Psychiatric Disorders in the Parents of Autistic Individuals

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Abstract. Eighty-one parents of 42 autistic probands and 34 parents of 18 Down syndrome probands were examined using a semistructured, investigator-based version of the Schedule for Affective Disorders and Schizophrenia Lifetime Version to estimate the lifetime risk of psychiatric disorder. The lifetime prevalence rate of anxiety disorder was significantly greater in parents of autistic probands than in parents of Down syndrome probands. The lifetime prevalence rate of major depressive disorder, while not significantly different in cases and controls, may be high in the parents of autistic probands (27%) in comparison with populations rates. *J. Am. Acad. Child Adolesc. Psychiatry*, 1991, 30, 3:471–478. **Key Words:** autism, anxiety disorder, major depressive disorder, genetics, stress.

Autism is a behavioral syndrome defined by the presence of marked social deficits, specific language impairments, stereotyped repetitive behaviors, and a characteristic course (Rutter and Schopler, 1988). Like most behavioral syndromes, autism is likely to be etiologically heterogeneous, and the causes are largely unknown. Studies of the familial aggregation of autism have demonstrated that hereditary factors play a significant role in the etiology of this disorder. The prevalence of autism in the siblings of autistic individuals is at least 50 times greater than the prevalence in the general population (Rutter, 1967). In studies of twins, the concordance rate for autism in the co-twins of autistic individuals is consistent with a strong genetic component (Folstein and Rutter, 1977; Ritvo et al., 1985; Steffenberg et al., 1989; LeCouteur et al., 1989a).

In addition to autism, cognitive disorders and particular personality characteristics may aggregate in the family members of autistic individuals. Folstein and Rutter (1977) first provided evidence for an increased rate of cognitive disorders (i.e., reading disorder, spelling disorder, articulation disorder, language delay, and mental retardation) in the co-twins of autistic probands. Several studies of the siblings of autistic individuals (August et al., 1981; Macdonald et al., 1989; Piven et al., 1990) as well as additional studies of twins (LeCouteur et al., 1989a, Steffenberg et al., 1989) support these findings. Other reports suggest that first-degree relatives of autistic probands have an increased frequency of certain personality characteristics (Wolfe et al., 1988; Piven et al., 1990). The common occurrence of both cognitive disorders and particular personality characteristics in the relatives of autistic individuals, along with their qualitative similarity to the behavioral features defining autism, have led investigators to postulate that these characteristics may be manifestations of the underlying genetic liability for autism (Folstein and Rutter, 1977; August et al., 1981; Wolfe et al., 1988; Piven et al., 1990).

In addition to cognitive disorders and particular personality characteristics, limited evidence suggests that some psychiatric disorders may aggregate in the family members of autistic individuals (Lotter, 1966; Lobascher et al., 1970; DeLong and Dwyer, 1988; Piven et al., 1989, 1990). Very early studies of autism noted a higher prevalence of schizophrenia in the parents of autistic children, but these early studies have not been replicated (Rutter and Schopler, 1988). These early associations were most likely a result of the overly broad diagnostic criteria used to define both autism and schizophrenia. Lotter (1966), in one of the first epidemiological studies of autism, reviewed the hospital records of the parents of autistic children and controls who reported a previous psychiatric hospitalization. He concluded that parents of autistic children had an increased rate of nonpsychotic mental disorders when compared with the parents of nonautistic handicapped children. Lobascher et al. (1970) compared the family histories of autistic children and normal controls and noted a greater incidence of "alcoholism, psychiatric illness and mental retardation . . ." in the parents of the autistic children. Two recent studies using the family history method and *DSM-III* criteria for the diagnosis of autism have reported an increased rate of major affective disorder in the family members of autistic individuals. Delong and Dwyer (1988) found that 5% of the first-degree relatives of probands with either autism or pervasive developmental disorder had a history of bipolar disorder as defined by the Family History Research Diagnostic Criteria (Andreasen et al., 1977). Piven et al. (1990) reported that 15% of the adult siblings of adult autistic individuals had received treatment for affective disorder; only 1.5% had received treatment for bipolar disorder. In both studies, the reported rate of affective disorder in the relatives of autistic probands was significantly higher than published rates from epidemiological studies. However, neither study incorporated a control group for direct comparison.

Accepted September 17, 1990.

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This research was supported by NIMH Grant RO1 MH39936-04 (Dr. Folstein) and The John Merck Fund (Dr. Piven). The authors are grateful to Marshal Folstein, M.D., and Alan Romanoski, M.D., for reviewing this manuscript and to Cindy Taylor for her assistance in its preparation.

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In the present study, results are reported from a study comparing the rates of psychiatric disorder in the parents of 42 autistic probands and 18 Down syndrome controls using a semistructured, investigator-based version of the Schedule for Affective Disorders and Schizophrenia Lifetime Version (SADS-L).

Method

SAMPLE

Cases

Ascertainment of families. Families were recruited for participation in an ongoing collaborative family study of autism presently underway at The Johns Hopkins University School of Medicine in Baltimore, Maryland and The Institute of Psychiatry in London, England. The families reported in this paper are from the Johns Hopkins site.

In order to obtain families that were unbiased with respect to familial aggregation of autism or other possibly related disorders, families were drawn from The Maryland Society for Autistic Adults and Children (MSAAC), a volunteer organization for parents of autistic individuals; The Linwood School for Autistic Children (LSAC), a private school for autistic children; and the three public schools in Baltimore County (BCS) with classrooms for autistic children. Letters to the families requested volunteers for "a study of the causes of autism." The first two sources (MSAAC and LSAC) allowed the authors to contact all the families on their mailing lists by telephone so that an estimation could be made of the representativeness of those families who volunteered.

Initial screening. One hundred and seven families from MSAAC and LSAC with children diagnosed as autistic or autistic-like were briefly interviewed by telephone to review (1) the proband's possible diagnosis of autism and general level of intelligence, (2) the proband's medical and neurological history, (3) the basic demographic information about the family, and (4) the family's interest in participating in the study. Medical records on all probands were requested and reviewed to further examine the diagnosis of autism, medical and neurological history, and previous IQ testing. Families were invited for a more detailed evaluation if (1) the proband was between 5 and 25 years of age at the start of the study and appeared likely to meet *DSM-III-R* criteria for autistic disorder; (2) the proband's performance IQ was 30 or greater, as measured by previous testing available through medical records or as estimated by information obtained on the telephone interview; (3) there was no indication of blindness, deafness, phenylketonuria, congenital rubella, neurofibromatosis, tuberous sclerosis, cerebral palsy, or fragile X; and (4) the family's primary language was standard English. Fifty-four families were eligible to enter the study by these criteria. Of these, 16 refused to participate leaving 38 families from these two (MSAAC and LSAC) sources. In general, nonparticipants stated that they declined because they had participated in many previous studies. Thus, in the refusing families, the average age of probands was 23 years (versus 16 years in participants) and of parents was 55 years (versus 47 years in participants). Other demographic variables (i.e., family size, birth order of the proband, social class) were similar in the 38 participating families and the 16 families who did not enter the study. Thirteen additional families with autistic children were included through BCS.

Proband assessment. These 51 families underwent a second stage of proband screening that included the following: (1) a more stringent examination of the diagnosis of autism with the Autism Diagnostic Interview (ADI) (LeCouteur et al., 1989) and the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 1989); (2) a neurodevelopmental examination; (3) further review of nonverbal IQ; and (4) a karyotype for the fragile X chromosome.

Proband Diagnosis

Parental informants for all autistic subjects were interviewed with the ADI, a standardized investigator-based diagnostic interview for autism. An algorithm constructed for use with the ADI (using ICD-10 criteria for autism) (World Health Organization, 1987) has been shown to adequately discriminate autistic from nonautistic IQ matched controls (LeCouteur et al., 1989). Interrater agreement on the ADI algorithm (using videotaped interviews) for a diagnosis of autism was high (kappa = 1.0, N = 10) across the four raters used in this study (J.P., R.L., M.W., J.G.). In addition, probands were directly assessed using the ADOS (Lord et al., 1989), a structured observation and interview schedule developed to aid in the diagnosis and assessment of autistic individuals. The information from the ADOS functioned as a check on the proband's current behavior as reported by the parents on the ADI. Clinical observations made using the ADOS were in agreement with the diagnosis as determined by the ADI algorithm on all cases.

Neurodevelopmental Examination

Neurodevelopmental examinations were performed by a physician (J.P.) to evaluate subjects for abnormalities that might exclude them from this study. No proband had evidence of cerebral palsy, tuberous sclerosis, neurofibromatosis, deafness, or blindness.

IQ Assessment

When the results of previous psychological testing were either unavailable or considered inadequate for classification of the proband's nonverbal IQ into one of three groups (30–49, 50–69 and 70+), an IQ test was administered. Test scores from the medical record were considered adequate if they were obtained by a licensed psychologist using either the performance scales of the Wechsler Intelligence Scale for Children-Revised (WISC-R), Wechsler Adult Intelligence Scale-Revised (WAIS-R), Leiter International Performance Scales, or Merrill-Palmer Scales. When multiple test results were available, those obtained closest to age 12 were used. When adequate test results were unavailable or the results were inconsistent, the proband's nonverbal IQ was assessed by members of the team (R.L., M.W.) using the performance scales of the WISC-R or WAIS-R whenever possible. The Leiter was used to establish nonverbal IQ group for lower functioning probands.

TABLE 1. *Sample Characteristics*

	Autism	Down Syndrome	t or χ^2 (df)	p
Probands				
Number				
Total	42	18		
M:F	33:9	10:8		
Age (years)				
Mean (SD)	15.7 (7.5)	11.6 (6.6)	2.01 (58)	0.05
Range	5–25	5–25		
Nonverbal IQ group				
70+	13	—		
50–69	11	—		
30–49	18	—		
Birth order				
Singleton	11	—		
Last	13	10		
Other	18	8		
Parents				
Number				
Total	81	34		
M:F	39:42	16:18		
Age (years)				
Mean (SD)	44.7 (9.8)	44.7 (12.9)	0.03 (49)	NS
Range				
Education	N %	N %		
<High school	18 22	7 20		
12–15	36 45	18 53		
16+	27 33	9 27	3.9 5	NS
Occupation				
Professional	43 53	21 61		
Skilled				
-nonmanual	18 22	6 18		
-manual	5 6	0		
Unemployed	4 5	1 3		
Other	11 14	6 18	5.3 5	NS
Full scale IQ				
Mean (SD)	110 (15)	113 (11)	−0.96 (99)	NS

Fragile X Testing

Fragile X testing was conducted by Dr. George Thomas in the Cytogenetics Laboratory at the John F. Kennedy Institute for Handicapped Children. Subjects were considered fragile X positive when the fragile site was identified on at least 4% of the spreads counted.

Final sample. Six families were excluded from the study at this level of assessment—two probands were found to be fragile X positive, and four did not meet ADI algorithm criteria for autism; three families dropped out. Eighty-one parents from 42 families participated in the study. Three parents (fathers) were unavailable for interview; two had moved away from the area and refused to participate, and one was deceased.

Controls

Parents of Down syndrome (DS) children served as controls. The rationale for choosing this control group was based on a need to control for the effect of caring for a handicapped child on the emotional and social functioning of parents. Parents of DS probands would not be expected to have an increased genetic liability for psychiatric disorder over that of the general population.

Eighteen families were ascertained through mailings to three Maryland area support groups for parents of DS children and to parents of DS children attending three BCS. Families were selected if the proband had trisomy 21 and if the family's primary language was English. Thirty-four parents participated in the study; two fathers had moved away and were unavailable for the study.

Parents of DS probands were comparable to parents of autistic probands on age, level of education, occupation, and full-scale IQ as measured by the WAIS-R (Table 1).

Procedure

Eighty-one parents of 42 autistic probands and 34 parents of 18 DS probands were interviewed by one of three interviewers (J.P., R.L., M.W.). The 2- to 3-hour interview included (1) an initial semistructured interview to elicit the subject's life story (including nodal life events, social life, and school and work history); (2) a semistructured interview to assess the parents' perceived effect on the family of having a handicapped child; (3) a semistructured personality

TABLE 2. *Lifetime Rates of Psychiatric Disorder[a] in Parents of Autistic and Down Syndrome Probands*

Disorder	Autism Parents (N = 81)		DS Parents (N = 34)		χ^{2b}	p
	N	%	N	%		
Anxiety disorders[c]	19	23.5	1	2.9	5.7	0.02
Generalized	10	12.3	1	2.9		
Panic disorder	3	3.7	0			
Phobic disorder	8	9.9	0			
Alcoholism	10	12.3	0		3.2	0.08
Major depressive disorder	22	27.2	5	14.8	1.4	NS
Recurrent	13	16.0	2	6.0	1.4	NS
Single episode	9	10.0	3	8.8		
Intermittent depressive disorder	2	2.5	1	2.9		
Minor depressive disorder	13	16.1	6	17.5		
Bipolar disorder						
with hypomania (II)	1	1.2	0			
with mania (I)	0		0			
Drug use disorder	3	3.7	1	2.9		
Somatization disorder	0		0			
Obsessive-compulsive disorder	0		0			
Schizophrenia	0		0			
Antisocial personality disorder	0		0			
Eating disorder[d]	0		1	2.9		

[a]Research Diagnostic Criteria, modified.
[b]Yates corrected chi-square (df = 1)
[c]Anxiety disorder = generalized anxiety disorder and/or phobic disorder and/or panic disorder.
[d]*DSM-III* criteria.

interview (available from the author); and (4) a semistructured investigator-based version of the SADS-L (Spitzer and Endicott, 1978; Harrington et al., 1988). Informant versions of the SADS-L were completed on two who refused to participate. The presence of a psychiatric disorder was rated in those two individuals only if (1) the subject had received treatment for that disorder, and (2) the informant was knowledgeable enough to give a clear report of symptoms experienced by the subject.

Lifetime prevalence rate of psychopathology was assessed by using a modified version of the SADS-L (Spitzer and Endicott, 1978; Harrington et al., 1988) in which the structure had been broadened to include diagnoses not covered in the original schedule (e.g., eating disorder). This version of the SADS-L has been shown to have substantial agreement with the more structured, respondent-based version of the SADS-L across most Research Diagnostic Criteria (RDC) categories (Harrington et al.,1988). Except for eating disorder, where *DSM-III* criteria were employed, diagnoses were made according to the RDC (Spitzer and Robins, 1978) with the revisions as described by Mazure and Gershon (1979). These revised diagnostic criteria are equivalent to the criteria of Spitzer and Robins (1978), except that major depressive disorders were diagnosed if duration of symptoms was 4 weeks rather than 2 weeks as specified by the RDC. In addition, simple phobias, limited to circumscribed areas of a subject's life and not associated with significant impairment, were not included in the diagnosis of phobic disorder. Interrater reliability among the four interviewers (all present at the interview) was high, with a mean kappa of 0.92 (range, 0.68–1.0; N = 10) for generalized anxiety disorder, phobic disorder, major depressive disorder, minor depressive disorder, alcoholism, drug use disorder, and eating disorder, and a mean percent agreement of 0.99 (range, 0.95–1.0; N = 10) across the remaining diagnostic categories (Table 2).

STATISTICAL ANALYSIS

Categorical data (e.g., social class, presence of psychiatric disorder) were analyzed by χ^2 tests. Between group differences on continuous variables were examined by means of Student's t test (two-sided).

The lifetime risk of anxiety disorder, in cases and controls, was compared using survival analysis. The survival function method allows the use of data from subjects for whom the response has not yet occurred (Chase et al., 1983). Such data are designated as incomplete or censored. Equality of survival functions for cases and controls were tested by the Generalized Wilcoxon (Breslow) statistic using the BMDP software package on an IBM 4381 mainframe computer (Breslow and Day, 1980).

For anxiety disorder the following covariates were examined: subject status (case vs. control), proband sex, subject sex, and proband IQ. These explanatory variables were examined by logistic regression using the SAS software package on a mainframe computer. Crude and adjusted odds ratios were computed to give the odds of an individual having an anxiety disorder given that he or she is a case as compared with a noncase (Schlesselman, 1982). Probability figures are noted only if they achieve significance at conventional levels ($p < 0.05$).

TABLE 3. *Logistic Regression Analysis of Sex and IQ Effects on the Rates of Anxiety Disorder*

Dependent Variable	Beta Coefficient	Crude Odds Ratio	Adjusted Odds Ratio	95% Confidence Interval	p*
Case/control	4.11	10.01	60.95	(1.62, 2289)	0.03
Proband sex	0.93	7.79	0.40	(0.08, 1.95)	NS
Subject sex	0.01	1.02	1.01	(0.37, 2.78)	NS
Proband IQ					
30–49	−2.09	3.03	0.12	(0.005, 3.03)	NS
50–69	−1.84	4.31	0.16	(0.006, 1.41)	NS
70+	−2.08	3.63	0.13	(0.005, 3.35)	NS

*p value refers to the significance of the adjusted regression coefficient in a multiple logistic regression.

Results

RATES OF PSYCHIATRIC DISORDER

The lifetime prevalence rates of psychiatric disorders for parents of autistic and DS probands are listed in Table 2. Several disorders including intermittent depressive disorder, bipolar disorder, somatization disorder, obsessive-compulsive disorder, schizophrenia, drug use disorder, eating disorder, and antisocial personality disorder were either not found or were rated too infrequently for further analysis.

Generalized anxiety disorder was diagnosed in 12.3% of the parents of autistic probands; 3.7% had panic disorder, and 9.9% had phobic disorder. Of those with phobic disorders, four had social phobias, three had simple phobias (one of whom also had a generalized anxiety disorder), and one had a mixed phobia. (See Appendix 1 for case vignettes). Only one parent of a DS proband had an anxiety disorder. Of parents with autistic children, 23.5% reported at least one episode of either generalized anxiety disorder, panic disorder, or phobic disorder versus 2.9% in controls, for a significantly greater lifetime prevalence rate of anxiety disorder in parents of autistic probands (Yates corrected $\chi^2 = 5.66$; $df = 1$; $p = 0.02$).

The lifetime risk of anxiety disorder was further examined using survival analysis. An onset curve was generated separately for relatives of autistic and DS probands using first occurrence of disorder as the principal decrement. The lifetime risk of an anxiety disorder was significantly greater for the parents of autistic individuals than for the parents of DS individuals (generalized Wilcoxon = 8.86, $p = 0.003$). Use of the Cox proportional hazards model confirmed the significant elevation in rate of anxiety disorders in the parents of autistic probands after adjustment for other covariates—proband sex, proband IQ, and subject sex. Logistic regression analysis, adjusting for these same covariates, indicated a relative odds for anxiety disorder in parents of autistic probands 61 times greater than for parents of DS probands (adjusted odds ratio = 61.0; $p = 0.03$). There were no significant effects of proband sex, proband IQ, or subject sex on lifetime history of anxiety disorder (Table 3).

Twenty-seven percent of the parents of autistic children and 15% of the parents of children with DS had at least one episode of major depressive disorder (MDD) (Table 2). Only one subject, the parent of an autistic proband, had a history of bipolar disorder. The rate of recurrent MDD in parents of autistic probands was 16%, nearly three times the 6% rate in parents of DS probands. This difference did not reach statistical significance. In addition, there was a nonsignificant trend toward increased rates of alcoholism in the parents of autistic probands (Table 2).

ONSET OF PSYCHIATRIC DISORDER

Twelve of the 19 parents (63%) in the autism group who qualified for the diagnosis of an anxiety disorder had experienced at least one episode before the birth of the proband. Seven of 10 autism parents with generalized anxiety disorder reported their first episode occurring before the birth of the proband. Of the 13 parents of autistic probands reporting recurrent MDD episodes, 10 (77%) had at least one episode occurring before the birth of the proband. Thus, 12.4% (10 of 81) of the parents of an autistic proband versus 2.9% (1 of 34) of the parents of DS probands had a history of recurrent MDD, the first episode of which occurred before the birth of the proband.

COMORBIDITY OF PSYCHIATRIC DISORDERS

There was no significant comorbidity between anxiety disorders and alcoholism ($\chi^2 = 0.45$; $df = 1$; $p = $ NS); anxiety disorders and MDD ($\chi^2 = 0.04$; $df = 1$; $p = $ NS); or alcoholism and MDD ($\chi^2 = 0.0$; $df = 1$; $p = $ NS).

Discussion

There are several strengths in the design of this study. First, by ascertaining families through parent groups and schools and by using a recruitment letter that did not specifically describe the genetic hypothesis of this study, the bias of the sample toward families with multiply affected members was minimized. Second, diagnosis of autistic probands was made using a standardized, investigator-based interview and algorithm with established reliability and validity. Third, autistic probands were screened for etiologies, such as fragile X, that might cause disorders in family members and confound the interpretation of the results. Fourth, a semistructured direct interview (SADS-L) was employed to assess rates of lifetime psychopathology in both cases and controls. Finally, controls were comparable to cases on a number of important demographic variables.

The fact that raters were not blind to family membership was an important limitation of this study. In order to understand an individual's life story and place in context the

diagnosis of a psychiatric disorder, it almost always seemed necessary to review the subject's experiences with his or her handicapped child. In subjects where the psychiatric diagnosis was not clear to the interviewer, the RDC diagnosis was made by a rater blind to the case/control status of the individual after a review of notes recorded from the interview. The small size of the sample in this study may have been an additional limitation—decreasing the power to detect significant differences between cases and controls in the rates of specific anxiety disorders and alcoholism.

The findings of the present study are in agreement with Lotter's early report of a higher rate of "non-psychotic psychiatric disorder" (Lotter, 1966) and with Lobascher's report of a higher rate of "psychiatric illness" (Lobascher et al., 1970) in the parents of autistic probands. In addition, these findings are not inconsistent with two recent family history studies that reported the rate of affective disorder in relatives of autistic individuals to be higher than in published population-based studies (DeLong and Dwyer, 1988; Piven et al., 1990). Neither study, however, reported higher rates of anxiety disorders in relatives, possibly because of the insensitivity of the family history method in detecting anxiety disorders. The family history method has been shown to have high specificity but low sensitivity for detecting psychiatric disorders, and accuracy has been noted to be better for affective disorders and alcoholism than for less severe disorders, such as generalized anxiety disorder and phobias (Thompson et al., 1982).

Both environmental (Blazer et al., 1987) and genetic (Fyer et al., 1990; Noyes et al., 1987; Crowe et al., 1983) causes have been implicated in the etiology of anxiety disorders, and both must be considered in exploring the meaning of the increased rate of these disorders in this sample. The presence of a handicapped child in the home has been associated with reports of increased parental stress (Beckman, 1983), depressive symptoms and feelings of guilt (DeMyer, 1979), and marital difficulties (Gath, 1977). A few studies have investigated the effects on parents of having an autistic child as compared with other handicapping conditions. Holroyd and McArthur, (1976), using the Questionnaire on Resources and Stress, noted that mothers of autistic children reported greater interference with family functioning than mothers of DS controls. Bartak (1974) reported that the behavior of autistic children interferes far more with family activities than that of dysphasic children. Cox et al. (1975), in comparing the parents of dysphasic children to those of autistic children, concluded that " . . . 2/3 of mothers in both groups reported that they had been depressed as a result of their child's difficulties" (page 154). Breslau and Prabucki (1987), however, in discussing the effects of disabled children on their parents and siblings, point out that the effects of a handicapped child on a family are clearly heterogeneous and complex, and the stress of childhood disability on the family is difficult to define.

Several aspects of this study suggest that differences in the amount of stress associated with having a handicapped child cannot entirely account for the high rates of anxiety disorders in parents of autistic probands. First, in the majority of subjects, the onset of anxiety disorder occurred before the birth of the proband. Secondly, while previous studies have demonstrated an association between the presence of a handicapped child in the home and depressive symptoms, an association has not been reported with either MDD or anxiety disorders (Breslau and Davis, 1986). If higher rates of anxiety disorders are a result of the stress of having an autistic child, then significantly higher rates of minor depressive disorder in the parents of autistic children might also be expected. In contrast, the rate of minor depressive disorder was exactly the same in cases and controls.

The importance of hereditary factors in autism has been demonstrated (reviewed by Folstein and Rutter, 1987; Piven et al., 1990) and suggests several possible explanations for the high rate of anxiety disorders found in the parents of autistic individuals. In addition to autism, cognitive disorders and particular personality traits have been shown to aggregate in the family members of autistic individuals. These characteristics, which are qualitatively similar to characteristics found in autistic individuals, have been hypothesized to be milder expressions of the underlying genetic abnormality in autism. While the stereotyped, repetitive behaviors that define autism have typically not been interpreted as anxiety symptoms, these behaviors (e.g., preoccupations and distress over changes in the environment) have a phenomenological resemblance to those that are described as anxiety symptoms in the nonautistic population (American Psychiatric Association, 1987). Moreover, anxiety symptoms have been reported to be prominent in high functioning autistic adults (Rumsey et al., 1985). The common occurrence of anxiety disorders in the parents of autistic individuals, in addition to the similar phenomenology found in these two disorders, may indicate that anxiety disorder is a milder expression of the underlying genetic liability in autism.

An alternative hypothesis is that cognitive deficits and particular personality characteristics that aggregate in the families of autistic individuals may make individuals more vulnerable to developing anxiety disorders. Hirschfeld et al. (1983) has described an association between the personality characteristic "social introversion" and major depressive disorder. Likewise, particular personality characteristics, such as singlemindedness and lack of response to social cues and pragmatic language deficits, both described in relatives of autistic individuals (Wolff et al., 1988; Landa et al., 1989), might predispose an individual to experiencing anxiety in social situations. Investigations of the co-occurrence of particular cognitive deficits, personality characteristics, and psychiatric disorders in the relatives of autistic individuals may clarify the mechanisms underlying higher rates of anxiety disorders in these individuals.

Previous studies have demonstrated the co-occurrence of anxiety disorders and alcoholism and anxiety disorders and depression (Merikangas et al., 1984; reviewed by Breier et al., 1985). In the present sample, anxiety disorders did not co-occur with either alcoholism or MDD. The possibility exists, however, that the modest trend for an increased rate of alcoholism in this study's cases was the result of self-medication of anxiety symptoms with alcohol as suggested by Merinkangas et al. (1984). An association may have

been missed between anxiety disorders and MDD because of the hierarchical nature of the RDC categories; concurrent anxiety disorders are not diagnosed during periods of MDD. Leckman et al. (1983a, b) have suggested that MDD associated with anxiety may be a distinct subtype, with relatives being at an increased risk for both depression and anxiety. The RDC diagnostic structures in this study did not allow a differentiation of subjects with MDD only from those with MDD associated with anxiety.

Finally, although there were no significant differences between the two groups in the lifetime rates of MDD, rates of MDD in both groups may be elevated in comparison to some published population rates. The Epidemiological Catchment Area (ECA) Study (Robins et al., 1984) reported that the lifetime prevalence rate for a major depressive episode (*DSM-III* criteria), based on lay interviewers' use of the Diagnostic Interview Schedule (Robins et al., 1981), anged from 3.7 to 6.7% across three sites. Clinical reappraisal of these results from the Baltimore site with psychiatrist interviewers using a semistructured psychiatric interview, the Standardized Psychiatric Examination (Romanoski, et al., 1988), revealed a 6.1% lifetime prevalence rate for a *DSM-III* major depressive episode (Romanoski, 1990, personal communication). Results from the present study show the rate of MDD in both parents of autistic children and parents of children with DS to be higher than both the ECA study and Baltimore site clinical reappraisal. Weisman and Myers (1978), using the SADS-L, reported an 18% lifetime prevalence rate for an episode of MDD based on application of the RDC. In comparison to these results, lifetime prevalence rates for an episode of MDD (modified RDC) in the parents of DS children do not appear elevated. The significance of a similar comparison to the rate in parents of autistic children is less clear. In addition, it should be noted that the difference in duration of an episode required for diagnosis of MDD (2 weeks in *DSM-III* and RDC and 4 weeks in our modified RDC criteria) make comparisons between the data in the current study and data from these population studies difficult to interpret. Additional study with a larger sample should clarify whether or not differences do exist.

In conclusion, this study demonstrates the familial aggregation of anxiety disorders in the parents of autistic probands. The etiology of these disorders is unclear. Based on the high frequency of subjects with onset before the birth of the proband, it seems unlikely that these disorders are entirely the result of the stresses involved in raising a handicapped child. The possibility of an increased genetic liability for anxiety disorders in the relatives of autistic individuals must be considered. Although the lifetime prevalence rates of MDD did not significantly differ between cases and controls, rates in the parents of autistic probands may be high in comparison with population rates. In order to confirm and further interpret these findings, the authors are currently collecting additional data from a larger sample to address the relationship of anxiety disorders and MDD to environmental stress, cognitive abilities, and personality and language attributes in the relatives of autistic individuals.

Appendix

Examples of behavior resulting in a diagnosis of phobic disorder in eight parents

1. A 54-year-old father of an adult autistic man was unable to attend his daughter's wedding as a result of social anxiety (social phobia).
2. A 34-year-old father of an 8-year-old autistic boy was unable to tolerate small social gatherings (three to four people), even in his own home, and frequently left the house at these times and sat in his car (social phobia).
3. A 28-year-old mother of a 6-year-old autistic boy quit a club that she belonged to as a result of anxiety she experienced attending club meetings (social phobia).
4. A 35-year-old father of a 10-year-old autistic boy had severe anxiety symptoms that often began several days before speaking in front of small and moderate size work-related groups to individuals with whom he was familiar (social phobia).
5. A 37-year-old mother of a 12-year-old autistic boy had a relatively sudden onset of anxiety associated with driving her car. As a result, she was unable to drive her car for several years and took the bus to and from work. These anxiety symptoms occurred in the setting of frequent worrying and nervousness. However, these symptoms were not present for sufficient duration (2 weeks) to be rated as a concurrent generalized anxiety disorder (mixed phobia).
6. A 40-year-old mother of a 15-year-old autistic boy had extreme anxiety associated with riding an elevator. She stated that she would walk up 20 flights or not go someplace she needed to go in order to avoid taking an elevator (simple phobia).
7. A 47-year-old father of an 8-year-old autistic boy was extremely fearful of riding an elevator. On one occasion, he reported making his wife (who was 8 months pregnant at the time) walk with him down eight flights of steps in a parking garage to avoid taking the elevator (simple phobia).
8. A 34-year-old mother of an 8-year-old autistic boy met criteria for a generalized anxiety disorder. She also reported a severe fear of heights (e.g., she was even unable to get on a step ladder) and severe claustrophobia (e.g., she experienced choking in closed rooms and often opened the doors of her home in winter because of anxiety associated with being closed in) (simple phobia).

References

American Psychiatric Association (1987), *Diagnostic and Statistical Manual of Mental Disorders, Third Edition-Revised.* Washington, DC: American Psychiatric Association.

Andreasen, N. C., Endicott, J., Spitzer, R. L. & Winokur, G. (1977), The family history method using diagnostic criteria: reliability and validity. *Arch. Gen. Psychiatry,* 34:1229–1235.

August, G. J., Stewart, M. A. & Tsai, L. (1981), The incidence of cognitive disabilities in the siblings of autistic children. *Br. J. Psychiatry,* 138:416–422.

Bartak, L., Rutter, M. & Cox, A. (1975), A comparative study of infantile autism and specific developmental receptive language disorder: the children. *Br. J. Psychiatry,* 126:127–145.

Beckman, P. (1983), Influence of selected child characteristics on stress in families of handicapped infants. *Am. J. Ment. Defic.*, 88:150–156.

Blazer, D., Hughes, D. & George, L. K. (1987), Stressful life events and the onset of a generalized anxiety disorder. *Am. J. Psychiatry*, 144:1178–1183.

Breier, A., Charney, D. S. & Heninger, G. R. (1985), The diagnostic validity of anxiety disorders and their relationship to depressive illness. *Am. J. Psychiatry*, 142:787–797.

Breslau, N. & Davis, G. C. (1986), Chronic stress and major depression. *Arch. Gen. Psychiatry*, 43:309–314.

—— Prabucki, K. (1987), Siblings of disabled children. *Arch. Gen. Psychiatry*, 44:1040–1048.

Breslow, N. E. & Day, N. E. (1980), General considerations for the analysis of case-control studies. In: *Statistical Methods in Cancer Research, Volume 1*. Lyon: International Agency for Research on Cancer, pp. 84–122.

Chase, G. A., Folstein, M. F., Breitner, J. C. S., Beaty, T. H. & Self, S. G. (1983), The use of lifetables and survival analysis in testing genetic hypotheses with an application to Alzheimer's disease. *Am. J. Epidemiol.* 117:590–597.

Cox, A., Rutter, M., Newman, S. & Bartak, L. (1975), A comparative study of infantile autism and specific developmental receptive language disorder: II. parental characteristics. *Br. J. Psychiatry*, 126:146–159.

Crowe, R. R., Noyes, R., Pauls, D. & Slymen, D. (1983), A family study of panic disorders. *Arch. Gen. Psychiatry*, 40:1065–1069.

DeLong, R. & Dwyer, J. T. (1988), Correlation of family history with specific austistic subgroups: Asperger's syndrome and bipolar affective disease. *J. Autism Dev. Disord.*, 18:593–600.

DeMyer, M. K. (1979), *Parents and Children in Autism*. Washington, DC: V. H. Winston and sons.

Folstein, S. & Rutter, M. (1977), Infantile autism: a genetic study of 21 twin pairs. *J. Child Psychol. Psychiatry*, 18:297–321.

—— —— (1987), Autism: familial aggregation and genetic implications. *J. Autism Dev. Disord.*, 18:3–29.

Fyer, A. J., Manuzza, S., Gallops, M. S. et al. (1990), Familial transmission of simple phobias and fears. *Arch. Gen. Psychiatry*, 47:252–258.

Gath, A. (1977), The impact of an abnormal child upon the parents. *Br. J. Psychiatry*, 130:405–410.

Harrington, R., Hill, J., Rutter, M., John, K., Fudge, H. & Zoccollollo, M. & Weissman (1988), The assessment of lifetime psychopathology: a comparison of two interviewing styles. *Psychol. Med.*, 18:487–493.

Hirschfeld, R. M. A., Klerman, G., Clayton, P. J. & Keller, M. B. (1983), Personality and depression: empirical findings. *Am. J. Psychiatry*, 40:993–998.

Holroyd, J. & McArthur, D. (1976), Mental retardation and stress on the parents: a contrast between Down's syndrome and childhood autism. *Am. J. Ment. Defic.*, 80:421–436.

Landa, R., Wzorek, M., Piven, J., Gayle, J., Cloud, D., Chase, G. & Folstein, S. (1989), Discourse Characteristics of Adult First Degree Relatives of Autistic Children. Paper presentation at the First World Congress on Psychiatric Genetics, Cambridge, England, August.

Leckman, J. F., Merinkangas, K. R., Pauls, D. L., Prusoff, B. A. & Weissman, M. M. (1983a), Anxiety and depression: contradictions between family study data and *DSM-III* conventions. *Am. J. Psychiatry*, 140:880–882.

—— Weissman, M. M., Merinkangas, K. R., Pauls, D. L. & Prusoff, B. A. (1983b), Panic disorder and depression. *Arch. Gen. Psychiatry*, 40:1055–1060.

LeCouteur, A., Bailey, A. J., Rutter, M. & Gottesman, I. (1989a, August), *Epidemiologically based twin study of autism*. Paper presented at the First World Congress on Psychiatric Genetics, Cambridge, England.

—— Rutter, M., Lord, C., Rios, P., Robertson, S., Holdgrafer, M. & McLennan, J. (1989b), Autism diagnostic interview: a standardized investigator-based instrument. *J. Autism Dev. Disord.*, 19:363–387.

Lobascher, M. E., Kingerlee, P. E. & Gubbay, S. S. (1970), Childhood autism: an investigation of aetiological factors in twenty-five cases. *Br. J. Psychiatry*, 117:525–529.

Lord, C., Rutter, M., Goode, S., Heemebergen, J., Jordan, H., Mawhood, L. & Schopler, E. (1989), Autism diagnostic observation schedule: a standardized observation of communicative and social behavior. *J. Autism Dev. Disord.*, 19:185–212.

Lotter, V. (1966), Epidemiology of autistic conditions in young children: I. prevalence. *Soc. Psychiatry*, 1:124–137.

Macdonald, H., Rutter, M., Rios, P. & Bolton, P. (1989, August) *Cognitive and social abnormalities in the siblings of autistic and Down syndrome probands.* Abstract presented at the First World Congress on Psychiatric Genetics, Cambridge, England.

Mazure, C. & Gershon, E. S. (1979), Blindness and reliability in lifetime psychiatric diagnosis. *Arch. Gen. Psychiatry*, 36:521–525.

Merinkangas, K. R., Leckman, J. F., Prusoff, B. A., Pauls, D. L. & Weissman, M. M. (1984), Familial transmission of depression and alcoholism. *Arch. Gen. Psychiatry*, 42:367–374.

Noyes, R., Clarkson, C., Crowe, R., Yates, W. R. & McChesney, C. M. (1987), A family study of generalized anxiety disorder. *Am. J. Psychiatry*, 144:1019–1024.

Piven, J., Landa, R., Wzorek, M. M. et al. (1989), *Personality characteristics and psychiatric disorder in the relatives of autistic individuals*. Paper presented at the First World Congress on Psychiatric Genetics, Cambridge, England.

—— Gayle, J., Chase, G. A., Fink, B., Landa, R., Wzorek, M. & Folstein, S. (1990), A family history study of the adult siblings of autistic individuals. *J. Am. Acad. Child Adolesc. Psychiatry*, 29:177–184.

Ritvo, E. R., Freeman, B. J., Mason-Brothers, A., Mo, A. & Ritvo, A. M. (1985), Concordance for the syndrome of autism in 40 pairs of afflicted twins. *Am. J. Psychiatry*, 142:74–77.

Robins, L. N., Helzer, J. E., Croughan, J., Williams, J. B. W., & Spitzer, R. L. (1981), *The NIMH Diagnostic Interview Schedule: Version III*. (Public Health Service (HSS) Publication ADM-T-42-3 [5-81, 8-81]). Washington, DC: U. S. Government Printing Office.

—— ——Weissman, M. M., Orvaschel, H., Gruenberg, E., Burke, J. D. & Regier, D. A. (1984), Lifetime prevalence of specific psychiatric disorders in three sites. *Arch. Gen. Psychiatry*, 41:949–958.

Romanoski, A. J., Nestadt, G., Chahal, R., Merchant, A., Folstein, M. F., Gruenberg, E. M. & McHugh, P. R., (1988), Interobserver reliability of a "Standardized Psychiatric Examination" (SPE) for case ascertainment (DSM-III). *J. Nerv. Ment. Dis.*, 176:63–71.

Rumsey, J. M., Rapoport, J. & Sceery, W. R. (1985), Autistic children as adults: psychiatric social and behavioral outcomes. *J. Am. Acad. Child Adolesc. Psychiatry*, 24:465–473.

Rutter, M. & Schopler, E. (1988), Concepts and Diagnostic Issues. In: *Diagnosis and Assessment in Autism*, eds. M. Rutter & E. Schopler. New York: Plenum Press, p. 15–30.

Schlesselman, J. J. (1982), *Case-Control Studies: Design, Conduct, Analysis*. Oxford University Press, pp. 235–240.

Spitzer, R. L. & Endicott, J. (1978), *Schedule for affective disorders and schizophrenia*, Ed. 3. NIMH Clinical Research Branch, Collaborative Program on the Psychology of Depression, Washington, DC: U. S. Government Printing Office.

—— Robins, E. (1978), Research diagnostic criteria. *Arch. Gen. Psychiatry*, 35:773–782.

Steffenburg, S., Gilberg, C., Hellgren, L., Anderson, L., Gilberg, I. C., Jakobssen, G. & Bohman, M. (1989), A twin study of autism in Denmark, Finland, Iceland, Norway and Sweden. *J. Child Psychol. Psychiatry*, 30:405–416.

Thompson, W. D., Orvaschel, H., Prusoff, B. & Kidd, K. (1982), An evaluation of the family history method for ascertaining psychiatric disorders. *Arch. Gen. Psychiatry*, 39:53–58.

Weisman, M. W. & Myers, J. S. (1978), Affective disorders in a U.S. urban community: the use of research diagnostic criteria in an epidemiological survey. *Arch. Gen. Psychiatry*, 35:1304–1311.

Wolff, S., Narayan, S. & Moyes, B. (1988), Personality characteristics of parents of autistic children. *J. Child Psychol. Psychiatry*, 29:143–153.

World Health Organization (1987), *ICD-10 1986 draft* (Chap. V, categories F80-F99: Mental, behavioral and developmental disorders). Geneva, Switzerland, World Health Organization.