Published in final edited form as:

Schizophr Res. 2011 March ; 126(1-3): 164–173. doi:10.1016/j.schres.2010.09.011.

A Closer Look at Siblings of Patients with Schizophrenia: The Association of Depression History and Sex with Cognitive Phenotypes

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Abstract

Background—Siblings of patients with schizophrenia show impaired cognition and an increased prevalence of depression history. Although sex has been shown to moderate cognition in patients, this effect has not been examined in siblings. Here we elucidate how a history of depression and sex influences cognition in siblings unaffected by schizophrenia.

Methods—Unaffected siblings of patients with schizophrenia and unrelated healthy controls were evaluated neuropsychologically and completed structured clinical interviews. Participants with a depression history or no psychiatric history were selected for the sample. Cognitive performance of siblings ($n = 366$) and controls ($n = 680$) was first examined. Second, cognition of participants with a depression history and those without a psychiatric history was compared while additionally investigating the role of schizophrenia risk and sex.

Results—Relative to controls, siblings, with and without a psychiatric history, demonstrated significant ($p < .05$) cognitive deficits. Depression history impaired cognition in siblings, but not in controls; whereas sex affected cognition in both siblings and controls. In siblings alone, sex significantly interacted with depression history to influence cognition. This interaction revealed that in male - but not female - siblings a history of depression was associated with greater cognitive impairments.

Conclusion—A history of depression impairs cognition in siblings, but not in controls. Moreover, depression history interacts with sex and demonstrates that only cognition in male siblings is significantly and additionally compromised by a history of depression. This interaction may be an important consideration for future phenotype and genetic association studies.

Keywords

schizophrenia; cognitive phenotypes; siblings; psychiatric history; depression; sex

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1. Introduction

Non-psychotic siblings of patients with schizophrenia share on average half the genes of their affected brother or sister. Though these siblings are unaffected by the illness, they demonstrate cognitive impairments similar to those observed in patients, albeit to a lesser degree (Snitz et al., 2006). In these siblings, deficits have been observed on tasks of episodic memory (Delawalla et al., 2006), working memory (Goldberg et al., 2003; Delawalla et al., 2006), psychomotor speed (Egan et al., 2001; Thompson et al., 2005), and executive functioning (Egan et al., 2001; Thompson et al., 2005; Delawalla et al., 2006). Such cognitive impairments in unaffected siblings have recently been utilized as potential intermediate phenotypes in studies of the genetics of schizophrenia (e.g. Kremen et al., 1994; Egan et al., 2001; Gottesman and Gould, 2003; Diaz-Asper et al., 2008). However, investigations of the neuropsychological performance of said siblings have produced inconsistent results (Kremen et al., 1998; Sitskoorn et al., 2004; Hughes et al., 2005; Szoke et al., 2005; Snitz et al., 2006). A recent meta-analysis of cognitive performance in first degree adult relatives of patients with schizophrenia found that design features of individual studies - including matching on age and education or asymmetries in psychiatric exclusion criteria - significantly impacted cognitive findings and contributed to the inconsistency among studies (Snitz et al., 2006).

Additional sibling characteristics could also affect cognition and contribute to inconsistent results. A history of psychiatric illness, and particularly a history of depression, is common among first degrees relatives of patients with schizophrenia (Maier et al., 1993; Maier et al., 2002; Argyropoulos et al., 2008; Mortensen et al., 2009). Although neuropsychological deficits have been observed in individuals with depression (Tsourtos et al., 2002; Rund et al., 2006), via treatment and illness remittance, the cognitive deficits have been shown to largely resolve (Levkovitz et al., 2002; Vythilingam et al., 2004). It is unclear, however, how the genetic liability to schizophrenia (e.g. as among siblings of patients with schizophrenia) may influence cognition in these individuals. In a large sample of non-psychotic siblings of patients with schizophrenia and unrelated controls we identified substantial subsamples of participants with a history of depression. Using this sample, we investigated how cognition is affected by such a history in the presence of the genetic risk for schizophrenia.

However, there are clear sex differences in the rates of depression in the general population reflecting the increased risk for female individuals to develop, or to be diagnosed with, depression compared to male individuals (Kuehner, 2003). In addition, there is a notable effect of sex on the clinical and cognitive phenotypes in patients with schizophrenia (Goldstein et al., 1989; Shtasel et al., 1992; Goldstein et al., 1998; Hafner, 2003; Rubin et al., 2008). Such studies have shown that male patients suffer worse symptomatology, illness course, and cognitive impairments compared to female patients. Yet, in terms of siblings, beyond the study by Faraone et al. (2000), few studies have investigated the effect of sex on sibling cognition. Therefore, we additionally examined how sex interacts with a history of depression in the presence of the genetic risk for schizophrenia.

Using a measure of general cognitive ability and six factor-analysis based cognitive domain scores we investigated how a history of depression and the participant's sex moderate cognition in non-psychotic siblings and how these effects differ from those in controls.

We hypothesized:

1. That unaffected siblings of patients with schizophrenia would demonstrate impairments in general cognitive ability as well as verbal memory, working

memory, executive functioning, and processing speed in accord with previous reports.

2. That cognitive deficits associated with a diagnosed history of depression would contribute to the impairments in siblings, but not in remitted controls.
3. That cognition in siblings would be moderated by sex in a pattern similar to that observed in patients with schizophrenia, with male siblings demonstrating greater impairments than female siblings, while controls would only show expected sex differences in verbal and spatial domains (e.g. Collaer and Hines, 1995).

2. Methods

2.1 Participants

Cognitive data was available from 482 unaffected (non-psychotic) siblings of patients with schizophrenia and 810 unrelated control participants who completed a comprehensive neuropsychological battery as part of the ongoing Clinical Brain Disorders Branch/National Institute of Mental Health (NIMH) “Sibling Study”, described previously (Egan et al., 2000; Egan et al., 2001). Index schizophrenia patients formed a clinical sample and were recruited from local and national outpatient resources. Unaffected siblings of patients with schizophrenia were recruited in concert with the recruitment of probands and controls were recruited through the volunteer office at the National Institutes of Health and through local outreach activities in the greater Washington DC area. Study participants were 18–55 years of age, spoke English by the age of five, and completed a neurological exam, laboratory blood tests, and a medical history review to assess for medical conditions that could affect brain functioning. Those found to have medical or neurological problems, or alcohol or drug abuse within the last 6 months, alcohol or drug dependence within the last year, or more than a 5-year history of alcohol or drug abuse or dependence were excluded. Additionally, participants with a current estimated IQ below 70 or evidence of a learning disability were also excluded and controls were further required to have no first degree relatives with a history of psychosis.

2.2 Procedures

From the large sample we selected four groups of participants using diagnostic data from the Structured Clinical Interview for DSM-IV Axis I (SCID-I) and Axis II (SCID-II) disorders (First et al., 1996a; First et al., 1996b): all available siblings and controls with no psychiatric history, and all those with a diagnosed history of major depression (or a history of dysthymic disorder), were selected for the analysis. To minimize heterogeneity among participant subgroups and to make inclusion and exclusion criteria symmetrical across siblings and controls (Snitz et al., 2006), participants with alternate psychiatric histories (e.g. bipolar disorder or obsessive compulsive disorder, etc.) and those found to have a current (or subthreshold) Axis I or Axis II diagnosis upon evaluation were not included. To further probe how the participant’s sex affects cognition, sibling and control subgroups were also parsed by this variable (see Figure 1).

To investigate how schizophrenia risk, depression history, and sex influence cognitive performance, we generated a composite measure of general cognitive ability, “g”, as described by Dickinson et al. (in press), calculated as the mean of the participant’s performance across 18 equally-weighted individual measures. Six factor analysis-based domain scores are included in “g” (Dickinson et al., in press), and were also calculated in order to examine the effects across individual cognitive domains. A list of the factor domains and the neuropsychological measures composing each domain is presented in Table 1. Factor scores and “g” were presented as z scores calculated using the means and standard

deviations from a larger group of controls ($n = 823$); demographic and cognitive information described by Dickinson et al. (in press).

2.3 Data Analysis

For each domain we included all participants with a factor score. After exclusions, the participants selected for the analyses included 680 unrelated controls (294 males, 386 females) and 366 siblings (144 males, 222 females). The 366 siblings were recruited with 259 index patients with schizophrenia (i.e., 1.41 siblings per proband). Analyses were completed using STATISTICA 7 (version 7.1. 2005, Statsoft Inc., Tulsa, OK). Preliminary analysis of variance (ANOVA) demonstrated that siblings were significantly older and had completed significantly fewer years of education than controls; additionally, chi-square analysis showed the proportion of Caucasian participants was greater in siblings. Subsequent analyses of group differences were therefore completed using analysis of covariance (ANCOVA) to control for age, education, and race; where required, post-hoc tests were performed using the same covariates.

To examine the demographic and cognitive differences between siblings and controls as unitary groups, schizophrenia risk was first entered as a between-group factor in a one-way ANCOVA. Subsequently, schizophrenia risk, depression history, and sex were entered as between-group factors in a three-way ANCOVA to examine performance across sibling and control subgroups. The alpha level for significance remained at 0.05 in order to remain sensitive to the previously unexamined effect of depression history and the interaction of depression history and sex in siblings.

3. Results

3.1 Demographic Differences between Siblings and Controls

The age of risk for the development of schizophrenia is 18–25 years of age in males and 25–35 years of age in females (APA, 2000). Using these criteria, 19.44% of male siblings and 28.38% of female siblings were within the respective “risk” age range; 36.73% of male controls and 40.93% of female controls were within the respective “risk” age range. A history of depression (or dysthymia) was significantly more prevalent in siblings than in control participants ($\chi^2(1, n = 1046) = 37.08, p < .001$). As previously stated, siblings were significantly older than controls, were more Caucasian, and completed fewer years of education; however, sex ratios did not differ between siblings and controls. After controlling for demographic differences, the putative premorbid IQ of siblings - as measured with the Wide Range Achievement Test - Revised Reading subtest (WRAT-R) (Jastak and Wilkinson, 1984; Kremen, 1996; Weickert et al., 2000) - did not differ from that in controls. Current IQ - estimated by four-subtests of the Wechsler Adult Intelligence Scale - Revised (WAIS-R) (Wechsler, 1981; Missar et al., 1994) - tended to be lower in siblings than that in controls. Demographic information is shown in Table 2.

3.2 Effect of Schizophrenia Risk on Cognitive Performance

General cognitive ability “g” was significantly lower in siblings than in controls (see Table 3). A multivariate analysis of covariance (MANCOVA) showed that across the six domains included in “g”, the cognition of siblings was impaired relative to the cognition of controls [Wilks = 0.96, $F = 3.59$, $df = 6, 585$, $p = .002$]. Examining the effect on individual domains revealed sibling’s compromised “g” corresponded to significant impairments in processing speed, n-back performance, and card sorting ability relative to the performance of controls (see Table 3 & Figure 2). The verbal memory and span working memory of siblings was also below - but not significantly different from - that in controls; visual memory did not differ between the groups.

Subsequent analyses excluding participants with a history of depression (remaining siblings $n = 271$, controls $n = 603$) revealed that siblings, even in the absence of psychiatric history, demonstrated cognitive deficits relative to controls in general cognitive ability [$F(1, 835) = 13.64, p < .001$], processing speed [$F(1, 865) = 18.56, p < .001$], n-back performance [$F(1, 721) = 23.04, p < .001$], and card sorting ability [$F(1, 837) = 4.78, p < .05$]; current IQ did not differ from controls in this refined sample [$F(1, 864) = 0.81, p = .367$].

3.3 Effects of Depression History and Sex on Cognition

3.3.1 General Cognitive Ability “g”—In the three-way model, schizophrenia risk was associated with impaired general cognitive ability “g”. The interaction of schizophrenia risk and sex was also significant for “g”, as was the three-way interaction of schizophrenia risk, depression history, and sex¹ (see Table 4). To explore which effects, in which domains, acted to drive the interactions manifest in “g”, the three-way analysis was completed for each cognitive domain included in “g”; where a significant interaction was observed, subsequent two-way analyses were completed in siblings and controls separately.

3.3.2 Processing Speed—Schizophrenia risk was associated with robust impairments in siblings relative to the performance in controls; the interaction between schizophrenia risk and sex was also significant (see Table 4). Additionally, an interaction between schizophrenia risk and depression history, as well as a three-way interaction between schizophrenia risk, depression history, and sex was observed as a trend¹. Underlying the interactions, a history of depression was associated with decreased processing speed in siblings [$F(1, 356) = 5.11, p = .024$], and among siblings, females performed better than males [$F(1, 356) = 4.57, p = .033$] (see Figure 3a). Post-hoc tests revealed that the processing speed of male siblings with a depression history was significantly below that of male siblings without a depression history ($p = .024$). There were no effects within controls.

3.3.3 Card Sorting Ability—Schizophrenia risk was associated with impaired performance in siblings. The interaction between schizophrenia risk and sex, as well as the three-way interaction between schizophrenia risk, depression history, and sex also significantly affected card sorting ability¹ (see Table 4). Two-way analyses revealed effects in siblings alone; trends were demonstrated for the effects of depression history [$F(1, 351) = 3.41, p = .066$] and sex [$F(1, 351) = 3.49, p = .062$], and a significant interaction of depression history and sex was also shown in siblings [$F(1, 351) = 8.79, p = .003$]. The interaction demonstrated that among male siblings, a history of depression was associated with greater impairments in card sorting ability; however among female siblings, performance was similar regardless of history (see Figure 3b). Post-hoc tests confirmed that the performance of male siblings with a depression history was significantly below that of male siblings without a depression history ($p = .004$).

3.3.4 N-back Performance—Schizophrenia risk was associated with impaired sibling performance relative to that in controls. Sex also significantly influenced n-back performance such that males, among both siblings and controls, performed significantly better than females. Moreover, the three-way interaction of schizophrenia risk, depression history, and sex had a significant effect on n-back performance¹ (see Table 4). Examining the effects within controls demonstrated male controls performed significantly better than females [$F(1, 605) = 10.53, p = .001$]. In contrast, depression history and sex alone did not

¹Given the current IQ of males with a history of depression differed significantly between said sibling and control subgroups (see Table 2), we tested whether IQ differences affected the significance of the three way interactions by repeating the analyses with WAIS-R as an additional covariate. The three-way interaction in card sorting ability remained significant ($p = .015$), whereas the three-way interactions in n-back performance and “g” were reduced to trends ($p = .058$ and $p = .069$ respectively); the three-way interaction for processing speed was not significant.

significantly affect n-back performance in siblings; however, the interaction of said effects displayed a trend [$F(1, 249) = 3.55, p = .061$], suggesting that a history of depression, in male - but not female - siblings, was associated with greater impairments on the n-back task (see Figure 3c).

3.3.5 Verbal Memory, Span Working Memory, and Visual Memory—Using the three-way model, the effects of schizophrenia risk and sex were separately associated with verbal memory ability at trend levels (see Table 4); siblings performed more poorly than controls, and males performed more poorly than females. Span working memory was also affected by sex and showed that males, overall, performed significantly better than females. No effects were observed for visual memory performance.

4. Discussion

In this study we investigated how unaffected siblings and healthy unrelated controls differed on measures of general cognitive ability and six cognitive domains, and we also examined how depression history and sex were associated with cognitive performance in these groups. There were several key findings. First, we found that the genetic risk for schizophrenia was associated with significant impairments in general cognitive ability (Cohen's $d = -0.402$). Furthermore, we found that this impairment was especially associated with the siblings' typically poor performance on measures of processing speed, card sorting ability, and spatial working memory as assessed with the n-back task ($d = -0.388, d = -0.279, \& d = -0.519$ respectively). The siblings in our sample demonstrated no visual memory impairment ($d = 0.005$) and a relatively small verbal memory impairment ($d = -0.159$), contrasting with findings in previous reports (Snitz et al., 2006). However, the disagreement between our verbal and visual memory findings and those in previous publications could be partly due to the differences in test batteries, the psychometric properties of our assessments, the covariates used, or other study details.

Second, we found that the prevalence of a depression history was significantly higher in siblings of patients with schizophrenia than in control participants and that such a history affected sibling cognition on measures of processing speed and card sorting ability, and to a lesser degree, n-back performance. We also confirmed that a history of depression did not affect cognition in controls. Third, and most notably, we observed an interaction between schizophrenia risk, depression history, and sex which revealed important subgroup differences. Primarily, depression history and sex interacted to influence cognition solely in siblings. Among our subgroups, the greatest cognitive impairments were observed in male siblings with a depression history; cognition in this subgroup was well below that of male siblings without a depression history. Although this effect was strongest in card sorting ability, the overall pattern of cognition associated with this interaction was observed in five out of six cognitive domains, indicating the cognitive compromise associated with depression history, in male siblings, has a broad rather than selective effect on cognition. However, in female siblings, cognition did not significantly differ as a function of depression history in any domain. Potentially important implications can be derived from the present study. Chiefly, cognition in siblings of patients with schizophrenia is not homogeneous, but differs as a function of subgroup characteristics. In turn, sex and depression history may be important factors to consider in future studies with siblings of patients with schizophrenia.

The results of the current study can be taken to suggest that, in addition to differences in study design, inconsistent previous results surrounding cognition in relatives of patients with schizophrenia could be partially due to participant heterogeneity. On the WCST for example, the performance of first degree relatives of patients with schizophrenia, as

compared to controls, has demonstrated mixed results (Cannon et al., 1994; Kremen et al., 1994; Laurent et al., 2000; Egan et al., 2001; Hughes et al., 2005; Diaz-Asper et al., 2008) and only small to moderate effect sizes have been gleaned from meta-analyses (Sitskoorn et al., 2004; Szoke et al., 2005; Snitz et al., 2006). However, previous studies have not been consistent with respect to exclusions based on psychiatric history (Snitz et al., 2006). In the present study, sibling card sorting ability was significantly impaired relative to controls. However, only male siblings with a history of depression demonstrated dramatically impaired performance. It may then be that variability in exclusion criteria, combined with the significant interaction of sex and psychiatric history, has led to inconsistent results among studies in which relatives were treated as a homogenous group.

It may be of interest that the effect of sex on cognition in siblings with a history of depression parallels sex differences in the cognitive profiles of patients with schizophrenia in that the performance of male patients is globally worse than the performance of female patients (Goldstein et al., 1998). In both patients with schizophrenia, and siblings with a depression history, the males are those who suffer the greatest cognitive impairments. Since this has been shown only for patients and the siblings with a depression history, it may be that siblings with a depression history are more informative concerning the susceptibility to schizophrenia than other siblings. This proposition is supported by evidence showing a familial predisposition to schizophrenia and depression in which the rate of depression is increased above most other psychiatric disorders among relatives of patients with schizophrenia (Maier et al., 1993; Argyropoulos et al., 2008). It is also supported by evidence illustrating shared genetic association for schizophrenia, depression, and bipolar disorder (e.g. Rietschel et al., 2008; Green et al., 2009; Knight et al., 2009). Further investigation into the effects of risk-associated loci on cognitive functioning in siblings of patients with schizophrenia may help elucidate the findings in our study. Other explanations for the current findings are also possible. The cognitive deficits observed in siblings with a history of depression may be a result of having experienced a depression. The cognitive deficits may also represent brain changes (existing prior to illness onset) that - in combination with a genetic predisposition - place the sibling at a greater risk for depression. Additionally, it is possible that depression, in some siblings of patients with schizophrenia, is a subclinical expression of schizophrenia itself, perhaps specifically associated with negative schizophrenia symptomatology.

There are limitations to the present study. Given that the index patients with schizophrenia recruited for the 'Siblings Study' represent a clinical sample, these patients may have a history of more severe psychopathology and, possibly, a higher genetic loading for the illness (compared to an epidemiological sample), which may have led to increased sub-clinical characteristics in the siblings of the index patients. By restricting psychiatric history to past depression, our findings may not generalize to siblings with current depression or to those with a history of other psychiatric disorders². The number of participants in some subgroups was relatively small, and thus replication should be completed with larger samples. Additional characteristics and environmental factors unique to the subgroups could underlie the observed cognitive differences. For example, the age of onset and duration of depression history, as well as the type of psychiatric treatment received, may have affected cognitive functioning (Vythilingam et al., 2004). Therefore, the current study cannot conclude how the subgroup characteristics relate to the observed cognitive impairments. It is also possible that an over-reporting of affective illnesses could have occurred when siblings were directly interviewed during the diagnostic assessment for the 'Sibling Study' (Davies

²However, we also completed the analyses described above using a broader inclusion of psychiatric history for both siblings and controls and these results did not differ substantially from those reported in the current publication [data available from authors upon request].

et al. 1997); such an effect could have potentially skewed the selection of the siblings for our analyses². Additionally, selection bias may be affecting our results. For example, participants with a history of major depression or with cognitive deficits may have been less likely to participate in the study. Furthermore, the impact of the selection bias may differ between the siblings of patients with schizophrenia and the healthy control comparison group; a control group of siblings from patients with a non-psychiatric illness may have had selection biases that were closer to the comparator group in our study. Lastly, the siblings and controls included in these analyses were not precisely matched on age, education, and race. To address this problem, these variables were included as covariates in each analysis.

In conclusion, the present study revealed core cognitive differences among subgroups of siblings of patients with schizophrenia defined by the siblings' psychiatric history and sex. Specifically, a history of depression predicted significantly worse cognitive performance in male - but not in female - siblings; this interaction was not observed in controls. To our knowledge, this is the first study to examine how these characteristics influence sibling cognition. Our results suggest it may be important to consider subgroup characteristics such as psychiatric history and sex when conducting genetic association studies of cognitive phenotypes in schizophrenia in order to reduce sample heterogeneity. Further research is needed to solidify the current findings and determine whether these subgroups also differ in other dimensions (e.g. neuroimaging), and how these phenotypes relate back to the affected probands.

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Figure 1.

Subgroup configurations of control participants and siblings of patients with schizophrenia. After excluding individuals who did not meet study criterion, sibling and control groups were discriminated into two subgroups based on a history of depression, 1) those without a psychiatric history and 2) those with a lifetime history of major depression (or dysthymia). Subgroups of participants with a history of depression and those without a psychiatric history were further divided by sex for additional analyses. Sample size in brackets.

Figure 2.

Bar graphs of cognitive performance in siblings and controls for general cognitive ability “g” and the six individual factor domains included in “g”. Performance for each measure is represented by z scores such that the zero-line denotes the average performance of controls. Error bars indicate SEM and indicates $p < .05$. Individual factor z scores for each participant were calculated using the means and standard deviations from a larger sample of controls (except those meeting exclusion criteria, $n = 823$); for some domains and subgroups, this resulted in the average of control z scores to equal a value below zero.

Figure 3c

Figure 3.

Interaction graphs illustrating the effects of a history of depression and sex on processing speed, card sorting ability, and N-back performance in sibling and control participants separately. Performance for each measure is represented by z scores such that the zero-line denotes the average performance of controls. Mean and SEM plotted for each of the four subgroups of siblings and of controls with separate lines plotted for male and female participants in each group. Individual factor z scores for each participant were calculated using the means and standard deviations from a larger sample of controls (except those meeting exclusion criteria, $n = 823$); for some domains and subgroups, this resulted in the average of control z scores to equal a value below zero.

Table 1

Composition of general cognitive ability “g” and factor domain scores.

General Cognitive Ability ^a “g”			All tests and corresponding measures forming the following factor domains.	
Factor Domains included in “g”	Tests comprising each factor		Measurement used	
Processing Speed (Processing and Psychomotor Speed)	WAIS-R Digit Symbol		Total completed in 90 seconds, scaled to age.	
	TMT - Trails A		T-score of the number of seconds to complete	
	TMT - Trails B		T-score of the number of seconds to complete	
N-back Performance ^a (Spatial Working Memory)	1-back		Number correct	
	2-back		Number correct	
	3-back		Number correct	
Span Working Memory (Verbal Working Memory)	WMS-R Digit Span Forward		Total raw score	
	WMS-R Digit Span Backward		Total raw score	
	WAIS-III ^b Letter-Number Sequencing		Total raw score	
Verbal Memory (Verbal Episodic Memory)	WMS-R Logical Memory I (Immediate Recall)		Total raw score	
	WMS-R Logical Memory II (30 minute Delayed Recall)		Total raw score	
	WMS-R Verbal Paired Associates I		Total raw score	
	California Verbal Learning Test		Total recalled over trials 1-5, Standardized to age and sex.	
Visual Memory (Episodic Visual Memory)	WMS-R Visual Reproduction I (Immediate Recall)		Total raw score	
	WMS-R Visual Reproduction II (30 minute Delayed Recall)		Total raw score	
Card Sorting Ability ^c (Concept formation and Executive Functioning)	Wisconsin Card Sorting Test		T score of the percent of perseverative errors	
	Wisconsin Card Sorting Test		Number of categories completed over all trials	
	Wisconsin Card Sorting Test		Number correct over all trials	

General cognitive ability “g” and cognitive factor domains as described by Dickinson et al (submitted). To generate each factor domain score and “g” the individual measures composing each were combined with equal weights. The individual measure(s) comprising each factor domain, the tests from which they were taken, and the type of cognition assessed by each domain are listed. WAIS-R, Wechsler Adult Intelligence Scale-Revised; TMT, Trails Making Test; WMS-R, Wechsler Memory Scale- Revised; WAIS-III, Wechsler Adult Intelligence Scale-III.

Except where noted, all tests are cited in Weickert et al. (2000)

^a As described by Goldberg et al. (2003)

^b As described by Wechsler (1997)

^c As described by Heaton et al. (1993)

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Table 2

Demographics information of sibling and control participants.

<i>Panel A. Comparison of unaffected siblings and control participants.</i>						
	Siblings (n = 366)	Controls (n = 680)	dferror	F or χ^2	p	
Age (y) ^a	36.19 (9.88)	31.89 (9.47)	1044	47.45	< .001	
Education (y) ^a	16.04 (2.41)	16.80 (2.52)	1044	22.46	< .001	
WRAT-R test score (IQ) ^{b, d}	107.12 (9.89)	108.13 (8.83)	1034	0.507	.477	
WAIS-R test score (IQ) ^{b, e}	106.87 (10.33)	107.87 (10.16)	1036	3.36	.067	
Sex, % male ^c	39.34%	43.24%	1046	1.48	.224	
Race, % Caucasian ^c	88.52%	81.18%	1046	9.44	.002	
<i>Panel B. Sibling subgroups</i>						
	No Psychiatric Hx		Depression Hx ^{j, k}			
	Male Siblings	Female Siblings	Male Siblings	Female Siblings		
	(n = 119)	(n = 152)	(n = 25)	(n = 70)		
Age (y) ^{a, f}	35.13 (9.15)	35.90 (10.48)	38.00 (9.12)	37.96 (9.91)		
Education (y) ^a	16.13 (2.16)	15.92 (2.35)	15.96 (3.17)	16.16 (2.66)		
WRAT-R test score (IQ) ^{b, d, f}	106.92 (9.29)	106.07 (9.99)	111.88 (8.00)	108.04 (10.86)		
WAIS-R test score (IQ) ^{b, e}	107.65 (10.10)	106.35 (11.13)	105.88 (9.00)	107.03 (9.46)		
<i>Panel C. Control subgroups</i>						
	No Psychiatric Hx		Depression Hx ^{j, k}			
	Male Controls	Female Controls	Male Controls	Female Controls		
	(n = 276)	(n = 327)	(n = 18)	(n = 59)		
Age (y) ^{a, g}	31.16 (9.24)	31.72 (9.31)	36.67 (8.83)	34.85 (10.73)		
Education (y) ^{a, h}	16.90 (2.71)	16.56 (2.28)	18.00 (3.31)	17.29 (2.42)		
WRAT-R test score (IQ) ^{b, d}	108.17 (8.12)	107.58 (9.08)	111.39 (9.81)	109.95 (9.95)		

Panel A. Comparison of unaffected siblings and control participants.

	Siblings (n = 366)	Controls (n = 680)	dferror	F or χ^2	p
WAIS-R test score (IQ) <i>b, e, i</i>	108.62 (9.39)	106.49 (10.48)	117.56 (9.33)	109.00 (10.15)	

Y, years, Hx, History, Analysis of variance (ANOVA), analysis of covariance (ANCOVA), and chi-square tests completed to compare demographic information of siblings and controls. Values shown as means and standard deviations except for the variables % male and % Caucasian. Bold indicates $p < .05$.

^aIndicates that statistic is F from ANOVA.

^bIndicates that statistic value F from analysis ANCOVA adjusting for age, education found as significant differences between groups.

^cIndicates that statistic value is from χ^2 chi-square.

^dWide Range Achievement Test-Revised Reading subtest (WRAT-R) (Jastak and Wilkinson, 1984) was used as a measure of putative premorbid intelligence (Kremen, 1996; Weickert et al., 2000).

^eA four subtest version of the Weschsler Adult Intelligence Scale – Revised (WAIS-R) (Wechsler, 1981) was used to assess current estimated IQ (Missar et al., 1994).

^fWRAT IQ was higher in siblings with a depression history [$F(1, 357) = 7.08, p < .01$] and in male siblings compared to female siblings [$F(1, 357) = 3.93, p < .05$].

^gControls with a history of depression were significantly older [$F(1, 676) = 10.67, p < .005$].

^hControls with a history of depression completed significantly more education [$F(1, 676) = 6.73, p < .01$].

ⁱWAIS IQ was higher in controls with a depression history [$F(1, 670) = 9.35, p < .005$] and in male controls [$F(1, 670) = 14.40, p < .001$] which contributed to significant interaction of depression history and gender in controls [$F(1, 670) = 6.77, p < .01$]. Post-hoc tests also showed the WAIS IQ of males with a history of depression significantly differed between said sibling and control subgroups ($p = .0003$).

^jThree male siblings had a history of dysthymia, four female siblings had a history of dysthymia, and two female controls had a history of dysthymia instead of depression

^kA history of depression or dysthymia was more prevalent in siblings ($\chi^2 (1, n = 1046) = 37.08, p < .001$); a history of depression or dysthymia was more prevalent among females in both siblings and controls ($\chi^2 (1, n = 366) = 9.13, p < .005$) and ($\chi^2 (1, n = 680) = 13.95, p < .001$) respectively).

Table 3

Performance of siblings and controls on the measure of general cognitive ability “g” and across individual cognitive domains.

	Siblings		Controls		dferror	F	p
	n	mean (SD)	n	mean (SD)			
General Cognitive Ability “g”	357	-0.232 (0.53)	649	-0.024 (0.50)	1001	16.52	<.001
Processing Speed	363	-0.346 (0.74)	679	-0.052 (0.78)	1037	30.28	<.001
N-back Performance	256	-0.508 (1.00)	612	-0.027 (0.85)	863	24.56	<.001
Span Working Memory	359	-0.150 (0.88)	545	-0.025 (0.84)	899	0.56	.455
Verbal Memory	363	-0.153 (0.84)	679	-0.019 (0.85)	1037	1.77	.184
Visual Memory	360	-0.036 (1.00)	407	-0.041 (0.94)	762	1.67	.196
Card Sorting Ability	358	-0.274 (0.90)	655	-0.030 (0.84)	1008	7.01	.008

Analysis of covariance (ANCOVA). ANCOVA controlling for age, education, and race differences examined how siblings and controls differed in “g”. Included in general cognitive ability “g” are the six cognitive domains listed above; “g” is a mean value of the performance in the six individual domains. Following significant effect of schizophrenia risk in a multivariate analysis of covariance (MANCOVA) of the six domains, ANCOVAs were completed for each domain. All statistic values are F from ANCOVA, adjusting for age, education, and race. Bold indicates $p < .05$.

Table 4

Results of three-way analyses examining the impact of schizophrenia risk, a history of depression, and participant's sex on cognitive performance.

General Cognitive Ability “g”	d _{error}	Schizophrenia Risk			Depression Hx			Sex			Schizophrenia Risk x Depression Hx			Schizophrenia Risk x Sex			Depression Hx x Sex			Schizophrenia Risk x Depression Hx x Sex		
		F	p		F	p		F	p		F	p		F	p		F	p		F	p	
		18.91	<.001		1.42	.233		2.47	.116		2.93	.087		4.48	.034		0.29	.591		8.55		.004
Processing Speed N-back Performance Span Working Memory Verbal Memory Visual Memory Card Sorting Ability	d _{error}	Schizophrenia Risk			Depression Hx			Sex			Schizophrenia Risk x Depression Hx			Schizophrenia Risk x Sex			Depression Hx x Sex			Schizophrenia Risk x Depression Hx x Sex		
		F	p		F	p		F	p		F	p		F	p		F	p		F	p	
		1031																				
		26.54	<.001		1.48	.224		1.54	.214		3.29	.070		3.94	.047		0.04	.846		3.27		.071
		857			0.16	.688		6.45	.011		0.24	.623		2.26	.133		0.50	.480		5.50		.019
		893			2.07	.150		6.79	.009		0.35	.557		0.22	.636		0.43	.513		0.64		.424
		1031			0.15	.695		3.65	.056		0.75	.386		1.94	.164		0.67	.412		1.41		.236
		756			1.23	.268		0.26	.609		0.16	.685		0.40	.525		0.29	.590		0.17		.682
		1002			0.71	.399		0.69	.405		2.88	.090		5.43	.020		1.27	.260		9.76		.002

Hx, History, ANCOVA, analysis of covariance. All analyses completed with an ANCOVA controlling for age, education, and race differences among siblings and controls. Included in general cognitive ability “g” are the six cognitive domains listed above; “g” is a mean value of the performance in the six individual domains. All statistic values are F from the ANCOVA, adjusting for age, education, and race. Bold indicates significant findings ($p < .05$); italic indicates trends.