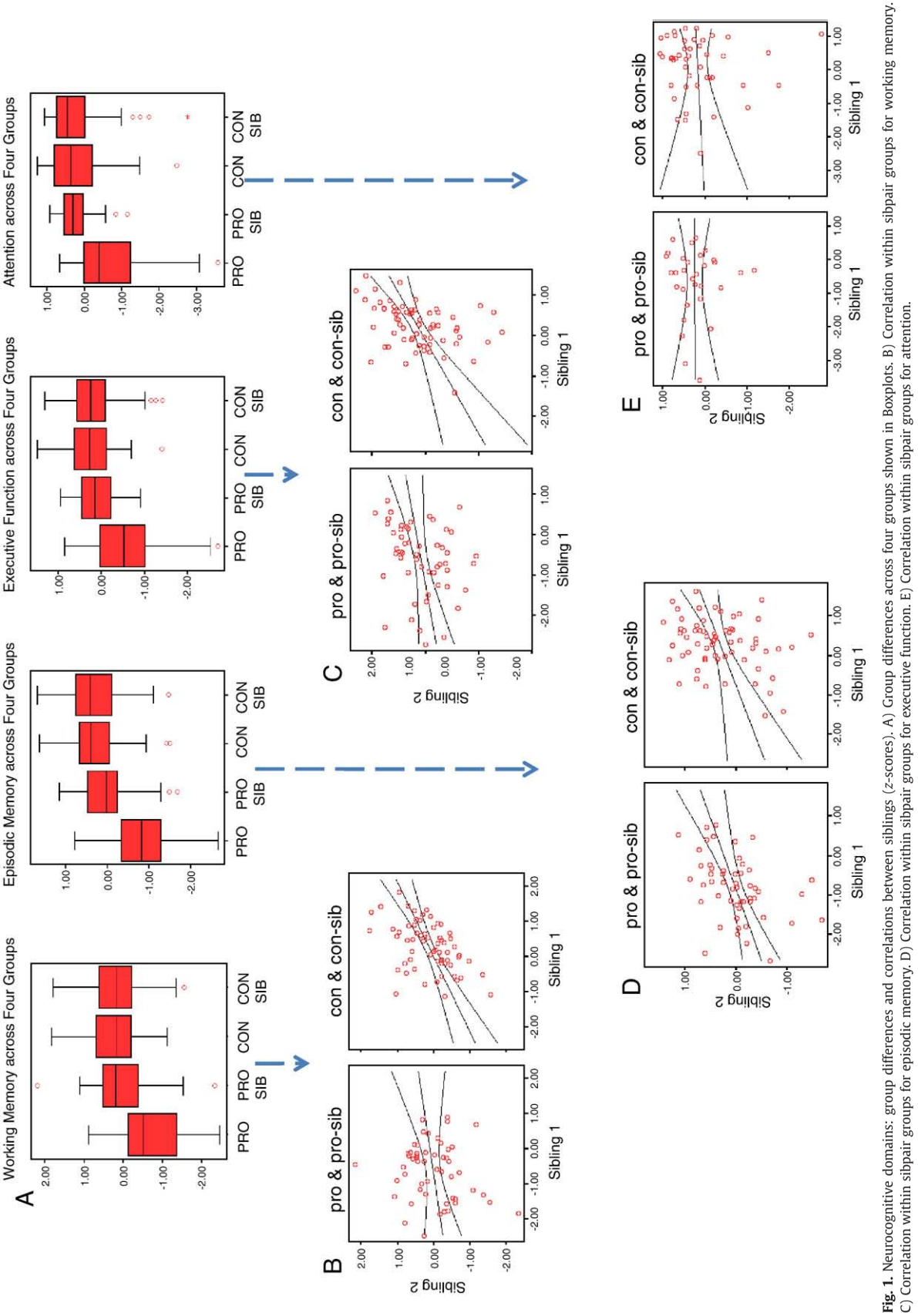

Fig. 1. Neurocognitive domains: group differences and correlations between siblings (*z*-scores). A) Group differences across four groups shown in Boxplots. B) Correlation within sibpair groups for working memory. C) Correlation within sibpair groups for episodic memory. D) Correlation within sibpair groups for executive function. E) Correlation within sibpair groups for attention.

Please cite this article as: Chen, L.-S., et al., Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.03.030

Table 3
Heritability estimates of the clinical and neurocognitive endophenotypes in all sibling pairs, control sibling pairs, and proband sibling pairs.

	All Sibpairs ($n=278$)			Control sibpairs ($n=157$)			Proband sibpairs ($n=121$)		
	h^2	SE	p Value	h^2	SE	p Value	h^2	SE	p Value
Clinical domains									
Positive Symptoms	.067	.055	.11	.20	.23	.20	0.0	–[a]	.50
Negative Symptoms	.32	.062	<.001	.67	.20	.0012	.19	.14	.092
Disorganization	.08	.057	.082	.35	.22	.060	0.0	–[a]	.50
Neurocognitive domains									
Working memory	.53	.11	<.001	.85	.19	<.001	.38	.23	.052
Episodic memory	.57	.11	<.001	.64	.22	.0032	.43	.17	.0070
Executive function	.40	.096	<.001	.55	.21	.0064	.27	.12	.015
Attention	.039	.16	.40	.055	.31	.43	0.0	–[a]	.50

All models used z-scored endophenotype measures, adjusted for covariates (age, gender) and ascertainment bias.
–[a]: not estimable.

(Almasy and Blangero, 1998). The total trait variance was partitioned into two components: (a) a component due to additive polygenic effects, and (b) a component due to the effects of random environmental factors that are uncorrelated among siblings. This method applied maximum likelihood estimation to a mixed effects model that incorporated fixed effects for known covariates and variance components for genetic and random environmental effects. No shared environmental influence was assumed (cite McGue M 1983). Age and gender were included as covariates. A correction for ascertainment bias was implemented in SOLAR involving conditioning on the trait values of the probands under the assumption that the probands are randomly selected. Since the neurocognitive domains were correlated, we computed bivariate genetic and environmental correlations using SOLAR to examine possible pleiotropy where a single gene or set of genes affect more than two traits simultaneously. The bivariate genetic correlation represents the percentage of variance that is common in the two traits due to the same genes. We estimated h^2 of all neurocognitive endophenotypes in all sibling pairs. To compare heritability in the two types of sibpairs, we first estimated h^2 in control sibling pairs, h^2 in proband sibling pairs, and h^2 in all sibling pairs. A log likelihood heterogeneity test was used to examine if the derived heritability estimates differed across the two types of sibling pairs by comparing the likelihood estimates in these 3 models. The difference of −2 Log Likelihood of these models follows a χ^2 distribution with degree of freedom being the difference of parameters estimated in the comparison (Rice et al., 1991).

3. Results

Demographic information for the four subject groups is summarized in Table 1. The age distribution of our sample is from 9 to 31 with mean = 21.1, standard error 0.26, standard deviation 4.25. The lowest to highest quartile are 19 and 24 years of age. The PRO group showed higher clinical symptoms and deficits in functioning on all neurocognitive domains when compared to the CON and CON-SIB groups (Table 2). In turn, the PRO-SIB group showed attenuated, but significant, increases in negative and disorganization symptoms but not positive symptoms, and significant deficits in working memory, episodic memory and executive function, but not attention. These data showed that having schizophrenia was associated with global neurocognitive impairment, while having the genetic vulnerability of schizophrenia was associated with more selective clinical and neurocognitive impairments. See Supplemental Table 2 for group comparisons for the individual tests within each domain.

Next, we computed the between-sibling correlations in neurocognitive domains. We found several different patterns in terms of between-sibling correlations in relationship to the group differences. Similar group differences were present for working memory, episodic memory, and executive function (see Fig. 1A). For working memory and executive function (see Fig. 1B/C), the moderate correlations observed in the CON/CON-SIB pairs ($r=.48$, $p<.001$; $r=.38$, $p=.002$) were decreased and not significant in the PRO/PRO-SIB pairs ($r=.16$, $p=.25$; $r=.26$, $p=.064$). However, the correlations for episodic memory (see Fig. 1D) were similar in both sibpair types ($r=.30$, $p=.017$ in CON/CON-SIB pairs, $r=.39$, $p=.004$ in PRO/PRO-SIB pairs). No significant correlations were observed for attention (see Fig. 1E) in either type of sibling pairs ($r=.046$, $p=.76$ in CON/CON-SIB pairs; $r=.011$, $p=.96$ in PRO/PRO-SIB pairs). This indicates that between-sibling correlations of neurocognitive measures can vary with the sibpair type (e.g., those with or without schizophrenia).

The heritability estimates for the clinical and neurocognitive domain measures are summarized in Table 3. Negative symptoms, but not positive or disorganization symptoms, were heritable. Working memory, episodic memory and executive function were all significantly heritable. Attention was found to be not heritable. Supplemental Table 3 shows the heritability estimates for individual neurocognitive tests within each domain.

Since the between-sibling correlations for some neurocognitive domains varied according to sibpair type (Fig. 1), we estimated heritabilities separately for each type of sibling pairs. We observed a general pattern of higher heritability estimates in the CON/CON-SIB pairs and lower heritability estimates in the PRO/PRO-SIB pairs. The heritability estimates were numerically attenuated for negative symptoms, working memory, episodic memory, and executive function among PRO/PRO-SIB pairs as compared to CON/CON-SIB pairs. The heterogeneity log likelihood χ^2 test of the difference between the two subgroups showed a statistically significant difference ($\chi^2=13.92$ with 6 d.f., $p=0.031$) for working memory. The attenuation in the heritability of negative symptoms, episodic memory and executive function among proband siblings did not reach statistical significance with the heterogeneity test, although the numerical patterns were in the same directions as for working memory. Comparisons of heritabilities for individual tests within domain measures are shown in Supplemental Table 2.

Please cite this article as: Chen, L.-S., et al., Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.03.030

Table 4a
Genetic correlations between clinical and neurocognitive domains (a) Pearson correlation between clinical and neurocognitive domains.

	Positive symptoms	Negative symptoms	Disorganization	Working memory	Episodic memory	Executive function	Attention
Positive symptoms	1						
Negative symptoms	0.61***	1					
Disorganization	0.52***	0.66***	1				
Working memory	−0.29***	−0.47***	−0.43***	1			
Episodic memory	−0.30***	−0.45***	−0.43***	0.53***	1		
Executive function	−0.29***	−0.55***	−0.47***	0.63***	0.57***	1	
Attention	−0.21**	−0.34***	−0.29***	0.51***	0.35***	0.42***	1

Controlling for age, gender and sibpair type.
** $p<.01$.
*** $p<.001$.

To test the hypothesis that at least some of the neurocognitive endophenotypic and clinical domain measures are linked construct (i.e., pleiotropy), we examined the correlations between the clinical and neurocognitive domain measures in all sibling pairs. Table 4a shows that there were moderate-to-high correlations among all clinical and neurocognitive domains, adjusting for age, gender and sibpair types. Table 4b shows the strength of the genetic/familial components of the observed correlations between each pair of all seven clinical and neurocognitive domains. After adjusting for age and sex, there were significant genetic bivariate correlations between negative symptoms and three neurocognitive domains (working memory, episodic memory and executive function). In addition, there were statistically significant genetic bivariate correlations between working memory, episodic memory and executive function. For these non-converging models, we conducted alternative analyses using only gender as a covariate given that age distributions were comparable across groups (mean 20–23 years) and age was not significantly associated with the disorganization domain ($p=0.80$). These alternative genetic correlation estimates suggest that disorganization is also significantly associated with working memory, episodic memory and executive function, but not attention. The results suggest there might be common genetic components that influence both negative symptoms and a cluster of neurocognitive deficits (i.e. pleiotropy).

4. Discussion

To our knowledge, this is the first study to directly compare the heritability of both clinical and neurocognitive domain measures in sibling pairs with and without schizophrenia, as well as to examine pleiotropy among these constructs. We confirmed the hypothesis that the neurocognitive domain measures were mostly heritable in healthy sibling pairs. Importantly, we observed statistically higher heritability estimates in CON/CON-SIB pairs compared to PRO/PRO-SIB pairs for working memory. Genetic pleiotropy was suggested by the strong genetic correlations between three major neurocognitive domains (working memory, episodic memory and executive function), and the strong genetic correlation between negative symptoms and the neurocognitive domain cluster consisting of working and episodic memory, and executive function.

The heritability estimates for neurocognitive measures used in the study by Greenwood and colleagues (e.g., CPT, LNS, and CVLT) were comparable to our heritability estimates in our PRO/PRO-SIB pairs, and it is notable that a number of the tests studied by COGS were included in our formulation of the working memory and episodic memory domain measures (Greenwood et al., 2007). The heritability estimate for working memory (.65) from the recent twin study in UK was also similar to our estimate using all sibpairs (Toulopoulou et al., 2007). As noted above, we found that the moderate heritability observed in the CON/CON-SIB pairs was significantly decreased in the PRO/PRO-SIB pairs for working memory, with similar patterns for executive function and episodic memory. This finding is consistent with the results of a prior twin study that found that ICC estimates for verbal episodic memory were attenuated in twin pairs discordant for schizophrenia as compared to healthy twin pairs (Cannon et al., 2000). While the results of our study provide further support for the hypothesis that domains of cognition thought to be central to the neurobiology of schizophrenia are heritable, they also suggest that this heritability is decreased in the presence of the disease and disease vulnerability.

Table 4b
Genetic correlations between clinical and neurocognitive domains (b) Genetic bivariate correlation between clinical and neurocognitive domains.

	Positive symptoms	Negative symptoms	Disorganization	Working memory	Episodic memory	Executive function	Attention
Positive Symptoms	1						
Negative Symptoms	–[a]	1					
Disorganization	–[a]	.67 (.40)	1				
Working Memory	−.53 (.42)	**−.53 (.22)***	**−.80(.30)**[a]	1			
Episodic Memory	−.93 (.63)	**−.84 (.34)***	**−.99(.49)**[a]	**.55(.18)****	1		
Executive Function	−.89 (.66)	**−.87 (.27)****	**−.94(.41)**[a]	**.76(.19)*****	**.50(.16)****	1	
Attention	.46 (1.18)	−.43(1.90)[a]	−.026(1.20)[a]	–[b]	–[b]	–[b]	1

Covariates used were age, gender. –[a]: estimable only when gender was the only covariate. [b]: not estimable even with no covariates.
* $p<.05$.
** $p<.01$.
*** $p<.001$.

Please cite this article as: Chen, L.-S., et al., Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.03.030

The attenuation of the heritability of neurocognitive measures in PRO/PRO-SIB pairs could be explained in several ways. First, the neurocognitive domain measures could be subject to increased unique environmental influence in PRO/PRO-SIB pairs, such as perinatal complications or medication. Alternatively, the neurocognitive domain measures could be subject to decreased genetic/familial influence in the PRO/PRO-SIB pairs. This latter explanation could reflect the fact that genes associated with the risk of developing schizophrenia are present in the ill sibling but not the well sibling. Shared environmental effect has been reported to be small compared to heritability for working memory (Toulopoulou et al., 2007), but tracing the source of heritability estimate changes between healthy and vulnerable twin pairs remains to be studied.

The results also suggest that there is a significant genetic correlation between negative symptoms and the neurocognitive domains of working memory, episodic memory and executive function. These results need to be replicated in future genetic studies of schizophrenia. However, they are consistent with the overarching hypothesis that epigenetic factors in schizophrenia influence potential phenotypic variance (Petronis, 2004).

There were several limitations to our study. First, we focused on neurocognitive domain measures instead of individual tests (see supplemental data for individual test results) because the domain scores were more reliable (see Supplemental Table 1). One could debate which tests should be included in which domain, and further research is needed to understand the way in which results may differ across specific tests thought to assess the same domain (e.g., differential reliability, construct validity, etc.) Furthermore, the variation in assessment tools of clinical symptoms between this study and the others may explain the difference between our findings and others. For example, disorganization symptoms were reported to be heritable by Cardno et al. (Cardno et al., 2001), but not in our study which used different assessment instruments. Based on Table 3, disorganization symptom domain was marginally heritable with $p = 0.082$, a trend level significance. In addition to the variances due to instruments and study populations, another source of variation may be the sibpair types. The studies suggesting disorganization to be most heritable had concordant schizophrenia sibling pairs, while we used a discordant sibling pair design consisted of the proband with schizophrenia and a healthy young sibling (mean age 22 years of age) who may or may develop schizophrenia later on. As such, the variance in positive and disorganization symptoms in healthy siblings may be limited and could have reduced the heritability estimates. Second, heritability was calculated as proportion of the total variance shared between sibling pairs. Unlike a twin study design where variances due to genes and unique environmental factors can be statistically separated, our estimation of heritability must be interpreted as familiality due to both shared genes and shared environments of the sibling pairs. Third, other factors which could influence the assessments of clinical and neurocognitive functioning, such as antipsychotic and other psychotropic medications, were not studied in the current analyses. Further understanding of the familiality of clinical and cognitive function requires studies of non-medicated sibling pairs and concordant unaffected sibling pairs. In addition, our current sample is susceptible to ascertainment bias because these are voluntary patients with siblings who would both consent to volunteer. Another limitation is the power. The statistical power in heritability estimation is a function of number of families, sibship size, type I error, and hypothesized heritability. In the current study with approximately 130 sibpairs, the power of detecting h2 of 0.4 or higher is 0.7–0.8 (Klein, 1974; Shaw, 1987). Therefore, the size of our sample may not possess the sufficient power to detect a smaller heritability than 0.40. The issue of power limits one's interpretation of negative findings. However, we were able to find significant heritability for most neurocognitive measures in our sample. When a higher statistical threshold is applied to adjust for multiple comparisons, most results remain significant, especially for the heritability estimates. When only a p-value less than .01 is considered significant, the bivariate genetic correlations between executive function and working memory, episodic memory and working memory, and executive function and negative symptoms remain significant. Because education may be associated with neurocognitive functioning, we conducted other analyses with age, gender and years of education as covariates and found similar results. The heritability estimates our results are similar and the differences are described in Tables 3 and 4b. Finally, multiple comparisons is always a concern, so the magnitude of actual p values were provided when possible in each table for more conservative significance standards.

Despite these limitations, our results suggest that familial aggregation of clinical and neurocognitive domains in healthy sibling pairs is stronger than that in sibling pairs affected by schizophrenia, especially for working memory, and that there was a significant genetic correlation between negative symptoms and three of our four neurocognitive domains. In future studies, this study model can be applied to test for the presence of specific genetic or environmental factors, while observing changes due to specific genetic and unique environmental influences. For example, the effects of candidate genes for specific or general cognitive features on the observed between-sibling correlations could be tested. Also, known environmental risk factors, such as a history of obstetrical complications, could be included in such models. In addition, one could include markers of brain structure or function as covariates in the estimation of heritability for specific cognitive domains.

Role of the funding source

This research was supported by NIH grants P50 MH071616 and R01 MH56584.

The NIH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Drs. Csernansky, Barch, and Thompson designed the study and wrote the protocol. Drs. Chen and Rice undertook the statistical analyses. Dr. Chen wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Dr. Csernansky has received research grants from the NIMH and NIA, and royalties from Medtronic for a patent held jointly with Washington University School of Medicine, has been a paid consultant for Eli Lilly and Sanofi-Aventis, and has received speakers' honoraria from Janssen Pharmaceutica, Eli Lilly and Bristol-Myers Squibb. Dr. Deanna Barch has received grants from the NIMH, NIA, NARSAD and the McDonnel Center for Systems Neuroscience. All other authors declare that they have no conflict of interest.

Acknowledgements

We thank the staff of the Administration/Assessment and Biostatistical Cores of the CCNMD at Washington University School of Medicine for

collection of the clinical and imaging data and data management. Dr. Li-Shiun Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.schres.2009.03.030.

References

Almasy, L., Blangero, J., 1998. Multipoint quantitative-trait linkage analysis in general pedigrees. Am. J. Hum. Genet. 62 (5), 1198–1211.

Ando, J., Ono, Y., et al., 2001. Genetic structure of spatial and verbal working memory. Beh. Genet. 31 (6), 615–624.

Andreasen, N.C., Arndt, S., Alliger, R., Miller, D., Flaum, M., 1995. Symptoms of schizophrenia. Methods, meanings, and mechanisms. Arch. Gen. Psychiatry 52, 341–351.

Benton, A.L., Hamsher, K., Sivan, A.B., 1976. Multilingual Aphasia Examination. AJA Associates, Iowa City, Iowa.

Berg, E.A., Grant, D.A., 2003. Wisconsin Card Sorting Test. Psychological Assessment Resources.

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 5 (1), 49–62.

Cannon, T.D., Huttunen, M.O., et al., 2000. The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. Am. J. Hum. Genet 67 (2), 369–382.

Cardno, A.G., Sham, P.C., et al., 2001. Twin study of symptom dimensions in psychoses. Br. J. Psychiatry 179, 39–45.

Chapman, J.P., Chapman, L.J., Kwapil, T.R., 1995. Scales for the measurement of Schizotypy. In: Raine, T., Lencz, T., Mednick, S. (Eds.), Schizotypal personality. Cambridge University Press, New York, pp. 79–106.

Delawalla, Z., Barch, D.M., et al., 2006. Factors mediating cognitive deficits and psychopathology among siblings of individuals with schizophrenia. Schizophr. Bull. 32 (3), 525–537.

Delis, D., Kramer, J., Kaplan, E., Ober, B., 1983. California Verbal Learning Test, Research Edition. Psychological Corportation, Cleveland, OH.

Dollfus, S., Lombardo, C., et al., 2002. Executive/attentional cognitive functions in schizophrenic patients and their parents: a preliminary study. Schizophr. Res. 53 (1-2), 93–99.

First, M.B., Spitzer, R.L., et al., (2001). *Structured clinical interview for DSM-IV-TR Axis I disorders - Patient Edition (SCID-I/P, 2/2001 revision)*. New York, Biometrics Research, New York State Psychiatric Institute.

Glahn, D.C., Almasy, L., et al., 2007. Adjudicating neurocognitive endophenotypes for schizophrenia. Am. J. Med. Genet. Part B, Neuropsychiatric Genetics: the Official Publication of the International Society of Psychiatric Genetics 144 (2), 242–249.

Goldberg, T.E., Ragland, J.D., et al., 1990. Neuropsychological assessment of monozygotic twins discordant for schizophrenia. Arch. Gen. Psychiatry 47 (11), 1066–1072.

Gottesman, I.I., Gould, T.D., 2003. The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry 160, 636–645.

Greenwood, T.A., Braff, D.L., et al., 2007. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. Arch. Gen. Psychiatry 64 (11), 1242–1250.

Gur, R.E., Nimgaonkar, V.L., et al., 2007. Neurocognitive endophenotypes in a multiplex multigenerational family study of schizophrenia. Am. J. Psychiatry 164 (5), 813–819.

Harms, M.P., Wang, L., Mamah, D., Barch, D.M., Thompson, P.A., Csernansky, J.G., 2007. Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. J. Neurosci. 27 (50), 13835–13842.

Johansson, B., Whitfield, K., et al., 1999. Origins of individual differences in episodic memory in the oldest-old: a population-based study of identical and same-sex fraternal twins aged 80 and older. J. Geront. Ser. B-Psychol. Sci. Soc. Sci. 54 (3), P173–P179.

Klein, T.W., 1974. Heritability and genetic correlation: statistical power, population comparisons, and sample size. Behav. Genet. 4 (2), 171–189.

Kremen, W.S., Jacobsen, K.C., et al., 2007. Genetics of verbal working memory processes: a twin study of middle-aged men. Neuropsychology 21 (5), 569–580.

Miller, T.J., McGlashan, T.H., Woods, S.W., Stein, K., Driesen, N., Corcoran, C.M., Hoffman, R., Davidson, L., 1999. Symptom assessment in schizophrenic prodromal states. Psychiatr. Q. 70, 273–287.

Mohamed, S., Paulsen, J.S., et al., 1999. Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Arch. Gen. Psychiatry 56 (8), 749–754.

Petronis, A., 2004. The origin of schizophrenia: genetic thesis, epigenetic antithesis, and resolving synthesis. Biol. Psychiatry 55 (10), 965–970.

Polderman, T.J., Gosso, M.F., et al., 2006. A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. Acta Neurol. Belg. 106 (4), 191–207.

Reitan, R., Wolfson, D., 1985. The Halstead-Reitan Neuropsychological Test Battery: Theory and Clinical Interpretation. Neuropsychology Press, Tuscon, Ariz.

Rice, T., Vogler, G.P., et al., 1991. Familial aggregation of lipids and lipoproteins in families ascertained through random and nonrandom probands in the Stanford Lipid Research Clinics Family Study. Am. J. Med. Genet. 39 (3), 270–277.

Shaw, R.G., 1987. Maximum-likelihood approaches applied to quantitative genetics of natural populations. Evolution 41, 812–826.

Snitz, B.E., Macdonald III, A.W., et al., 2006. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr. Bull. 32 (1), 179–194.

Taylor, J., 2007. Heritability of Wisconsin Card Sorting Test (WCST) and Stroop Color-Word Test performance in normal individuals: implications for the search for endophenotypes. Twin Res. Human Genet.: the Official J. Int. Soc. Twin Stud. 10 (6), 829–834.

Toulopoulou, T., Rabe-Hesketh, S., et al., 2003. Episodic memory in schizophrenic patients and their relatives. Schizophr. Res. 63 (3), 261–271.

Toulopoulou, T., Picchioni, M., et al., 2007. Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. Arch. Gen. Psychiatry 64 (12), 1348–1355.

Wechsler, D., 1997. Wechsler Memory Scale, third ed. Psychological Corporation, San Antonio, Tex.

Wedenoja, J., Loukola, A., et al., 2008. Replication of linkage on chromosome 7q22 and association of the regional Reelin gene with working memory in schizophrenia families. Mol. Psychiatry 13 (7), 673–684.

Wright, M., De Geus, E., et al., 2001. Genetics of cognition: outline of a collaborative twin study. Twin Res. 4 (1), 48–56.

Please cite this article as: Chen, L.-S., et al., Familial aggregation of clinical and neurocognitive features in sibling pairs with and without schizophrenia, Schizophr. Res. (2009), doi:10.1016/j.schres.2009.03.030