At Issue

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Abstract

Recently published data from the Roscommon Family Study show that a parental diagnosis of schizotypal disorder (SPD) has a significant and specific impact on the risk for schizophrenia in siblings of index probands with schizophrenia spectrum disorders. The distribution patterns of risks for schizophrenia and SPD in parents were of opposite magnitude to those of patients’ siblings and children. These patterns can be predicted from the diminished reproductive fitness of patients with schizophrenia if subjects with SPD belong in the schizophrenia spectrum but have no diminished fitness. We briefly review how the few available data about the distribution of risks for schizophrenia and SPD in families may support this interpretation. There is some indirect evidence that, unlike what is usually reported for people with schizophrenia, reproductive fitness may not be diminished in SPD. This might partially account for the opposite patterns of distribution of risks for schizophrenia and SPD in families.


In a recently published report of the Roscommon Family Study, Kendler and Walsh (1995) showed that the presence of a parental diagnosis of schizotypal disorder (SPD) has a significant and specific impact on the risk for schizophrenia in siblings of index probands with schizophrenia spectrum disorders. Previously published findings from the same study showed that the risk for schizophrenia in parents of probands with schizophrenia is substantially lower than in their siblings or offspring (Kendler et al. 1993b), as predicted (Risch 1983; Kendler 1986) by the reduced reproductive rate in schizophrenia (Saugstad 1989). The same authors (Kendler et al. 1993b) predicted that if SPD is a phenotype of milder liability to schizophrenia and if the ability to reproduce successfully is appreciably less impaired in subjects with SPD than in those with schizophrenia, then the pattern of risk in relatives would be expected to be the opposite of that seen in people with schizophrenia, that is, the rates of SPD should be higher in parents than in siblings or offspring.

The distribution of risks for schizophrenia and SPD in the Roscommon families turned out to actually follow these patterns (Kendler et al. 1993b). Kendler et
al. (1993b) suggest that in any generation subjects with the highest liability to the illness develop chronic schizophrenia but have fewer offspring, whereas subjects with SPD, who are considerably less impaired in finding a mate and therefore are the most likely among those at increased liability for schizophrenia to reproduce, are more likely to have children who will manifest schizophrenia. While a variety of factors could have influenced the distribution of risks observed in the Roscommon Family Study (Kendler et al. 1993a), the results are consistent with the hypothesis that people with schizophrenia, but not people with SPD, are of diminished reproductive fitness. In the only other study cited by Kendler et al. (1993b) that examined this question—Baron et al. (1985)—however, the rates of both schizophrenia and SPD were lower in parents than in siblings of patients with schizophrenia.

Two genetic-epidemiological studies carried out on two independent samples at H San Raffaele Hospital in Milan, Italy, have provided results compatible with Kendler et al.'s hypothesis (1993b). We studied the families of non-psychotic index probands with SPD. (All index probands with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, dementia, evidence of an organic mental disorder, or mental retardation were excluded from personality assessment in these studies.) We found that the risk for schizophrenia was considerably higher in siblings than in parents of probands with SPD (Battaglia et al. 1991, 1994, 1995). The risk for SPD, however, showed the opposite tendency, that is, it was about twice as high in parents than in siblings of probands with SPD (Battaglia et al. 1995). Further, Axis I diagnoses of mood or anxiety disorders had no significant influence on the distributions of the morbidity risks, in keeping with the report of Kendler and Walsh (1995). These are the only published genetic-epidemiological studies starting with SPD probands in which the risks for schizophrenia and SPD are specified for parents and siblings. In addition to providing support for the findings of the Roscommon Family Study (Kendler et al. 1993b; Kendler and Walsh 1995), the figures in our studies suggest that SPD functions as a familial indicator of liability to schizophrenic illness in a manner that shares some qualitative features with schizophrenia itself, at least when SPD is diagnosed in nonpsychotic psychiatric outpatients, that is, in those subjects who have the more severe form of this personality disorder.

Schizophrenia Spectrum Disorders and Darwinian Fitness

The interpretation provided by Kendler et al. (1993b; Kendler and Walsh 1995) to explain the observed distribution of familial risks for SPD and schizophrenia across generations is based on (1) the notion that people with SPD have a milder phenotype of liability to the illness and (2) the hypothesis that they have an appreciably less impaired ability to reproduce successfully than people with schizophrenia. While the latter hypothesis is interesting, it needs empirical support.

Specific studies of fertility in SPD are lacking, but some hints may be extrapolated from the schizophrenia literature and from observation of the marital status of people with SPD. The phenomenon of childlessness in schizophrenia has been reported in both European (Ødegård 1975) and North American (Erlenmeyer-Kimling 1978) samples. While there is no evidence of primary impairment of fecundity in this illness, reduced fertility (Erlenmeyer-Kimling et al. 1969), which implies a lack of fitness or a diminished relative probability of survival and reproduction for the genotype (Gottesman 1991), can be satisfactorily accounted for by fewer marriages (Saugstad 1989) of people with schizophrenia. Slater et al. (1971) showed that in the London area the fertility rate of married people with schizophrenia (2.2 children) was as high as 95 percent of that seen in the population. This rate dropped, however, when it was measured in all patients independently of their marital status: 0.9 for women and 0.5 for men. Only 54 percent of the women and 33 percent of the men of the approximately 2,000 subjects in the study ever got married (Slater et al. 1971), demonstrating that the reduced fertility rate should be attributed mainly to the difficulty that patients with schizophrenia have in finding a sexual partner. Assuming that there is no primary defect of fecundity in people with SPD, and in the absence of direct data about this group's fertility, one may obtain a gross index of their ability to find a mate and reproduce by observing their marital status in comparison with that of subjects without SPD.

Table 1 shows the results of the few published studies in which the
Table 1. Marital status of subjects with schizotypal disorder (SPD) in controlled studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects with SPD</th>
<th></th>
<th>Non-SPD subjects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (% never married)</td>
<td>Mean age (SD)</td>
<td>n (% never married)</td>
<td>Mean age (SD)</td>
</tr>
<tr>
<td>Torgersen 1984¹</td>
<td>40 (39)</td>
<td>41.6</td>
<td>69 (17)</td>
<td>39</td>
</tr>
<tr>
<td>McGlashan 1986²</td>
<td>28 (43)</td>
<td>not specified</td>
<td>81 (30) with BPD</td>
<td>not specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>144 (65) with schizophrenia</td>
<td></td>
</tr>
<tr>
<td>Zimmerman and Coryell 1989³</td>
<td>23 (33)</td>
<td>35.6 (13)</td>
<td>654 (17) with no</td>
<td>42.8 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Axis II disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>119 (23) with</td>
<td>30.3-43.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Axis II disorders</td>
<td></td>
</tr>
<tr>
<td>Battaglia et al. 1991⁴</td>
<td>21 (43)</td>
<td>35.6 (14)</td>
<td>21 (38) outpatients</td>
<td>42.5 (12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>42 (48) medical and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>surgical patients</td>
<td>33.4 (14.8)</td>
</tr>
<tr>
<td>Battaglia et al. 1995⁵</td>
<td>15 (80)</td>
<td>31.7 (9.5)</td>
<td>19 (68)</td>
<td>28.8 (5.4)</td>
</tr>
</tbody>
</table>

Note.—All comparisons by chi-square test (df = 1); BPD = borderline personality disorder; NS = not significant.

¹Twin study in which controls are nonpsychotic psychiatrically ill twins of the Norwegian Registry.
²Followup study in which retrospective diagnoses were based on clinical charts; 64% of SPD patients also had BPD.
³Nonpatient sample made up of relatives of controls and of psychiatric patients.
⁴Family history study of outpatients seen at an anxiety/depression facility.
⁵Family study of outpatients seen at an anxiety/depression facility.

The marital status of probands with SPD is specified. The data from the Torgersen (1984), McGlashan (1986), and Battaglia et al. (1991, 1995) studies are based on subjects with SPD without schizophrenia or other co-occurring psychotic disorders. In the Zimmerman and Coryell (1989) study, a diagnosis of schizophrenia based on the Diagnostic Interview Schedule (DIS; Robins et al. 1981) was not an exclusion criterion for SPD, and a nonsignificant proportion of the subjects with SPD also had schizophrenia according to the DIS. However, Zimmerman and Coryell (1989) seem more prone to believe that the DIS-based diagnoses of schizophrenia in their sample could actually "reflect the transient, reactive psychotic episodes characteristic of certain types of personality disorders" more than chronic schizophrenia (p. 687). Therefore, the studies reviewed here seem to be reasonably homogeneous for having excluded SPD subjects who were psychotic, and, in the Zimmerman and Coryell (1989) investigation, at least excluding those who were chronically psychotic. With the exception of Torgersen's (1984) study, there are no significant differences between the marital status of subjects with SPD and patients with other personality disorders, patients without personality disorders, medical or surgical controls, or subjects from groups within the same geographical area. One study (McGlashan 1986) shows significantly more never-married subjects among probands with schizophrenia than among patients with SPD. Although this evidence is indirect, it seems to support the idea that people with SPD have no more problems in finding sexual partners than do subjects with a variety of psychiatric disorders or people at large. Also, according to the results of the McGlashan (1986) study, people with SPD are significantly more likely to find spouses than subjects with schizophrenia. Therefore, their apparently greater reproductive fitness is consistent with the hypothesis suggested by Kendler et al. (1993b) and may at least partially explain the different distribution of risks.
for SPD and schizophrenia across successive generations. However, it should be noted that none of the few published genetic-epidemiological studies of SPD provide any data about the psychiatric diagnoses of the probands' children, usually because of their youth. Risks for the schizophrenia spectrum are known only for the siblings and parents of subjects with SPD.

Limitations and Conclusions

The method of inferring the reproductive fitness of a certain category of subjects from their marital status, the paucity of available studies, and the relatively small samples are general limitations of our approach. Some specific points also must be taken into account. First, the studies reviewed here dealt with individuals in both clinical settings and nonclinical populations. In family studies of schizophrenia, most subjects with SPD have not been in psychiatric treatment. Therefore, it may be that treated samples are only partially representative of the population of people with SPD for several variables, perhaps even including the familial risks for the schizophrenia spectrum and fertility. The percentages of never-married subjects across the reviewed studies vary considerably, but age is quite consistent, at least for the subjects with SPD, in the cross-sectional samples. An alternative, and possibly better, strategy would have been to contrast the marriage rates of people with SPD to age-matched general population figures for the areas in which they lived. While this was obviously not possible for all the studies reviewed here, it may be important to know that all single subjects in our two genetic-epidemiological studies of SPD (Battaglia et al. 1991, 1995) had a current age older than the mean age for marriage in our country: 28.7 for men and 25.4 for women (Istat-Istituto Centrale di Statistica 1988; Battaglia and Bellodi 1992). The people with SPD in the McGlashan (1986) study had high copresence of borderline personality disorder, which may suggest that they were more "extroverted," and therefore more likely to find a partner, than other people with SPD without Cluster B traits (DSM-III; American Psychiatric Association 1980). Although the data in the Zimmerman and Coryell (1989) study do not contradict the hypothesis of normal reproductive fitness in SPD, they do not support a familial aggregation for schizophrenia spectrum disorders, perhaps because of some methodological limitations (Kendler 1988). These data therefore argue against another major point—that schizophrenia is familial and that SPD is a phenotype of liability to the schizophrenic illness.

In conclusion, some evidence in the available literature indicates that people with SPD, a phenotypic expression of liability to schizophrenia, may not have a significantly reduced marriage rate. This suggests, at least indirectly, that reproductive fitness may not be diminished in SPD and is likely to be considerably greater than fitness in schizophrenia. In addition, even if individuals with SPD had some impairment of fertility compared with the very large reduction of fertility of individuals with schizophrenia, it is still possible that a higher proportion of such individuals in the parental generation would be those who will reproduce and whose children will be at higher risk for schizophrenia.

The preserved fitness of subjects with SPD may therefore at least partially account for the transmission of schizophrenia in families and may account for the observed higher risk for schizophrenia in siblings than in parents of probands with schizophrenia spectrum disorders.

References


Battaglia, M.; Gasperini, M.; Scuito, G.; Scherillo, P.; Diaferia, G.; and Bellodi, L. Psychiatric disorders in


The Authors

Marco Battaglia, M.D., is University Lecturer of Psychiatry at the University of Milan School of Medicine, and Vice Psychiatrist-in-Chief, Department of Neuropsychiatric Sciences; Laura Bellodi, M.D. is Associate Professor of Psychiatry, University of Milan School of Medicine, and Psychiatrist-in-Chief, Department of Neuropsychiatric Sciences, Istituto Scientifico H San Raffaele, Milan, Italy.