Familial Liability to Schizophrenia: A Sibling Study of Negative Symptoms

by Judith Crown Craver and Michael F. Pogue-Geile

Abstract

Negative symptoms are important features in schizophrenia, so in milder form they might also serve as indicators of "unexpressed" liability to schizophrenia among patients' adult relatives without schizophrenia. To address this question, we assessed negative symptoms in 39 stable schizophrenia or schizoaffective outpatients, 39 of their siblings, 38 well control probands, and 38 of their siblings. Negative symptom measures included standard behavior ratings of the core negative symptoms of affective flattening and alogia, as well as a self-report measure of social anhedonia. As expected, even stable outpatients with schizophrenia exhibited significantly more negative symptoms than control probands and control siblings. However, negative behavioral symptoms of affective flattening, alogia, and anhedonia did not significantly differentiate the siblings of the schizophrenia patients from the control probands or their siblings, although there were some trends for anhedonia. The findings suggest that core negative symptoms of observed affective flattening and poverty of speech are not likely to be useful as strong indicators of "unexpressed" liability to schizophrenia.

Key words: Negative symptoms, family study, genetics, anhedonia, schizophrenia.


Findings from twin, family, and adoption studies support genetic influences on schizophrenia, but the precise nature of this genetic contribution is largely unknown (McGue and Gottesman 1989; Pogue-Geile and Gottesman 1999). One obstacle to progress on this question is the presence of undetected genetic liability to schizophrenia. Evidence from studies of the offspring of discordant monzygotic (MZ) twins, as well as other findings (Gottesman and Bertelsen 1989), suggests the existence of relatives of schizophrenia patients who carry the genes for schizophrenia but never develop schizophrenia themselves. Failure to identify such genetically liable but non schizophrenic relatives can weaken results from traditional linkage studies, which are important in identifying susceptibility genes. One way to address this issue is to examine characteristics other than the clinical diagnosis of schizophrenia among patients and their relatives in hopes of identifying indicators of such "unexpressed" genetic liability.

We examined the usefulness of negative symptoms as potential indicators of a genetic liability to schizophrenia among the siblings of schizophrenia patients. Negative symptoms are usually conceptualized as deficits in normal behavior shown by schizophrenia patients, especially such core phenomena as flattening of affect (reduced emotional expressivity) and poverty of speech (reduced amount of speech) (Strauss et al. 1974; Crow 1980; Andreasen and Olsen 1982). Research has shown that negative symptoms have some specificity to schizophrenia, are frequently present during nonpsychotic phases of the disorder, show relative stability over time, and are prognostic of later poor functioning. There are also individual differences in their severity among patients (Pogue-Geile and Zubin 1988; Pogue-Geile and Keshavan 1991; McGlashan and Fenton 1992). These points suggest that negative symptoms are an important symptom dimension and feature of schizophrenia and therefore in milder form are possible "candidate" indicators of liability to the disorder in patients' relatives.

Despite the hypothesized importance of core negative symptoms in schizophrenia, relatively few studies have examined them in the relatives of schizophrenia patients, and those that have report conflicting results. Of reports from three samples comparing flat affect and poverty of speech based on standard behavior ratings (e.g., Scale for the Assessment of Negative Symptoms, SANS; Andreasen 1984) between relatives of schizophrenia patients and control subjects, one found significant

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increases in negative symptoms among patient relatives (Dworkin et al. 1991), one found nonsignificant trends ($p's < 0.09$) (Tsuang et al. 1991), and one indicated no significant group differences (Dworkin et al. 1990). Although anhedonia is less frequently considered a core negative symptom, six reports have also compared patients' relatives to well control subjects based on self-report questionnaires (Physical or Social Anhedonia Scales; Chapman et al. 1976); five of these reports found significantly increased anhedonia among patients' relatives (Katsanis et al. 1990; Clementz et al. 1991; Grove et al. 1991; Franke et al. 1993; Kendler et al. 1996), while one did not (Erlenmeyer-Kimling et al. 1993).

In addition, there has been increasing interest in examining the “negative” traits of schizotypal personality disorder in patients’ relatives (Siever and Gunderson 1983; Kendler 1985). However, to date, this approach has primarily emphasized deficits of social functioning rather than affective flattening and alogia. Of the four studies using structured personality disorder interviews to measure symptoms most closely resembling core negative symptoms (i.e., poor rapport or inappropriate affect), the findings are mixed: Two found significant differences between relatives of schizophrenia patients and control subjects (Torgersen et al. 1993; Kendler et al. 1995) and two did not (Squires-Wheeler et al. 1988, 1989).

These results on the potential role of negative symptoms as indicators of “unexpressed” liability to schizophrenia are mixed, and their interpretation is complicated by several methodological factors that could influence differences between index relatives and control subjects. First, the “high-risk” studies (Squires-Wheeler et al. 1988, 1989; Dworkin et al. 1990, 1991; Erlenmeyer-Kimling et al. 1993) have assessed offspring prior to the peak age at onset of schizophrenia, which makes it difficult to distinguish among prodromal signs in eventual schizophrenia cases, environmental effects of having a parent with schizophrenia, and indicators of never-to-be expressed liability. As a result, high-risk studies may overestimate effects of never-to-be expressed liability. Studies of relatives past the age of risk for schizophrenia (i.e., siblings and parents) do not have this difficulty, but they may have others. Of the “non–high-risk” studies (Katsanis et al. 1990; Clementz et al. 1991; Grove et al. 1991; Tsuang et al. 1991; Franke et al. 1993; Kendler et al. 1996), all but two (Franke et al. 1993; Kendler et al. 1996) included relatives with schizophrenia in the patient relative group, which tends to confound the question of whether negative symptoms may indicate unexpressed liability. Results for different classes of relatives (i.e., parents, siblings, and offspring) have also been combined in these reports (except Franke et al. 1993). These different classes of relatives may differ in their manifestation of liability because of age and cohort effects and their different genetic and environmental risks (i.e., differing genetic dominance effects between offspring and siblings, reduced reproductive fitness effects in parents, and differing environmental exposure of offspring compared with siblings). With the exception of Kendler et al. (1996) and Tsuang et al. (1991), control subjects in these studies have also included “super-normal” subjects who are screened both for all personal as well as all family psychopathology (Kendler 1990), which may artifactually increase index/control differences. In addition, only a few of the studies clearly matched controls to index subjects on age, sex, ethnic group, and parental socioeconomic status. Overall, only one of the studies on these questions avoided all of the above methodological complications and it found a slight (odds ratio = 1.07), but significant increase ($p = 0.05$) on a shortened Social Anhedonia Scale among relatives of schizophrenia patients compared with control subjects (Kendler et al. 1996). All the other positive studies (as well as the negative studies) had at least one of the above methodological problems.

Therefore, this study sought to address the two general questions of the role of negative symptoms as indicators of an “unexpressed” liability to schizophrenia and the etiology of individual differences in negative symptoms among patients, while incorporating as many methodological improvements as possible. Specifically, we asked the following questions:

1. Are negative symptoms increased in the nonschizophrenia adult siblings of schizophrenia patients as compared with well control subjects and their siblings?
2. Are negative symptoms increased in the psychiatrically diagnosed siblings of schizophrenia patients as compared with well control subjects and their siblings?
3. Are individual differences in negative symptoms correlated between schizophrenia patients and their siblings, and how does this correlation compare with that between well control subjects and their siblings?

**Method**

To address these questions, negative symptoms and other psychopathology were assessed in four groups of subjects: schizophrenia or schizoaffective index probands, their biological siblings, demographically matched well control probands, and their biological siblings. All subjects were part of the University of Pittsburgh Sibling Study of Schizophrenia and Neuropsychology, a multivariate family study (Brunet et al. 1991; Hall et al. 1991; Pogue-Geile et al. 1991; Huxley et al. 1993).
Subject Ascertainment

Patient probands. Schizophrenia or schizoaffective outpatient probands were ascertained from the Schizophrenia Treatment and Research Center, an outpatient facility at Western Psychiatric Institute and Clinic (WPIC) of the University of Pittsburgh, which is responsible for a defined catchment area and is also a tertiary referral facility. Screening criteria were a DSM-III (American Psychiatric Association 1980) chart diagnosis of schizophrenia or schizoaffective disorder; age between 18 and 45 years; English as a first language; no history of alcohol or substance abuse that would question the diagnosis of schizophrenia (i.e., index probands could have diagnoses of alcohol/substance abuse, but not such that the schizophrenia diagnosis was unclear because of timing or extent of substance abuse); no history of diagnosed neurological disease; at least one full biological sibling in the greater Pittsburgh area; minimum of 6 months since last hospital discharge; and current symptom stability as judged by clinicians. All patients who met the above criteria and who gave informed consent for their own participation as well as permission to contact at least one of their full biological siblings were interviewed with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L; Endicott and Spitzer 1978) to confirm that they met the Research Diagnostic Criteria (RDC; Spitzer et al. 1978) for a lifetime definite diagnosis of schizophrenia or schizoaffective disorder.

Patient siblings. One full biological sibling was recruited for each participating index patient proband. To ascertain siblings matched as closely as possible to the patients on demographics, siblings of the patients were ranked and recruited based on their similarity in sex and age to their patient relative, with sex similarity having the higher priority. Only siblings without RDC diagnoses of schizophrenia or schizoaffective disorder or diagnosed neurological disease were included in analyses. Otherwise, psychopathology of these patient siblings was free to vary.

Well control probands. Well control probands were ascertained through notices in a mailed weekly advertising publication. Initial inclusion criteria, determined through a telephone interview, were age between 18 and 45 years; English as a first language; no personal history of psychiatric treatment; no history of diagnosed neurological disease; no history of schizophrenia or psychosis among first-degree relatives; and at least one full biological sibling in the greater Pittsburgh area interested in participating in the study. Attempts were also made to select respondents who as a group matched the siblings of the schizophrenia probands on sex, age, ethnic group, and years of education. Individuals meeting these initial criteria were further screened over the telephone with a modified version of the SADS-L for any probable RDC diagnosis and with a modified version of the Structured Interview for DSM-III Personality (SIDP; Pfohl et al. 1982) for schizoid, schizotypal, and paranoid personality disorders before in-person interviews.

Control siblings. One full biological sibling of each well control proband was ascertained. Similar to the patient siblings, control siblings were ranked and recruited based on their sex- and age-match to their relative. Otherwise, all characteristics of these siblings were free to vary except for the exclusion criteria of any personal lifetime history of RDC schizophrenia, schizoaffective disorder, or diagnosed neurological disease.

Measures

General psychopathology. All subjects were interviewed in person (videotaped) with the SADS-L by trained research associates or graduate students in clinical psychology, and hospital chart information was collected if available. Additionally, all subjects except the schizophrenia patients were interviewed with the complete SIDP to assess the presence of DSM-III Axis II personality disorders. RDC diagnoses and DSM-III Axis II diagnoses derived from the SADS-L and SIDP, respectively, were made by a diagnostic team chaired by an experienced licensed clinical psychologist (M. P.-G.) who trained on the SIDP with its developers at the University of Iowa. The chair of the diagnostic team was blind to group membership, although the interviewers were not.

Negative symptoms. Negative symptoms were assessed for all subjects with a revised version of the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), which included ratings of only two of the five original scales—Affective Flattening and Alogia. These scales were chosen because they are rated from observed interview behavior and they measure best the “core” negative symptoms originally proposed to compose the negative symptom construct (e.g., Crow 1980). The Avolition-Apathy and Anhedonia-Asociality scales from the SANS were not included here because they are largely rated from subject self-report without benefit of a structured interview. The Attention scale was not included because its relevance to the negative symptom construct is theoretically and empirically uncertain (Pogue-Geile and Zubin 1988). The inappropriate affect and affective nonresponsivity items were omitted from the Affective Flattening scale and the poverty of content of speech item was omitted from the Alogia scale because these items have been reported to have low item-total correlations (Pogue-Geile and Zubin 1988). Analyses were performed on both the global ratings and the summed scale scores with similar results; the results for global ratings are presented here.
Research associates and graduate students were trained using Andreasen’s SANS training tapes and other tapes to intraclass correlations for the global scores of 0.90 or greater between rater and criterion ratings. Once raters were trained to reliability, the modified SANS was used to assess negative symptoms for subjects from the same 15-minute segment of each of the videotaped interviews. The section of the interview that was rated, covering questions about childhood and adolescence functioning, occurred about midway through the interview to avoid any interview “warmup” effects and contained no questions about psychopathology to minimize clues to group membership. The videotaped ratings were made blind to the subjects’ group membership and diagnostic status. If an interview was not videotaped because of camera unavailability or subject refusal, SANS ratings were made by interviewers (trained to reliability on the SANS) at the completion of interviews based on behavior during the entire session.

All subjects were also administered the Revised Social Anhedonia Scale (Eckblad et al. 1982), a 40-item, true-false, self-report questionnaire measuring an inability to experience interpersonal pleasure. The Social Anhedonia Scale was used rather than the related Physical Anhedonia Scale (Chapman et al. 1976), because we hypothesized that social anhedonia would be more sensitive to schizophrenia liability than physical anhedonia. The Social Anhedonia Scale has also been found to be more predictive of later psychosis than the Physical Anhedonia Scale (Chapman et al. 1994).

Given a priori hypotheses and to maximize statistical power, planned comparisons and one-tailed significance levels without adjustment for multiple tests were used whenever specific effects were hypothesized.

Results

Recruitment and Demographic Characteristics

Patient probands. Fifty-six schizophrenia or schizoaffective outpatient probands were recruited and interviewed. Sixteen of these probands were not included in the final data analyses because the patient was unwilling to give permission to contact any siblings or all biological siblings refused to be interviewed. These 16 index probands did not differ significantly on any of the negative symptom measures from those whose siblings participated. Forty patient-sibling pairs were interviewed, but one patient-sibling pair was dropped from the data analyses because the interviewed sibling was diagnosed with schizophrenia. Thus, 39 patient-sibling pairs were included in the final data analyses.

Based on the RDC, 22 of these 39 index probands had only schizophrenia episodes, 13 had both schizophrenia and schizoaffective episodes (9 schizoaffective depressed, 2 schizoaffective mixed, 2 schizoaffective manic), and 4 had only schizoaffective episodes (2 schizoaffective depressed, 1 schizoaffective mixed, 1 schizoaffective manic). There were no significant differences on any of the negative symptom measures between the schizophrenia and the schizoaffective (schizoaffective plus schizophrenia episodes and schizoaffective episodes only) probands. Seventy-eight percent of the patient probands were chronic RDC course type, 19 percent were subchronic, and 3 percent were acute. Table 1 presents the demographic characteristics of these index probands as well as the other subject groups. The clinical characteristics of the index probands were as follows: years since first hospitalization (mean 8.1, standard deviation [4.7]); total months hospitalized (6.4 [4.7]); months since last hospital discharge (36.9 [29.1]); percentage taking antipsychotic medication (97%); total chlorpromazine dose equivalents (283.0 [232.0]); and percentage taking antiparkinsonian medications (56%).

Patient siblings. The 39 patients had a total of 158 full siblings, 154 who were alive at the time of testing and 97 who resided in the greater Pittsburgh area. An 85 percent success rate was achieved in ascertaining the sibling either closest or second closest in match to the patient proband from among those living in the Pittsburgh area.

Well control probands. A total of 305 potential control probands responded to the advertisements for the study, 50 of whom could not be recontacted to complete the telephone screen or refused to participate upon being recontacted. An additional 162 respondents were ruled out based on initial exclusion and demographic matching criteria, and 50 were screened out due to the presence of a probable or definite lifetime RDC diagnosis or a DSM-III diagnosis of schizoid, schizotypal, or paranoid personality disorder based on telephone interview. Of the 43 remaining respondents, 1 refused the in-person interview and 4 additional control pairs were dropped because of either diagnostic exclusion criteria assessed during the in-person interview or later sibling refusal. Thus, 38 control proband-sibling pairs were included in the final data analyses.

Control siblings. The 38 control probands had a total of 128 siblings, 123 who were alive at the time of testing and 96 who resided in the greater Pittsburgh area. An 82 percent success rate was achieved in ascertaining the sibling either closest or second closest in match to the control proband from among those living in the Pittsburgh area.
Table 1. Demographic characteristics

<table>
<thead>
<tr>
<th>Demographic variable</th>
<th>Index probands (n = 39)</th>
<th>Index siblings (n = 39)</th>
<th>Control probands (n = 38)</th>
<th>Control siblings (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; mean (SD)</td>
<td>32.2 (6.4)</td>
<td>31.8 (7.8)</td>
<td>29.0 (6.0)</td>
<td>28.1 (6.7)</td>
</tr>
<tr>
<td>Sex, male; n (%)</td>
<td>25 (64)</td>
<td>18 (46)</td>
<td>18 (47)</td>
<td>11 (29)</td>
</tr>
<tr>
<td>Ethnic group, White; n (%)</td>
<td>31 (80)</td>
<td>31 (80)</td>
<td>35 (92)</td>
<td>35 (92)</td>
</tr>
<tr>
<td>Years of full-time education; mean (SD)</td>
<td>13.2 (2.1)</td>
<td>13.9 (3.0)</td>
<td>14.1 (2.7)</td>
<td>13.5 (2.1)</td>
</tr>
<tr>
<td>Father's SES; mean (SD)</td>
<td>3.5 (1.1)</td>
<td>—</td>
<td>3.3 (1.0)</td>
<td>—</td>
</tr>
<tr>
<td>Sibling rank; n (%)</td>
<td>—</td>
<td>27 (69)</td>
<td>—</td>
<td>23 (61)</td>
</tr>
<tr>
<td>Rank = 1</td>
<td>—</td>
<td>6 (15)</td>
<td>—</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Rank = 2</td>
<td>—</td>
<td>6 (15)</td>
<td>—</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Rank &gt; 3</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

Note.—SD = standard deviation; SES = socioeconomic status.

1 Biological father's social class rated according to Hollingshead's (1957) two-factor index (1 highest – 5 lowest).
2 Sibling rank indicates the position of the sibling tested regarding sex- and age-match to the proband among all siblings living in the greater Pittsburgh area.

Group demographic comparisons. Based on the a priori questions of interest in this study, control probands and control siblings were first compared with the patient probands on demographic variables (see table 1). Planned comparisons (2-tailed) indicated that both the control probands, \( t = 2.26, df = 75, p < 0.05 \), and the control siblings, \( t = 2.77, df = 75, p < 0.01 \), were significantly younger than the patient probands, although the mean difference was only 3 years. There were significantly more females in the control sibling group than in the patient group \( n = 77; \chi^2 = 8.20, df = 1, p < 0.01 \). No other demographic comparisons were significant.

Next, demographic characteristics of the control probands and the control siblings were compared with the siblings of the schizophrenia probands. The control siblings were significantly younger than the patient siblings, \( t = 2.28, df = 75, p < 0.05 \) (mean of 3 years' difference only). There were no significant differences on any other variables, indicating that the attempt to match the control subjects to the patient siblings was generally successful. Similarly, social class of subjects' fathers and ascertainment rank of siblings tested did not differ significantly between patient and control siblings.

SANS Ratings and Reliability. From 123 tapes, 50 tapes were assigned consensus ratings (group viewing of tape with independent ratings followed by group discussion and resolution of disagreements) by four trained raters, and the remaining 73 tapes were rated by only one trained rater (J.C.). To assess interrater reliability in the study, 30 tapes that had been assigned consensus ratings were also rated (by J.C.), with intraclass correlations (based on 2-way analyses of variance [ANOVAs] with raters as fixed effects [Shrout and Fleiss 1979]) ranging from 0.68 to 0.98 for the individual SANS items and from 0.91 to 0.99 for the global scores. (The consensus ratings were used in the data analyses for these 30 tapes.) Thirty-one subjects were not videotaped; 25 received negative symptom ratings made by the interviewer and the remaining 6 were missing ratings.

Negative Symptoms in the Index Probands Versus Control Probands and Control Siblings. Mean scores for the negative symptom variables for each subject group are presented in table 2. To replicate previous findings regarding schizophrenia patients and to confirm that our ratings were sensitive to detecting negative symptoms in patients, negative symptomatology in the index probands was compared first separately to that in the well control probands and the control siblings. Because of skewness of the data, logistic regression analyses were used with age and sex as covariates. Interactions with sex were also examined. As can be seen in table 3, the index probands exhibited significantly more negative symptomatology than the well control probands and their siblings on all negative symptom measures, individually and jointly, with generally "large" effect sizes of about one and one-half standard deviations separating group means. There were no significant interactions with sex.

Patient Siblings Versus Control Probands and Control Siblings. To test the hypothesized familial association of schizophrenia and negative symptoms, negative symptomatology in the patient siblings was next compared separately with that of the control probands and control siblings. The logistic regression results (table 3) indicate that
Table 2. Group means of negative symptom variables

<table>
<thead>
<tr>
<th>Negative symptom variable</th>
<th>Index probands</th>
<th>Index siblings</th>
<th>Control probands</th>
<th>Control siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised SANS Global</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective flattening</td>
<td>1.97 (1.30)</td>
<td>0.57 (1.15)</td>
<td>0.58 (0.98)</td>
<td>0.50 (0.86)</td>
</tr>
<tr>
<td>Alogia</td>
<td>0.78 (1.29)</td>
<td>0.17 (0.62)</td>
<td>0.29 (0.87)</td>
<td>0.11 (0.39)</td>
</tr>
<tr>
<td>Revised Social Anhedonia Scale</td>
<td>11.83 (6.97)</td>
<td>6.94 (4.68)</td>
<td>5.42 (4.75)</td>
<td>5.18 (4.29)</td>
</tr>
</tbody>
</table>

Note.—Values are mean (standard deviation); SANS = Scale for Assessment of Negative Symptoms.

1 Data missing on both SANS scales for 2 patient probands and 4 patient siblings; data missing on the Revised Social Anhedonia Scale for 4 patient probands and 3 patient siblings. Anhedonia counted as missing if more than 2 items were left blank.

the patient siblings did not exhibit significantly more negative symptoms on any of the three measures (individually or jointly) than the well control probands or control siblings, although there was a nonsignificant trend for social anhedonia in the comparison with control probands ($p = 0.095$, 1-tailed). There was one significant interaction with sex, which occurred for alogia in the comparison of index siblings versus control probands ($p = 0.04$). Contrary to the hypothesis, among males, index siblings showed lower alogia than control probands ($p = 0.09$), and there was no significant difference among females. Additional analyses indicated that there were also no significant differences in variances. To investigate potential effects of outliers, the negative symptom variables were dichotomized a priori using a customary but arbitrary cutoff of two standard deviations above the relevant control mean. In these analyses, only anhedonia scores were significantly increased in patient siblings compared with control subjects (patient siblings (33%) vs. control probands (13%), $X^2 = 4.25$, $df = 1$, $p = 0.020$ (1-tailed); patient siblings (36%) vs. control siblings (16%), $X^2 = 4.00$, $df = 1$, $p = 0.023$ (1-tailed)).

Table 3. Negative symptoms in index probands and index siblings versus control probands and control siblings

<table>
<thead>
<tr>
<th>Negative symptom variable</th>
<th>Index probands versus</th>
<th>Index siblings versus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control probands</td>
<td>Control siblings</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revised SANS Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective flattening</td>
<td>1.42</td>
<td>1.71</td>
</tr>
<tr>
<td>$X^2$ improvement$^2$</td>
<td>22.19</td>
<td>21.78</td>
</tr>
<tr>
<td>$p$ value$^3$</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Alogia</td>
<td>0.56</td>
<td>1.72</td>
</tr>
<tr>
<td>$X^2$ improvement$^2$</td>
<td>4.04</td>
<td>6.70</td>
</tr>
<tr>
<td>$p$ value$^3$</td>
<td>0.022</td>
<td>0.005</td>
</tr>
<tr>
<td>Revised Social Anhedonia Scale</td>
<td>1.35</td>
<td>1.55</td>
</tr>
<tr>
<td>$X^2$ improvement$^2$</td>
<td>15.97</td>
<td>11.91</td>
</tr>
<tr>
<td>$p$ value$^3$</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>All Negative Symptoms Jointly</td>
<td>26.20</td>
<td>22.05</td>
</tr>
<tr>
<td>$X^2$ improvement$^2$</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Note.—SANS = Scale for Assessment of Negative Symptoms (Andreasen 1984).

1 Effect size = (index mean – control mean)/standard deviation control.

$^2 X^2$ improvement from logistic regression model with only age and sex covariates to model with age, sex, and relevant negative symptom measure (1 df for single measure, 3 df for joint set of three measures).

$^3 p$ value (1-tailed).
Familial Liability to Schizophrenia

Diagnosed and Nondiagnosed Patient Siblings Versus Control Probands. A potentially more sensitive test was used to evaluate the hypothesis that genetic liability to schizophrenia might be increased among patients' siblings who themselves have some diagnoses. Negative symptomatology in the patient siblings receiving any lifetime diagnosis was compared with that in the control probands and their siblings. There were too few schizophrenia spectrum cases among the siblings of patients to justify analyzing them alone. Nineteen patient siblings received at least one probable or definite lifetime RDC or at least one DSM-III Axis II diagnosis and were included in the diagnosed group. Two of these patient siblings received schizophrenia spectrum diagnoses, but most diagnoses consisted of past episodes of unipolar depression, alcoholism, or drug abuse. Twenty of the patient siblings received no RDC or Axis II diagnosis.

Results of logistic regression analyses comparing the diagnosed patient siblings with well control probands and control siblings indicated no significant differences between groups on either SANS measure, although social anhedonia was significantly increased in diagnosed patient siblings compared with control probands ($X^2 = 2.75, df = 1, p = 0.049$ (1-tailed)) and control siblings ($X^2 = 2.58, df = 1, p = 0.054$ (1-tailed)).

To evaluate these trends further, the patient siblings with no diagnoses were also compared with the control groups, which is a particularly stringent test because any observed negative symptomatology among such nondiagnosed patient siblings could not be secondary to a history of psychopathology. In contrast to the trends found for anhedonia in diagnosed patient siblings, there were no significant differences between nondiagnosed patient siblings and either control group for any negative symptom. There were also no significant differences between diagnosed and nondiagnosed index siblings on any of the three negative symptom measures.

Familiality of Negative Symptoms. To investigate the origins of individual differences in negative symptoms among patients, the familiality of negative symptoms in patient and control sibships was examined. Pearson correlations (1-tailed) were calculated between the index patients and their siblings and between the control probands and their siblings on negative symptom variables adjusted for age, sex, and ethnic group separately for each group. In the patient sibships, there were no significant sibling correlations for affective flattening ($r = -0.10, p = 0.28$), alogia ($r = -0.13, p = 0.23$), or social anhedonia ($r = 0.09, p = 0.31$). In contrast, in the control sibships, there were significant positive sibling correlations for alogia ($r = 0.44, p = 0.003$) and social anhedonia ($r = 0.31, p = 0.03$), and a low nonsignificant correlation for affective flattening ($r = 0.14, p = 0.20$). Fisher's $Z$ tests indicated that only the sibling correlation for alogia was significantly less in the patient than in the control families.

Discussion

The findings of this sibling study of schizophrenia and negative symptoms are summarized as follows:

1. Nonschizophrenia adult siblings of schizophrenia patients did not exhibit significantly more core negative symptoms using standard behavioral ratings than control probands or their siblings, although a self-report measure of social anhedonia showed some nonsignificant trends.

2. Siblings of patients who had at least one diagnosis themselves also did not differ significantly from control probands or control siblings in behavioral negative symptoms, although there were some trends for social anhedonia. No significant differences were found between nondiagnosed patient siblings and control subjects.

3. No evidence was found for the familiality of individual differences in negative symptoms among index sibships, although some significant positive sibling correlations were found in control sibships.

Comparison With Findings From Other Studies. The finding that the nonschizophrenia adult siblings of the schizophrenia patients did not exhibit significantly more affective flattening or alogia than either of the control groups is consistent with reports from the New York High-Risk Project of no significant differences in SANS Affective Flattening or Alogia in the child, early adolescent (Dworkin et al. 1991), and adolescent (Dworkin et al. 1990) offspring of schizophrenia patients versus the offspring of well parents. In contrast, a second independent sample from the New York High-Risk Project found a significant increase in negative symptoms among the offspring of patients during late adolescence (Dworkin et al. 1991). However, at this late age any difference using a high-risk design may reflect a prodromal schizophrenia state rather than the effect of liability that would never be expressed as clinical schizophrenia. The one other report, by Tsuang et al. (1991), showed nonsignificant increases for SANS Affective Flattening and Alogia ($p < 0.09$) among relatives (parents and siblings combined) of schizophrenia patients versus relatives of depressed patients. However, patient relatives diagnosed with schizophrenia were not removed from the analyses, demographic characteristics of the samples were not described, and parents and sibling relatives were combined. In short, the reports from these three independent samples of core negative symptoms based on behavior ratings are also largely negative and include methodological features that complicate...
the interpretation of any positive trends as indications of unexpressed liability.

In this study, patient siblings also did not report significantly more social anhedonia than either of the control groups, although there were some trends in the predicted direction. These results are generally consistent with the nonsignificant findings from the study of social anhedonia in patients' relatives by Katsanis et al. (1990) (calculated by the present authors) and the significant, but small effect size reported by Kendler et al. (1996). However, of the five reports on a presumably related measure of physical anhedonia, only Erlenmeyer-Kimling et al.'s (1993) nonsignificant findings are consistent with ours. In contrast, Katsanis et al. (1990), Grove et al. (1991), Clementz et al. (1991; which was based on Katsanis' and Grove's samples along with a third sample), and Franke et al. (1993) reported significantly increased physical anhedonia in the first-degree relatives of schizophrenia patients in comparison with well controls. One explanation for these differences is that physical anhedonia may be a better indicator than social anhedonia of liability to schizophrenia, although most studies report substantial correlations between the two among patients, relatives, and normal subjects (Chapman et al. 1976; Katsanis et al. 1990). It may also be that methodological features contributed to the positive findings for physical anhedonia in these four reports, all of which included schizophrenia relatives in their analyses (except Franke et al. 1993), employed super-normal control subjects, did not clearly match control subjects demographically (except Franke et al. 1993), and combined both siblings and parents in the analyses (except Franke et al. 1993). Given our own marginally significant findings for social anhedonia, this variation among studies is largely one of degree and may suggest that self-reported social anhedonia actually is somewhat elevated among relatives of schizophrenia patients. Interestingly, however, this increased social anhedonia was most apparent here among patient siblings with diagnoses compared with those without, suggesting that self-reported social anhedonia may be secondary to more general psychopathology (or vice versa). With the exception of Franke et al. (1993), previous studies have not separated diagnosed from nondiagnosed relatives of patient probands.

To our knowledge, no published studies have specifically examined the familial association between individual differences in these negative symptom measures in patients and their nonschizophrenia relatives. However, positive correlations in various negative symptoms have been reported among MZ twins concordant for schizophrenia (i.e., homotypia) (Berenaub et al. 1987, 1990; McGuffin et al. 1987). In addition, four analyses that examined negative symptoms among twin or sibling pairs without regard to concordance for schizophrenia also generally found significant concordance (Dworkin and Lenzenweger 1984; Berenaub et al. 1985, 1987, 1990; Clementz et al. 1991; Grove et al. 1991). The discrepancy with our findings of nonsignificant sibling correlations among patient families may result from differences in measures (none of the other studies used SANS ratings from videotapes or the Social Anhedonia Scale), the potential increase of correlations in the other studies by the inclusion of twin or sibling pairs concordant for schizophrenia, or the potential inflation of sibling correlations based on scores uncorrected for age and sex effects.

We did find alogia and anhedonia to be familial in control sibships. To our knowledge, no studies have reported on the familiality of behavior ratings of negative symptoms in nonpatient families. However, our results are consistent with Dworkin and Saczyński's (1984), Kendler and Hewitt's (1992), and MacDonald et al.'s (1996) findings of significant correlations in normal twins for self-reported anhedonia and with Berenaub and McGrew's (1993) findings of significant familiality for self-reported anhedonia in normal families.

Methodological Considerations. Before interpreting the findings from this study, potential methodological constraints need to be considered that might explain our general lack of significant differences between patient siblings and control subjects. First, it is possible that the measures and their use produced too much error variance to detect true differences. However, large effect sizes were detected between stable outpatients and control subjects. Furthermore, the blind rating procedure was based on close study of videotapes, and the high intrarater reliability shown in the study also argues against excessive error variance. Despite these points, it may be that the SANS ratings, although reliably employed, suffer from floor effects and are relatively insensitive to particularly mild deficits. Although liberal use of the "questionable" rating on the SANS was encouraged in order to avoid this problem, it remains a possibility that future research needs to address with more quantitative measures of emotional expressiveness and verbal output (Ekman and Friesen 1978; Alpert 1983; Katz et al. 1993). The use of 15-minute ratings rather than a longer period may also have decreased sensitivity. It is also possible that laboratory manipulations of emotional state (e.g., viewing emotion-inducing videotapes (Berenaub and Oltmanns 1992)) may produce more sensitive indicators than were found during a naturalistic structured interview. The self-report measure of social anhedonia is less affected by such factors, although it is possible that relatives of patients might selectively underreport pathology.
It is also possible that the patient siblings were biased toward health. Twenty-nine percent of eligible patient probands were not included in the study because no siblings could be assessed and it may be that refusals were more likely to come from siblings with more negative symptoms. However, there were no significant differences on negative symptoms between probands with and without participating siblings. Among those index sibships who were ascertained, we were relatively successful in recruiting siblings according to a plan that was random with respect to psychopathology, and this did not differ from the rate in control siblings. Furthermore, there were no significant differences for negative symptoms between siblings with an ascertainment rank of 1 and those with a lower rank. Nevertheless, it is difficult to rule out completely such selection biases as long as participation is not close to 100 percent. Similar attrition issues also hold for all previous studies in this area.

The control groups might also have contributed to nonsignificant findings. The well control probands were screened for psychopathology, but their siblings were not, which improves their resemblance to the general population. In any case, screening of control probands could only potentially serve to increase artificially differences with patient siblings (Kendler 1990) and thus would not contribute to nonsignificant results. In addition, the control probands were carefully matched to the patient siblings on demographics. The case for matching on age, sex, and ethnic group is clear, but the case for matching on education is somewhat more complex. Overmatching is possible if the matching variables are associated with schizophrenia (Meehl 1970). However, this is unlikely in our study because matching was based on the patient sibling’s education (not the patient’s) and there is no convincing evidence that reduced education is both familial and negatively correlated with schizophrenia and phenotypically correlated with negative symptoms in the general population. There were no significant negative correlations between education level and negative symptoms in the current control samples. Therefore, it is unlikely (although not impossible) that matching control probands to index siblings on education artificially reduced index sibling versus control differences on negative symptoms.

Low statistical power might also explain the lack of significant differences between siblings of patients and controls. Effect sizes predicted for relatives may be fairly small, depending on the hypothesized mode of transmission. For example, in a simple, but undoubtedly unrealistic example (Pogue-Geile and Gottesman 1999), assuming a homogeneous, infrequent, single major locus effect on schizophrenia liability without shared environmental effects, it can be predicted that 50 percent of patient siblings would be liable under a dominant model and only 25 percent would be liable with a recessive model, thus reducing expected effect sizes by these percentages. Similarly, polygenic additive models predict effect sizes in siblings that are 50 percent of the heritability of the trait. It is difficult to estimate the effects on liability of the currently favored epistatic models, in which multiple genes interact to produce the schizophrenia diagnosis. Nevertheless, given these bounds, the power of the current study (alpha = 0.05, 1-tailed) to detect a large effect (effect size = 0.80 SD in an index sample of 100% susceptibility) ranges between 0.54 among siblings for a dominant model and only 0.23 among siblings for a recessive model (Cohen 1987). Alternatively, one may use the observed effect size among patients as a guide in predicting the effect size among a sample of 100-percent susceptibles, although this is fallible because inatrogenic and nonshared environmental effects may inflate this estimate and treatment effects may reduce it. Nevertheless, given the average patient/control effect size observed here of about 1.5 SD, the power of the study is more optimistically estimated to be 0.95 under a dominant model and about 0.50 for a recessive one. In any case, insufficient power may play a role in the lack of significant results, although this seems less likely in the case of the SANS ratings (average observed effect size for siblings = 0.02 SD) than Social Anhedonia (average observed effect size for siblings = 0.37 SD). In addition, these nonsignificant findings among patient siblings for negative symptoms contrast with significant results from this same sample for other measures, such as neuropsychological performance (Pogue-Geile et al. 1991), social functioning (Brunke et al. 1991), and mild thought disorder (Hall et al. 1991). These findings also point to the distinction recommended by Strauss et al. (1974) between self-reported social functioning and the core negative symptoms of reduced emotional expression and reduced verbosity.

A related issue concerns elimination of siblings with schizophrenia from the analyses. Although this is important to directly address the practical question of the ability of these measures to detect “unexpressed” liability, it also effectively reduces the sample of potential susceptible siblings, thus reducing power somewhat. One sibling with schizophrenia (2.5%) was identified and omitted from analyses, which is within expectations given that the average age of the siblings was about halfway through the risk period and that the lifetime morbid risk for operationally diagnosed schizophrenia among siblings is approximately 5 to 10 percent (Kendler et al. 1993).

Other methodological points that should strengthen the weight given to these findings include our assessment of index probands during a clinically stable period, which presumably enhances the stability of patient individual differences. There are also several advantages to studying
siblings because they are (1) less affected by any environmental effects of being reared by a parent with schizophrenia (in contrast to high-risk offspring studies), (2) are through much of the age of risk (which minimizes the rate of prodromal signs of eventual schizophrenia), (3) are roughly age-matched to probands (which should maximize any age-dependent genetic effects (Pogue-Geile 1991)), and (4) share genetic dominance effects (in contrast to parents and offspring).

Conclusions

First, we observed that the core negative symptoms of affective flattening and poverty of speech, as measured by our revised SANS from videotapes, were not increased in the adult nonschizophrenia relatives of schizophrenia patients. This suggests that they are unlikely to be strong, useful indicators of "unexpressed" genetic liability to schizophrenia in linkage studies. Investigators searching for such robust indicators would be advised to search elsewhere. Similarly, inclusion of these core negative symptoms in diagnostic criteria for schizophrenia spectrum diagnoses does not appear useful at this time. However, it remains possible that core negative symptoms may act as prodromal signs in younger at-risk samples. In contrast, the results for self-reported social anhedonia are less clear-cut and may suggest some association with liability that is worthy of additional study. In any case, neither this nor previous studies that have omitted control groups of other nonschizophrenia patient probands can speak to the specificity of such measures to schizophrenia familial liability versus nonspecific liability to psychopathology in general.

Second, regarding the etiology of individual differences in negative symptoms among patients, the finding of familiality among control subjects but not index siblings is evidence against several hypothetical models (Pogue-Geile and Keshavan 1991). In particular, they do not support the hypothesis that familial factors (either genetic or environmental) that are independent of liability to schizophrenia contribute to negative symptoms in patients. If this were the case, then negative symptoms would be familial in both index and control families (e.g., height). Similarly, the data do not support a model in which familial factors cause both schizophrenia and negative symptoms. In this case, negative symptoms would be elevated among index relatives as well as showing familiality in index families. These data are also inconsistent with a multiple threshold model in which negative symptoms in nonschizophrenia individuals reflect a less extreme threshold of liability than schizophrenia itself. Otherwise, negative symptoms would be more common in index siblings than control subjects. Instead, the present data are consistent with several different models. First, they may suggest that nonfamilial environmental experiences idiosyncratic to some patients, such as medication dosage, head trauma, or obstetrical complications, may contribute to negative symptoms among patients with schizophrenia. However, other familial models also remain consistent with the findings. It may be that familial factors contribute to negative symptoms, but only because they interact with schizophrenia liability. For example, the causes of low intelligence may also produce negative symptoms only among schizophrenia patients and not among nonschizophrenia individuals. A multiple threshold model in which schizophrenia with negative symptoms reflects a particularly severe threshold of liability is also consistent with these data in that it would predict no familiality for negative symptoms among index families and no increased rate of negative symptoms among relatives of schizophrenia probands. Further studies of homotypia for negative symptoms among relatives with schizophrenia and of the association between negative symptoms in patients and risk for schizophrenia among relatives are needed to begin to distinguish among these alternative models that remain consistent with the results presented here (Pogue-Geile and Keshavan 1991).

References


Familial Liability to Schizophrenia


Acknowledgments

Preparation of this article was supported in part by grants MH-43666 and MH-30915 (MHCRC seed monies program) from the National Institute of Mental Health, and National Institutes of Health grant RR07084 (BRSG program) to Michael Pogue-Geile, Ph.D. A preliminary version of this report was first presented at the annual meeting of the Society for Research in Psychopathology (1991). We gratefully acknowledge the invaluable assistance in data collection and protocol development of the Family Studies Group, Ann Garrett, Jennifer Brunke Stempel, John Hall, and Nancy Huxley. Gerard Hogarty and the staff of the Environmental/Personal Indicators in the Course of Schizophrenia (EPICS) project also provided important help and access to patients as did the staff of the Schizophrenia Treatment and Research Center. Most important, thanks go to the patients and families for their participation.

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