A Family Study of Schizotypal Disorder

by Marco Battaglia, Luana Bernardeschi, Linda Franchini, Laura Bellodi, and Enrico Smeraldi

Abstract

Direct, blind interviews were used to study the risk for and prevalence of DSM–III–R Axis I and II disorders in 93 first-degree relatives of outpatients with schizotypal personality disorder (SPD) and outpatients with other personality disorders. Risks for SPD (at a slightly loosened diagnostic threshold) and schizoid personality disorder were significantly higher in the families of probands with SPD. Schizophrenia was present only among relatives of probands with SPD, accounting for a morbid risk of 4.1 percent. Neither familial risks for mood and anxiety disorders nor the prevalence of other Axis II disorders significantly differed in the two groups of relatives. It is suggested that SPD is a familial disorder representing a phenotypic expression of liability to schizophrenia.


The uncertainty of the phenotypic boundaries is a common feature of the so-called complex phenotypes, including schizophrenia (Kendler 1990). The recent advances in genetic epidemiology and the possibility of applying linkage analyses to the human genome have made it necessary to rigorously define the schizophrenic spectrum (Cloninger 1987; Smeraldi 1988; Levinson and Mowry 1991).

Blind family studies using restrictive operational criteria generally suggest that schizophrenia is a familial disorder in which genetic factors play an important role (Kendler 1987), although some studies (Pope et al. 1982; Abrams and Taylor 1983; Coryell and Zimmerman 1988; critically reviewed by Kendler 1988b) do not support this view. Current evidence also indicates that liability to schizophrenia is not expressed in families through a single disorder (Kendler 1988a), but much remains to be understood about the nature and extent of the schizophrenic spectrum.

It is of particular interest that some specific personality types may be related to schizophrenia, and some personality disorders are found more frequently than full-blown schizophrenia among the relatives of schizophrenia patients (Kety et al. 1968; Kendler and Gruenberg 1984). Together with information from clinical observations, the data from the Danish adoption studies of schizophrenia (Kety et al. 1968) influenced the development of criteria for DSM–III (American Psychiatric Association 1980) and DSM–III–R (American Psychiatric Association 1987) schizotypal personality disorder (SPD) (Spitzer et al. 1979), a personality disturbance possibly related to chronic schizophrenia.

Two issues are of major importance for the validation process of SPD: the degree of familial aggregation of the disorder and the relationship of SPD to chronic schizophrenia. The first issue can be explored by family studies, starting from index probands with SPD, assessing the presence of the same disorder in relatives. Four studies, including an adoption study and a twin study, have ad-
dressed this question (Kendler and Gruenberg 1984; Torgersen 1984; Baron et al. 1985a; Siever et al. 1990, table 1). Although both Kendler and Gruenberg (1984) and Torgersen (1984) employed powerful strategies that produced results suggesting genetic influences for SPD, their findings were not based on structured interview schedules. In addition, the schizotypal index probands in the Danish adoption studies (Kendler and Gruenberg 1984) constitute a rather small group, and Torgersen's (1984) twin study—although based on explicit DSM-III criteria—was not done with the investigator blind as to who was cotwin to whom. The studies of Baron et al. (1985a) and Siever et al. (1990) were based on a family history design, a method usually described as less sensitive than face-to-face interviews. Moreover, in Baron et al.'s (1985a) study, the researchers who performed the assessment of relatives were not blind to the probands' diagnosis, although the authors provided evidence of no significant impact of this possible source of bias.

To clarify the possible relationship of DSM-III and DSM-III-R SPD to schizophrenia, two complementary designs from genetic epidemiology can be employed. The first, starting from schizophrenia probands, estimates the risk for SPD among relatives. Reanalyses of the data from the Danish adoption studies with DSM-III criteria (Kendler et al. 1981; Kendler and Gruenberg 1984) confirm a genetic link between schizophrenia and SPD. However, these studies suffer from a somewhat circular methodology, because they were carried out on the same sample from which the original criteria for DSM-III SPD were derived (Kendler et al. 1981). Other published studies starting from probands with schizophrenia yielded both positive (Kendler et al. 1984; Baron et al. 1985b; Bellodi et al. 1986) and negative (Coryell and Zimmer-

### Table 1. Family studies starting from probands with DSM-III or DSM-III-R schizotypal personality disorder

<table>
<thead>
<tr>
<th>Study</th>
<th>Index probands</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soloff and Millward (1983)</td>
<td>Inpatients with SZT-BDL PD</td>
<td>No familial cases of schizophrenia</td>
</tr>
<tr>
<td>Kendler and Gruenberg (1984)</td>
<td>6 adoptees with SPD from the Danish adoption studies</td>
<td>2 cases of SPD and no cases of schizophrenia in relatives</td>
</tr>
<tr>
<td>Torgersen (1984)</td>
<td>Same-sex twins from Norwegian psychiatric registry</td>
<td>Concordance for SPD 8 times higher in monozygotic than in dizygotic pairs; no cases of schizophrenia among cotwins of schizotypal probands</td>
</tr>
<tr>
<td>Baron et al. (1985a)</td>
<td>13 college students with definite SPD</td>
<td>14.8% morbid risk for SPD among relatives</td>
</tr>
<tr>
<td>Schulz et al. (1986)</td>
<td>Outpatients with SPD</td>
<td>No familial cases of schizophrenia</td>
</tr>
<tr>
<td>Schulz et al. (1989)</td>
<td>Inpatients with SZT-BDL PD</td>
<td>8.4% rate of schizophrenia in relatives</td>
</tr>
<tr>
<td>Siever et al. (1990)</td>
<td>Patients with SZT and/or paranoid PD</td>
<td>14.4% morbid risk for SZT and paranoid PD and 2% risk for schizophrenia in relatives</td>
</tr>
<tr>
<td>Battaglia et al. (1991)</td>
<td>Outpatients with SPD</td>
<td>4.6% morbid risk for schizophrenia in relatives</td>
</tr>
<tr>
<td>Thaker et al. (1993)</td>
<td>Community sample subjects with traits or full diagnosis of cluster A PDs</td>
<td>3.3% morbid risk for schizophrenia and 15.6% morbid risk for schizophrenia spectrum disorders in relatives</td>
</tr>
</tbody>
</table>

**Note.**—DSM-III and DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980, 1987); SZT-BDL PD = schizotypal borderline personality disorder; PD = personality disorder; SPD = schizotypal personality disorder; SZT = schizotypal.

*Kendler and Gruenberg (1984) and Torgersen (1984) were based on direct interviews; all others were family history studies.*
mann 1988) results with regard to whether SPD belongs in the schizophrenic spectrum. But the key to demonstrating the existence of a spectrum of liability lies not only in finding the excess of SPD among relatives of patients with chronic schizophrenia, but also in applying the reverse design, that is, assessing the proportion of relatives with chronic schizophrenia among the relatives of index subjects with SPD (Cloninger et al. 1988). This has been tried in only a limited number of studies (table 1), none of which employed direct interviews to assess psychopathology in relatives. Familial risks for schizophrenia in these studies vary from 0 to 8.4 percent; moreover, when familial ascertainment was made for schizotypal probands, data from adoption and twin studies failed to show a relationship between SPD and schizophrenia. This considerable variability of results emphasizes the need for a family study starting from probands with SPD.

In the present study, index probands with DSM-III-R SPD and probands with other DSM-III-R Axis II diagnoses, all coming from the same sample of consecutive outpatients, were the starting point for blind assessment of first-degree relatives through structured interviews for Axis I and II disorders.

Methods

Selection Criteria. All index probands in this study were drawn from a population of 396 outpatients seen consecutively at the Department of Neurosciences, S. Raffaele Hospital, Milan, Italy, over 26 months. All subjects were self-referred or were referred to our department by general practitioners or psychiatrists working in other facilities in the same geographical area, always on a voluntary basis. This is a clinical sample for whom we made systematic diagnostic assessments with structured interviews to be employed in family and epidemiological studies currently being undertaken by our department.

To assess DSM-III-R Axis I disorders, the Italian version of the Diagnostic Interview Schedule—Revised (DIS-III-R) checklist interview (Robins et al. 1989) was routinely administered by a group of four residents in psychiatry. The residents were trained in the use of the instrument and interrater reliability for interview-generated diagnoses was good (mean $k$ [chance-corrected for DIS-R generated diagnoses] = 0.86). When possible, available clinical material, including medical charts and clinical reports, was employed to corroborate Axis I diagnoses.

To assess DSM-III-R Axis II disorders, the Italian version of the Semistructured Interview for DSM-III-R Personality Disorders—Revised (SIDP-R; Pfahl et al. 1989) was employed. This instrument was chosen for two main reasons. First, in addition to diagnosing the cluster A disorders usually thought to be connected to schizophrenia and psychotic disorders, it covers the full DSM-III-R range of personality disorders and therefore explores a wider range of possible familial aggregation of personality disturbances. Second, the SIDP (Stangl et al. 1985) and SIDP-R have been used reliably in several studies and by our group since 1987, making it possible to compare results with those obtained in previous studies by our own and other groups.

The personality assessment always followed the Axis I assessment. Interviewers using the SIDP-R were a group of residents in psychiatry who were trained in the use of the instrument and had satisfactory interrater reliability (mean $k$ [chance-corrected for SIDP-R-generated Axis II diagnoses] = 0.83; $k$ [chance-corrected for SIDP-R diagnosis of SPD, evaluated on 10 repeated interviews] = 0.89).

In accordance with DSM-III-R criteria, all outpatients meeting five or more criteria for SPD in the SIDP-R were considered to have the personality disorder. For each subject, the DIS-III-R and the SIDP-R were always administered by different interviewers. As in previous studies (Battaglia et al. 1993), all patients with a DIS-III-R diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, or dementia, or with evidence of an organic mental disorder or mental retardation, were excluded from personality assessment; in all these conditions, for different reasons, such an assessment would be of limited meaning, unreliable, or both. Therefore, subjects in this study were basically derived from outpatients seen at our facilities for anxiety and mood disorders.

Since the presence of a clinically important state of anxiety (Reich et al. 1986) or depression (Hirschfeld et al. 1983) may influence personality evaluation, the SIDP-R was always administered when patients were in a state of at least moderate remission from symptoms, according to the judgment of the clinicians who were following them in treatment. In conformity with the SIDP-R instructions, during the interviews the subjects were repeatedly invited to answer according to their most typical
personality style, that is, without taking into account temporary changes occurring in the course of episodes of psychiatric syndromes. During the personality assessment, when pathologic traits were elicited, the interviewers asked for clarification to make sure that the traits were not the temporary consequences of psychiatric symptoms. In the total outpatient sample, 22 subjects had DSM-III-R SPD according to the SIDP-R interview. They were included in the schizotypal group, regardless of the possible codiagnoses with other DSM-III-R Axis II disorders.

After the proband’s informed consent had been obtained, first-degree relatives were contacted for personal interviews. Of the 22 subjects with SPD, 4 did not give consent for their relatives to be interviewed; the family of 2 were geographically distant (400 km or more), which made interviews impractical; and 1 patient was without a fixed abode. Therefore, the data in the study refer to 15 index probands with SPD (9 women, 6 men) and their first-degree relatives. The SIDP-R includes a section for interviewing an informant (usually a relative); however, since we had a limited number of interviewers, we decided not to use this source of information, thereby ensuring maximum blindness when assessing subjects from the same family.

From the same clinical sample of 396 outpatients, we randomly chose 22 subjects similar to the schizotypal probands in age, sex, social class, education, family size (mean number of first-degree relatives), Axis I disorders, and type of Axis II disorders other than schizotypal, schizoid, or paranoid. (This means that all nonschizotypal probands had at least one personality disorder on Axis II, not belonging in the cluster A, and homogeneous to the other personality disorders codiagnosed in the schizotypal probands.) The families of these 22 subjects were to be compared with those of the schizotypal probands. Nineteen of the 22 nonschizotypal subjects (10 women, 9 men) gave permission to contact their family members and to proceed with the family study.

**Family Study.** All diagnostic interviews of first-degree relatives of probands with and without SPD reported in this study were done with the interviewers blind to the index proband’s Axis I or Axis II diagnosis and to kinship status. The same instruments, criteria, and procedures were used for the patients and their relatives.

For uninterviewed relatives, the Family History–Research Diagnostic Criteria (FH–RDC) interview (Andreasen et al. 1986; Gasperini et al. 1991) was used to collect family history data, with the help of the proband and at least one first-degree relative, to generate DSM-III-R Axis I diagnoses. The family history interviews were done blind to the probands’ Axis I or II diagnoses by psychiatrists different from those who conducted interviews with the DIS–R checklist and the SIDP-R. Only definite diagnoses obtained with the family history were computed. A previous analysis of the reliability of diagnoses obtained with the FH–RDC method in our group yielded a mean k value of 0.83 (Battaglia et al. 1991).

Only direct, face-to-face interviews were used to evaluate the presence of possible Axis II disorders in relatives. In fact, when assessing important behavioral traits, such as an odd or guarded appearance, an expression of aloofness, or poor eye contact, only direct interviews can be considered reliable (Kendler 1988b); telephone interviews and family history collection of personality traits do not ensure enough sensitivity and specificity.

Consequently, Axis II diagnoses in the study are based exclusively on direct assessment of the available first-degree relatives interviewed at the Department of Neurosciences or in their homes. As in the procedure employed for index probands, DIS–R diagnoses of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, mental retardation, dementia, or organic mental syndromes were defined a priori as criteria for the exclusion of relatives from personality assessment. While SPD was considered to be present in index probands when five or more schizotypal traits were counted in the SIDP-R, we considered SPD to be present in a relative when he or she had four or more traits of SPD at the SIDP-R. This procedure, established before assessments are undertaken, slightly lowers the threshold for diagnosis of SPD recommended by DSM-III-R. The four-traits threshold for SPD has been used in all studies using DSM-III criteria; we adopted it because, with our small sample size, we wanted to enhance the sensitivity of the study. Therefore, both SPD definite (five-traits threshold) and SPD probable (four-traits threshold) are counted as positive cases of SPD among relatives in the family study. All other DSM-III-R Axis II disorders in relatives were diagnosed by strictly following the DSM-III-R criteria and recommended thresholds.

Direct interviews were obtained
for 38 of the 57 living first-degree relatives of probands with SPD (35 of whom were eligible for both the Axis I and Axis II assessment, according to the inclusion criteria) and 55 of the 67 living first-degree relatives of nonschizotypal probands (all but one of whom were eligible for both Axis I and Axis II assessment), for a total direct assessment with structured interviews of 75 percent of living relatives in the study. There were five dead relatives among the families of probands with SPD and one among the families of nonschizotypal probands.

**Data Analyses.** Familial risks for psychiatric disorders are expressed as Morbid Risks (%) (MR = no. affected/no. affected + no. at risk). To calculate the risk for unaffected relatives and to facilitate the comparison with previous studies from other groups (Kendler et al. 1984; Siever et al. 1990), we used Weinberg’s abridged method (Stendstedt 1952), with an age of risk ranging from 15 to 45 for schizophrenia, schizoaffective disorder, and DSM-III-R schizotypal, schizoid, and paranoid personality disorder. However, since personality disorders are lifelong, early-onset disorders, we also provide the percentages of cluster A personality disorders in the families.

The Weinberg method was also used to calculate the risks for anxiety disorders in unaffected relatives, with an age range of 12 to 60 for panic disorder/agoraphobia and generalized anxiety disorder, 7 to 50 for obsessive-compulsive disorder, and 15 to 59 for major depression, both recurrent and single-episode, and bipolar disorder.

The data for the schizotypal versus nonschizotypal patients and their families were analyzed chi-square, Student’s t, and two-tailed tests for the difference between two proportions, as appropriate.

**Results**

Table 2 shows the sociodemographic and clinical characteristics of the index probands, divided according to the presence of schizotypal disorder. There are no statistically significant differences between the two groups for mean age (t = 1.1, df = 32, not significant [NS]), years of education (t = 1.06, df = 32, NS), social class, or marital status (chi-square test applied to the contingency tables).

The lifetime Axis I diagnoses in index probands are almost exclusively limited to mood and anxiety disorders, owing to the type of inclusion and exclusion criteria in the original sample; their distribution in the two groups is homogeneous, as tested by the chi-square test applied to the contingency tables.

The absence of SPD, as well as other cluster A personality disorders, was an inclusion criterion for the nonschizotypal probands; other Axis II disorders are homogeneously distributed in the two groups, except for a significantly greater presence of avoidant personality disorder in the schizotypal group (χ² = 5.4, df = 1, p = 0.02).

Schizotypal and nonschizotypal probands had families of similar size (mean number of relatives 4.2 ± 1.9 vs. 3.5 ± 1.4; t = 1.2, df = 32, NS), and the mean age of relatives was similar (46.3 ± 16.0 vs. 47.5 ± 15.4; t = -0.46, df = 128, NS). There is a significant difference in the success rate (the number of first-degree relatives who agreed to be interviewed) of interviews with relatives of schizotypal probands (67%) versus control probands (82%) (χ² = 3.9, df = 1, p = 0.05).

Table 3 shows the MRs, adjusted by Weinberg’s abridged method for unaffected relatives, for DSM-III-R schizotypal, schizoid, and paranoid personality disorders, schizophrenia, and schizoaffective disorder in the first-degree relatives of subjects with and without SPD. Data on children are not shown because none had yet reached the age of risk. According to the SIDP-R interview, SPD definite (five-traits threshold) was present in one parent and SPD probable (four-traits threshold) was present in three parents and one sibling of the schizotypal index probands. No cases of SPD definite were found among the relatives of nonschizotypal index probands; SPD probable was present in one parent. Therefore, the crude percentages are 2.9 percent for SPD definite and 14.3 percent for SPD definite plus probable in the families of schizotypal probands. In the families of nonschizotypal probands, the percentages are 0 percent for SPD definite and 1.8 percent for SPD probable.

The percentages for schizoid and paranoid personality disorder are 14.3 and 17 percent in the families of schizotypal probands and 0 and 9.2 percent in the families of nonschizotypal probands.

There is a significantly higher MR for schizotypal and schizoid personality disorders in the relatives of subjects with SPD (p = 0.04 and p = 0.01, test of the difference between two proportions); no other differences are statistically significant. Both schizoid and SPD were present in only one relative, while both paranoid and SPD were diagnosed in three relatives.
Table 2. Sociodemographic and clinical characteristics of outpatients with schizotypal and nonschizotypal personality disorders

<table>
<thead>
<tr>
<th></th>
<th>SPD (n = 15)</th>
<th>Non-SPD (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females, %</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td>Mean age, yr (± SD)</td>
<td>31.73 ± 9.5</td>
<td>28.84 ± 5.4</td>
</tr>
<tr>
<td>Mean education, yr (± SD)</td>
<td>11.8 ± 2.3</td>
<td>10.8 ± 3.0</td>
</tr>
<tr>
<td>Social class, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Lower middle</td>
<td>80</td>
<td>94</td>
</tr>
<tr>
<td>Higher middle</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Marital status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>80</td>
<td>68</td>
</tr>
<tr>
<td>Married</td>
<td>13</td>
<td>32</td>
</tr>
<tr>
<td>Divorced</td>
<td>7</td>
<td>—</td>
</tr>
<tr>
<td>Axis I diagnosis (lifetime), %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panic disorder</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>Generalized anxiety</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>Social phobia</td>
<td>27</td>
<td>16</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Depression</td>
<td>46</td>
<td>58</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Mania</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Axis II diagnosis, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoic</td>
<td>47</td>
<td>—</td>
</tr>
<tr>
<td>Schizoid</td>
<td>13</td>
<td>—</td>
</tr>
<tr>
<td>Schizotypal</td>
<td>100</td>
<td>—</td>
</tr>
<tr>
<td>Obsessive-compulsive</td>
<td>40</td>
<td>21</td>
</tr>
<tr>
<td>Histrionic</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Dependent</td>
<td>53</td>
<td>42</td>
</tr>
<tr>
<td>Antisocial</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>13</td>
<td>26</td>
</tr>
<tr>
<td>Avoidant</td>
<td>67</td>
<td>21</td>
</tr>
<tr>
<td>Borderline</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Passive-aggressive</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Sadistic</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Self-defeating</td>
<td>20</td>
<td>—</td>
</tr>
</tbody>
</table>

Note.—Total percentages of Axis I and Axis II diagnoses exceed 100% because of multiple diagnoses. SPD = schizotypal personality disorder; SD = standard deviation.

1Patients with DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders–Revised, American Psychiatric Association 1987) SPD.
2Patients with DSM-III-R PDs other than schizotypal, schizoid, or paranoid.

of the schizotypal probands. All familial cases of schizoid personality disorder were found in relatives of nonschizoid schizotypal probands. One of two cases of DSM-III-R schizophrenia found among the relatives of subjects with SPD was chronic undifferentiated (one parent) and one was chronic paranoid (one sibling). If one pools schizophrenia and schizotypal disorder in a putative common spectrum, the MR for schizophrenia spectrum disorders is significantly higher in the families of schizotypal probands than in the families of nonschizotypal probands (14.4% [7/48.5] vs. 1.9% [1/52.5]; 2 = 1.97, p = 0.048, test of the difference between two proportions). This is a conservative estimate, since familial risks for SPD are calculated exclusively on the basis of direct interviews, with all uninterviewed relatives (which means 34% of eligible relatives of schizotypal probands and 18% of relatives of nonschizotypal probands) being counted as nonschizotypal.

The greater MRs for schizophrenia and schizotypal disorder in the families of subjects with SPD were not the result of one or a few families with an unusually high prevalence of these two disorders: the seven subjects with these two diagnoses were, in fact, found in seven separate families (frequency of families with schizophrenia spectrum disorders: 7/15 vs. 1/19, 2 = 5.85, df = 1, p = 0.016).

Axis I diagnoses among probands with SPD did not significantly influence the familial risks for schizophrenia or SPD; after dividing the families according to presence or absence of a lifetime diagnosis of a mood disorder in the proband, familial risks for schizophrenia or schizotypal disorder did not differ significantly (1/21.5 vs. 1/27; 2 = 0.56, NS; 2/10.5 vs. 3/16; 2 = 0.48, NS). The only case of schizoaffective disorder was found among the relatives of subjects with SPD and was...
Table 3. Morbid risks for DSM-III-R-defined schizophrenia, cluster A personality disorders, and schizoaffective disorder in relatives of outpatients with schizotypal and other personality disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>SPD¹</th>
<th>Non-SPD²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(no. affected/no. affected + no. at risk)</td>
<td>(no. affected/no. affected + no. at risk)</td>
</tr>
<tr>
<td></td>
<td>MR</td>
<td>MR</td>
</tr>
<tr>
<td>SPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>4/18</td>
<td>1/33</td>
</tr>
<tr>
<td>Siblings</td>
<td>1/8.5</td>
<td>0/11.5</td>
</tr>
<tr>
<td>Total</td>
<td>5/26.5</td>
<td>1/44.5</td>
</tr>
<tr>
<td>Schizoid PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>4/18</td>
<td>0/33</td>
</tr>
<tr>
<td>Siblings</td>
<td>1/8.5</td>
<td>0/11.5</td>
</tr>
<tr>
<td>Total</td>
<td>5/26.5</td>
<td>0/44.5</td>
</tr>
<tr>
<td>Paranoid PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>3/18</td>
<td>4/33</td>
</tr>
<tr>
<td>Siblings</td>
<td>3/8.5</td>
<td>1/11.5</td>
</tr>
<tr>
<td>Total</td>
<td>6/26.5</td>
<td>5/44.5</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>1/30</td>
<td>0/38</td>
</tr>
<tr>
<td>Siblings</td>
<td>1/18.5</td>
<td>0/14.5</td>
</tr>
<tr>
<td>Total</td>
<td>2/48.5</td>
<td>0/52.5</td>
</tr>
<tr>
<td>Schizoaffective disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>0/30</td>
<td>0/38</td>
</tr>
<tr>
<td>Siblings</td>
<td>1/18.5</td>
<td>0/14.5</td>
</tr>
<tr>
<td>Total</td>
<td>1/48.5</td>
<td>0/52.5</td>
</tr>
</tbody>
</table>

Note—For Axis II cluster A disorders, only direct interview results have been computed. DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1987); SPD = schizotypal personality disorders; MR = morbid risk; PD = personality disorder; NS = not significant.

¹Relatives of patients with DSM-III-R SPD.
²Relatives of patients with DSM-III-R PDs other than schizotypal, schizoid, or paranoid.

mainly of the depressive subtype, according to DSM-III-R.

Table 4 shows the MRs for panic/agoraphobia and generalized anxiety, obsessive-compulsive, major depression, and bipolar disorder in relatives of the two groups of probands. None of the differences was statistically significant. The other Axis I diagnoses found among relatives (not shown in the tables) were anorexia nervosa, substance abuse, and delusional disorder, each in one relative among the relatives of nonschizotypal probands and each accounting for a 2.6 percent frequency. The relative with delusional disorder was a parent with a typical late-onset form of the jealous type. Dementia was diagnosed in two relatives of nonschizotypal subjects and one relative of a schizotypal subject.

Overall, 29 percent of the relatives of probands with SPD and 33 percent of the relatives of nonschizotypal subjects had lifetime diagnoses of DSM-III-R Axis I disorder.

Table 5 shows the frequencies of DSM-III-R cluster B and C Axis II disorders among the relatives of probands with SPD and with other personality disorders. There are no significant differences in these distributions, according to a chi-square test applied to the contingency tables.

Discussion

Familial Aggregation of Schizotypal and Cluster A Disorders.

The significantly higher MR for SPD found among the relatives of
Table 4. Morbid risks for major depression, bipolar disorder, panic and generalized anxiety disorder, and obsessive-compulsive disorder in relatives of outpatients with schizotypal and other personality disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>SPD¹ (no. affected/ no. at risk)</th>
<th>Non-SPD² (no. affected/ no. at risk)</th>
<th>MR</th>
<th>MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>6/42.5</td>
<td>4/44.5</td>
<td>0.141</td>
<td>0.089</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1/42.5</td>
<td>1/44.5</td>
<td>0.023</td>
<td>0.022</td>
</tr>
<tr>
<td>Panic and generalized anxiety disorder</td>
<td>6/42</td>
<td>7/44.5</td>
<td>0.143</td>
<td>0.157</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
<td>2/45.5</td>
<td>1/51.0</td>
<td>0.043</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Note.—SPD = schizotypal personality disorder; MR = morbid risk.
1 Relatives of patients with DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders—Revised, American Psychiatric Association 1987) SPD.
2 Relatives of patients with DSM-III-R PDs other than schizotypal, schizoid, or paranoid.

Table 5. Frequencies of DSM-III-R cluster B and C disorders in relatives of patients with schizotypal and other personality disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>SPD¹ (n = 35)</th>
<th>%</th>
<th>Non-SPD² (n = 54)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive-compulsive</td>
<td>4</td>
<td>11.4</td>
<td>8</td>
<td>14.8</td>
</tr>
<tr>
<td>Histrionic</td>
<td>4</td>
<td>11.4</td>
<td>7</td>
<td>12.9</td>
</tr>
<tr>
<td>Dependent</td>
<td>3</td>
<td>8.6</td>
<td>3</td>
<td>5.5</td>
</tr>
<tr>
<td>Antisocial</td>
<td>2</td>
<td>5.7</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>Narcissistic</td>
<td>1</td>
<td>2.9</td>
<td>3</td>
<td>5.5</td>
</tr>
<tr>
<td>Avoidant</td>
<td>3</td>
<td>8.6</td>
<td>4</td>
<td>7.4</td>
</tr>
<tr>
<td>Borderline</td>
<td>1</td>
<td>2.9</td>
<td>2</td>
<td>3.7</td>
</tr>
<tr>
<td>Passive-aggressive</td>
<td>2</td>
<td>5.7</td>
<td>2</td>
<td>3.7</td>
</tr>
<tr>
<td>Sadistic</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Self-defeating</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.9</td>
</tr>
<tr>
<td>Subjects with any PD</td>
<td>24</td>
<td>69</td>
<td>29</td>
<td>53</td>
</tr>
<tr>
<td>Subjects with no PD</td>
<td>11</td>
<td>31</td>
<td>25</td>
<td>47</td>
</tr>
</tbody>
</table>

Note.—All differences are nonsignificant by 2 x 2 chi-square test. DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1987); SPD = schizotypal personality disorder; PD = personality disorder. The number of subjects with any PD and percentage of diagnoses do not overlap because of multiple diagnoses.
1 Relatives of patients with DSM-III-R SPD.
2 Relatives of patients with DSM-III-R PDs other than schizotypal, schizoid, or paranoid.

Schizotypal probands is in keeping with data from adoptive (Kety et al. 1968; Kendler et al. 1984), twin (Torgersen 1984), and family history (Baron et al. 1985a; Siever et al. 1990) studies of schizotypy, supporting the existence of a familial-genetic component for this personality disorder.

The MR for SPD of 18.9 percent in relatives of schizotypal probands is in agreement with the 14.8 percent and 14.4 percent values (Baron et al. 1985a; Siever et al. 1990) for SPD and schizophrenia-related personality found in previous studies employing the family history approach, a method less sensitive than direct interviews. The MR for SPD found in the relatives of our schizotypal patients is lower than the 26 percent MR for definite plus probable SPD found among the relatives of chronic schizophrenia probands, in whom a higher incidence of all schizophrenia-related disorders can be expected, in a blind family study based on structured interviews (Baron et al. 1985b).

The MR for SPD found in the relatives of our nonschizotypal control patients closely resembles the risk found (Siever et al. 1990) for the families of probands with personality disorders not belonging to cluster A and is consistent with the rate for SPD reported by Kendler (1988a) for relatives of controls from their Roscommon Family Study pilot data.

These observations suggest that SPD may be a relatively common disorder, but it tends to aggregate in the families of subjects having the same disorder and in the families of schizophrenia patients.

The risk for schizoid, but not paranoid personality disorder is significantly higher among the relatives of our SPD probands. This is not an effect of comorbidity with schizoid personality disorder in index schizotypal probands, since all familial cases of schizoid personality disorder were found in the families of nonschizoid schizo-
typical probands, and may suggest that schizotypal and schizoid personalities are variants along the schizophrenia spectrum (Siever and Kendler 1987). However, some (Shields et al. 1975) but not all (Kety et al. 1968) authors feel that schizoid personality belongs in the schizophrenia spectrum.

On the contrary, paranoid personality disorder, although frequently diagnosed in schizotypal probands and in their relatives, fails to show a significant familial aggregation in our sample. Since paranoid personality disorder is found in only slight excess even among the relatives of schizophrenia patients (Kendler and Gruenberg 1982), the lack of significant aggregation in the families of schizotypal probands is not surprising and can be accounted for by sampling variation or by the limited sample size.

Siever et al. (1990) also found that paranoid personality disorder alone was not significantly associated with the schizophrenia spectrum. If one looks at these data with a more dimensional view, it appears that SPD behaves as an indicator of familial aggregation of a spectrum of disorders that include the feature of suspiciousness (the central characteristic of DSM-III-R paranoid personality disorder; Widiger et al. 1988) and schizoid introversion. This function may derive from the copresence of both these factorially independent traits (Kendler et al. 1990) within the set of diagnostic criteria for SPD.

Relationship of Schizotypal Personality to Schizophrenia. The large majority of studies looking at the schizophrenia spectrum have started with index probands with chronic schizophrenia. From the viewpoint of genetic epidemiology, our reverse design—starting familial assessments from schizotypal probands and looking for schizophrenia and SPD in relatives—is a key element in defining a spectrum of common liability between two disorders (Cloninger et al. 1988). In fact, when patients with a narrowly defined disorder (e.g., schizophrenia) are the index probands, the amplitude of the range of affected relatives is a function of the width of the inclusion criteria (Sherrington et al. 1988), while starting the familial assessment from index probands with the putative broad form (i.e., schizotypal disorder) provides a way to test the degree of familial-genetic association between the two disorders (Cloninger et al. 1979).

The overall adjusted MR for DSM-III-R schizophrenia in the families of probands with SPD is 4.1 percent, which is not significantly different from the 0 percent risk for schizophrenia among relatives of patients with personality disorders other than SPD. The lack of statistical significance, however, is not surprising given the sample size. The risks we observed, on the contrary, appear to confirm that the familial-genetic relationship between schizophrenia and schizotypal personality holds true even when families are ascertained through schizotypal index probands. In fact, in family studies the average estimated MRs for schizophrenia of siblings and parents of schizophrenia probands are 8.5 and 4.4 percent, respectively (Slater and Cowie 1971), compared with 5.5 and 3.3 percent in siblings and parents of our schizotypal patients. The expectancy estimate for schizophrenia in the European general population of 0.85 percent (range = 0.42%-1.25%) is in accordance with our estimate of a 0.6 percent population risk for schizophrenia in the Milan area (Battaglia et al. 1991). The lower risk found for schizophrenia among relatives of SPD subjects than among relatives of schizophrenia patients is compatible with a multifactorial polygenic model of schizophrenia, predicting that relatives of probands with the milder form should not have greater risk for the more severe form than relatives of probands with the more severe form.

For the schizotypal probands, the familial MR for the schizophrenic spectrum, encompassing schizophrenia and SPD in our study, is similar to the risk reported (with a broader spectrum definition) for the families of schizotypal/paranoid personality disorder probands (Siever et al. 1990). It is lower, as expected, than the 20.4 and 32.6 percent risk found in a blind family study of schizophrenia (Baron et al. 1985b) in which spectrum definitions included schizophrenia and SPD definite, and definite plus probable.

Other Diagnoses in Index Probands and Their Relatives.

Among our index probands with SPD, there are several Axis I disorders belonging to the mood and anxiety syndromes. They reflect the inclusion criteria we employed and the type of facility from which probands were taken. These features make our sample similar to that studied by Siever et al. (1990), in which over half of the probands had a lifetime diagnosis of Research Diagnostic Criteria (Spitzer et al. 1978) major depression. The types and rates of Axis II personality disorder, comorbid
with SPD, are also similar in the two samples. These data suggest that, at least in clinical populations, SPD is present together with a variety of symptomatological conditions, and that "purely schizotypal" subjects may be rare, if one adopts lifetime structured interviews to assess Axis I psychopathology.

Several disorders in addition to those included in the schizophrenia spectrum are present in the relatives of our schizotypal patients, but the lack of significantly different risks suggests no adjunc-
tive, specific aggregation of diagnoses in their families. However, the reduced sample size may have influenced these results. The prevalence of Axis I disorders is very similar for relatives of schizotypal and nonschizotypal patients in our sample; about 70 percent of relatives have no lifetime Axis I disorder and 50 percent have no Axis II disorder. These findings are in keeping with those obtained in a blind family study of schizophre-
nia (Baron et al. 1985b) using structured interviews, in which 35 percent of relatives of schizophrenia probands and 70 percent of relatives of controls showed no evidence of any DSM-III Axis I or Axis II disorders. The overall fami-

Conclusions and Methodologic Considerations

Our results suggest that SPD is a familial disorder and support the view that the liability to schizo-

phrenia runs in families along a spectrum of variable phenotypic expressions. This is consistent with the view that although the two disorders are separated on two different axes in DSM-IV (American Psychiatric Association 1994) (Battaglia and Bellodi 1992), there is likely to be a genetic link be-

This is, to our knowledge, the first published study to start with schizotypal probands from an un-
selected sample of nonpsychotic outpatients and assess schizophrenia and schizotypal disorder in relatives with direct interviews. The size of the sample, obviously, constitutes the main limitation of this study, and the findings need to be replicated in larger groups to gain strength. The fact that all probands were patients may have caused an overestimation of the role of SPD as a familial indicator of psychopathology. However, the low prevalence of SPD in clinical settings is a recognized problem in research (Lenzenweger and Korfine 1992). Power analyses can show that with these figures one would need to screen samples six times larger to obtain 80 percent power with a two-tailed \( p \) of 0.05. Moreover, some specific traits of schizo-
typic may constitute a more infor-
mative core for the genetics of schizotypy.
schizophrenia (Smeraldi 1988; Lenzenweger and Loranger 1989), and population-based family studies of SPD may help us clarify these issues in the future. Family and genetic studies of schizophrenia can enhance their analytic power by adding structured interview schedules assessing schizotypy to their diagnostic tools.

References


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