Published in final edited form as:

Schizophr Res. 2009 May ; 110(1-3): 24–27. doi:10.1016/j.schres.2009.02.020.

Family History of Affective Illness in Schizophrenia Patients: Symptoms and Cognition

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Abstract

This study examined the relationship between having a family history of affective disorder and neuropsychological functioning and PANSS symptoms in schizophrenia patients falling into four exclusive family history groups (affective spectrum disorders, schizophrenia spectrum disorders, both, or neither). Schizophrenia patients with a family history of affective illness had the best performance on IQ tests and executive function measures. Symptoms showed fewer family history group differences. Schizophrenia patients with a family history of affective disorder may be a distinct subtype in the group of schizophrenias and may be biologically more similar to patients with serious affective disorder.

1. Introduction

Schizophrenia is highly variable with respect to symptoms, cognitive capacity and outcomes. One way to study this heterogeneity is to examine phenomenological differences between etiologic groups. The familial-sporadic (non-familial) strategy (Lewis *et al.* 1987; Malaspina *et al.* 1998; Wolitzky *et al.* 2006) groups patients by family history of chronic (i.e., consistent and persistent) schizophrenia and differentiates patients on a number of important clinical variables such as patterns of abnormalities in psychophysiology (Schwartz *et al.* 1995; Malaspina *et al.* 1998). Patients with a family history of schizophrenia show a greater degree of cognitive and neuropsychological impairment than those without (Asarnow *et al.* 1978; Walker & Shaye 1982; Sautter *et al.* 1997). In our previous investigation, patients with a family history of schizophrenia spectrum psychoses demonstrated greater deficits in visual attention and scanning, visuomotor control, and spatial processing and reasoning skills, compared to those without a family history (Wolitzky *et al.* 2006).

An unstudied subgroup of patients without a family history of schizophrenia includes those with a family history of affective disorder. It is not known how a history of affective disorders, which share common gene linkages with schizophrenia, alters the expression of the illness. Affective disorders, particularly bipolar disorder, and schizophrenia have much more in

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common than was previously thought. In particular, genes for neuroregulin-1 (Greene et al. 2005) and G72/G30 (Hattori et al. 2003; Schumacher et al. 2004) have been implicated in both disorders as well as similar cognitive deficits (Hill et al. 2008) (e.g. working memory, attention, and executive functioning), albeit more pronounced in schizophrenia patients. That said, patients with either schizophrenia or bipolar disorder may share common genetic risk factors. Furthermore, such heritable genes may be found in affected family members and may alter disease symptom expression and the cognitive profile of the respective illnesses. One way to examine gene-dependent effects on illness expression is to examine the impact of different family histories on the patient population. In this study, we examine the extent to which family history of affective disorders versus schizophrenia disorders in patients with schizophrenia disorders alters neuropsychological and symptom characteristics.

2. Method

2.1 Participants

The study group was drawn from a sample of 396 consecutive, voluntary patients admitted to an inpatient schizophrenia research unit. Patients who participated in family history assessments, neuropsychological testing or received PANSS symptom ratings were included in the analyses. Diagnoses were made by trained raters using the Diagnostic Interview for Genetic Studies (Nurnberger et al. 1994) with kappa values of 0.95 for diagnosis. Diagnoses were based on these interviews, clinical data, past records and symptom ratings, and represented a consensus between clinical and research staff. Sociodemographic data were available from the DIGS (See Table 1).

2.2 Assessments

Family history assessments were conducted by researchers blind to patient information with the Family Interview for Genetic Studies (NIMH-Molecular Genetics Initiative, 1991) or through extensive chart review. Probands were considered to have a positive family history if at least one interviewed family informant indicated at least one first or second degree relative had a disorder. All Axis I and II diagnoses were made for the relatives. Disorders were grouped into three categories: 1) schizophrenia spectrum disorders, 2) affective spectrum disorders, 3) both 1) and 2) and 4) family history negative. Patients for whom definitive information could not be ascertained were treated as missing data. The schizophrenia spectrum family history group includes: schizoaffective-depressed, schizoaffective-manic and all DSM-IV schizophrenia subtypes, and psychotic disorder-NOS. Family history of affective disorders includes, major depressive disorder, depressive disorders, and bipolar disorder.

Subjects were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987). In addition to the three original subscales of the PANSS (positive, negative, and general psychopathology), the five factors derived from the PANSS (i.e., positive, negative, dysthymia, activation, and autistic preoccupation) (White et al. 1997) were used in our analyses. PANSS assessments were performed by Master's level psychologists achieving high reliability (i.e. Kappa > .80 for individual symptom ratings and 95% agreement on diagnosis) before evaluating participants.

The neuropsychological battery was administered to patients by psychologists blind to family history group and included global measures of intellectual functioning (i.e., Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) and specific neuropsychological measures of 5 executive functioning domains (i.e., verbal fluency, speed of processing, problem solving, cognitive flexibility and selective attention).

2.3 Data Analysis

Significant multivariate ANCOVA's (MANCOVA), which were used to decrease the chance of type 2 error, were followed with univariate ANCOVA's. Since gender differences are implicated in the etiology and course of schizophrenia, we independently examined gender main effects and interactions with family history. Two four-by-two (family history category and gender) MANCOVA's to examined group differences in PANSS original scale and 5 factor scores. Five four-by-two (family history category and gender) MANCOVA's examined group differences in neurocognitive test scores. All multivariate and univariate tests were two-tailed with alpha set at $p < 0.05$.

3. Results

Of the 396 patients, 73 (18.4%) had a family history of schizophrenia spectrum (FHSD+) only, 111 (28%) had a family history of affective-spectrum disorder only (FHAD+), 53 (13.4%) had a family history of both spectrums (FHSAD+), and 159 (40.2%) had no family history of either class of disorder (FH-). The groups did not differ by gender distribution, age, age at onset of symptoms, age at first treatment, or global assessment of function (See Table 1). FHAD+ patients completed more years of education than FHSD+ and FH- ($F(3,336)=3.70, p=.012$). Current age, age at onset of first symptoms and age at first treatment were lower in men than women and all subsequent multivariate models adjust for these variables.

The multivariate effects of family history group on PANSS scores and the derived PANSS five factors were not significant in the adjusted models. However, a significant multivariate effect of gender on PANSS scale scores (Wilks' Lambda $F(3,211)=3.07, p=.029$) and five-factor model scores (Wilks' Lambda $F(5,209)=2.91, p=.014$) revealed females scored higher than males on positive subscale scores ($F(1,213)=8.07, p=.005$) and activation factor scores ($F(1,213)=9.61, p=.002$).

A significant multivariate effect for family history group on WAIS-R index scores (Wilks' Lambda $F(9,365)=2.68, p=.005$) was attributed to Full, Verbal, and Performance IQ scores. FHAD+ patients scored higher than the other three family history groups (Table 2). There was no significant multivariate effect for gender on WAIS-R scores. A significant multivariate effect on the Stroop color word test scores (i.e., selective attention) (Wilks' Lambda $F(9,343)=2.59, p=.007$) was specific to the Stroop Color subscore. FHAD+ patients scored the highest compared to the other groups. Significant multivariate effects were found for verbal fluency domain measures (Wilks' Lambda $F(6,320)=2.57, p=.019$) and processing speed and cognitive flexibility measures (Wilks' Lambda $F(6,310)=3.53, p=.002$). The former was primarily due to animal naming, and the latter two, Trails A and Trails B, respectively. FHAD+ patients scored highest on number of animals named and FH- patients did the worst on both Trails tasks (Table 2). A significant multivariate effect was found for the interaction between family history group and gender for problem solving measures (i.e., Wisconsin card sort) (Wilks' Lambda ($F(6/356)=2.14, p=.048$), attributed to total number of perseverative errors. Males in all three groups with positive family histories exhibited more perseverative errors than their female counterparts, however, in the FH- group, females exhibited the most perseverative errors of all.

4. Discussion

This study demonstrated that FHAD+ schizophrenia patients exhibited better cognitive and neuropsychological performance compared not only to FHSD+ patients or FHSAD+ patients, but also to FH- patients. Specifically, the affective family history group performed better on tasks of cognitive flexibility that involved visual scanning with a motor component, selective visual attention, and verbal fluency. While women in the group with no family history of disorder exhibited the most perseverative errors on a problem solving task, men in this family

history group performed the best, suggesting there may be gender effects within schizophrenia subgroups. That said, patients with a family history of affective disorder may represent another distinct subgroup of schizophrenia, a subgroup of cases with better cognition that are symptomatically very similar to cases with a family history of schizophrenia and to cases with no reported family history. Future familial-sporadic schizophrenia studies may examine whether affective family history patients are represented among those patients with no family history of schizophrenia.

Even though the family history method is imprecise with regard to the specificity of diagnoses, the method does identify subgroups with similar biological vulnerabilities. Cross-sectional assessments make it difficult to explain why having a family history of affective disorder seems to be protective in schizophrenia. In addition, it is unclear the extent to which the relative differences in cognition between the family history groups are functionally meaningful, however; previous studies found significant relationships between poorer WAIS scores and poorer levels of independent living and work functioning in patients with a family history of schizophrenia (Brekke *et al.* 1997).

Studying the genetics and neurobiology of the subgroup of schizophrenia patients with a family history of affective illness may increase our understanding of the genetics of complex psychiatric disorders. Understanding the gene-dependent links to better cognitive functioning may also illuminate ways in which psychopharmacological treatment can better target cognitive deficits in patients with schizophrenia. The plausibility of finding interventions that are individually superior for these patients seems promising as we enter an age where we are expecting to individualize the treatments for specific patients.

Acknowledgments

Role of Funding Source: This work was supported by The National Alliance for Research on Schizophrenia and Depression, the G. Harold and Leila Y. Mathers Charitable Foundation, and The National Institute of Mental Health Grant Nos. K24 MH01699 (to D. M.) and RO1 MH56422 (to J.H.F.)

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Table 1
 Characteristics of Patients with Schizophrenia Spectrum Disorders by Family History of Illness

	Family History of Illness			
	None (N=159)	Affective (N=111)	Schizophrenia (N=73)	Both (N=53)
Characteristic	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	32 (10.75)	32 (10.25)	33 (11.54)	33 (9.94)
Age of Onset (years)	22 (6.89)	21 (6.01)	22 (9.35)	22 (7.42)
Age at First Treatment (years)	22 (8.85)	20 (6.9)	21 (8.47)	21 (7.42)
Education (years)	12.78 (2.62)	13.66 (2.74)	12.42 (3.06)	13.22 (2.07)
Global Assessment of Functioning Scale score				
Worst period in current episode	31.05 (7.02)	30.49 (10.26)	28.82 (7.97)	28.64 (9.27)
Last month	38.95 (7.94)	36.85 (34.18)	34.18 (6.86)	38.26 (7.92)
% Frequency (N)				
Gender				
Male (n=254)	67% (107)	60% (66)	70% (51)	57% (30)
Female (n=142)	33% (52)	40% (45)	30% (22)	43% (23)

Table 2
Neurocognitive Outcomes of Patients with Schizophrenia Spectrum by Family History of Illness

	None (N=159)	Affective (N=111)	Schizophrenia (N=73)	Both (N=53)	ANCOVA F -value
Neurocognitive Measures	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
** WAIS FSIQ (n=163)	82.82 (12.29)	90.48 (12.78)	82.00 (10.98)	84.36 (12.75)	5.35**
Male (n=99)	84.49 (13.05)	90.07 (12.61)	83.76 (10.80)	83.69 (15.10)	
Female (n=64)	80.05 (10.66)	91.00 (13.24)	76.71 (10.47)	85.08 (10.23)	
* WAIS PIQ (n=163)	80.66 (12.24)	86.28 (13.05)	76.14 (11.70)	81.72 (13.67)	3.51*
Male (n=99)	81.89 (13.27)	85.90 (12.92)	77.10 (12.38)	81.85 (16.41)	
Female (n=64)	78.62 (10.26)	86.75 (13.49)	73.29 (9.62)	81.58 (10.69)	
*** WAIS VIQ (n=163)	86.38 (13.22)	95.11 (13.55)	85.32 (11.84)	87.80 (12.37)	7.07***
Male (n=99)	88.43 (13.83)	94.80 (14.19)	86.71 (11.65)	86.46 (14.25)	
Female (n=64)	82.95 (11.63)	95.50 (12.99)	81.14 (12.29)	89.25 (10.39)	
** Stroop Color in Seconds	52.83 (13.83)	60.98 (13.60)	56.15 (12.32)	51.64 (12.22)	5.15**
* Animal Naming Task	15.84 (5.27)	18.66 (6.83)	14.64 (5.27)	15.74 (4.76)	3.69*
** Trails A (time in seconds)	57.38 (36.30)	39.53 (15.52)	49.93 (20.08)	52.59 (20.76)	5.04**
** Trails B	154.19 (81.25)	100.95 (65.20)	130.07 (64.86)	132.22 (58.60)	5.79**
WCS Categories (n=190)	3.42 (2.15)	4.11 (2.27)	3.69 (2.45)	3.62 (2.11)	
Male (n=119)	3.82 (2.25)	3.67 (2.23)	3.83 (2.31)	3.73 (2.22)	
Female (n=71)	2.59 (1.71)	4.66 (2.22)	3.17 (3.13)	3.50 (2.07)	
* WCS Perseverative Errors	33.19 (24.44)	25.60 (23.22)	27.31 (26.14)	32.14 (21.96)	3.83*
Male (n=119)	27.93 (22.98)	30.81 (26.04)	29.00 (28.85)	35.53 (23.84)	
Female (n=71)	43.96 (24.28)	19.14 (17.51)	20.83 (10.02)	28.50 (19.98)	

* $p < .05$

** $p < .01$

*** $p < .001$