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Overrepresentation of Mood and Anxiety Disorders in Adults with Autism and Their First Degree Relatives: What Does it Mean?

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Abstract

Research indicates that relatives of individuals with autism have higher rates of affective disorders than both the general population and families of children with other developmental disabilities. In addition, individuals with autism have high rates of co-morbid mood and anxiety disorders. This study sought to identify possible reasons for these previous findings by documenting the presence of affective disorders in both probands (the individuals with autism) and their family members. A sub-sample of 17 adults with autism and their first degree relatives from the Baltimore Family Study of Autism completed a structured psychiatric interview. The results indicated that the rates of mood and anxiety disorders were 35% and 77% respectively for probands, and these disorders were present in at least one first degree relative at rates of 71% and 29% respectively. Exploring patterns *within* families revealed that 80% of probands with a mother who had a mood disorder history also had a mood disorder themselves, compared to only 16% of probands whose mothers did not have a mood disorder history. The results must be considered preliminary given the small sample size. Replicating these findings in a larger sample would help clarify whether a true increased risk of mood disorder exists, which would have potential implications for prevention efforts and understanding possible genetic mechanisms.

Keywords

Familial aggregation; Affective disorders; Family History; Autism; Co-morbidity

INTRODUCTION

Accumulating research suggests that rates of mood and anxiety disorders are higher in families of children with autism than both the general population and families of children with other developmental disabilities, such as Down's syndrome (e.g. Bolton et al., 1998; Piven et al 1991; Piven & Palmer, 1999). Studies have also noted that the majority of parents of children with autism who have affective disorder histories reported an age of onset *prior* to the child with autism's birth (e.g., Bolton et al., 1998). Finally, familial history of major depression also seems to be independent of familial history of the broader autism phenotype (Bolton et al., 1998; Piven & Palmer, 1999). Based on all of these findings, the possibility that affective disorders pose a specific genetic risk for autism has

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been raised (e.g. Delong, 2004; Piven & Palmer, 1999). However, the true meaning of the overrepresentation of affective disorders in family members of individuals with autism remains unknown.

It is unclear if the presence of affective disorders in family members increases liability to autism, co-morbid features, or both. It may be that family history of affective disorders is particularly pertinent to the subpopulation of autism with co-morbid emotion dysregulation. Although true prevalence rates are unknown, studies suggest that children with autism also have higher rates of both anxiety (7 – 84%) and depression (4.4 – 57.6%) than the general population (e.g. Brereton et al., 2006; Ghaziuddin, Ghaziuddin, & Greden, 2002; Gillot, Furniss, & Walter, 2001; Lainhart, 1999; Stewart et al; 2006). The widely varying prevalence estimates provide testament to the poor measurement and limited understanding of co-morbid psychiatric disorders in autism. Assessment measures have varied across studies, and typically involve either use of questionnaires (e.g. Gillot et al., 2001) or measures not validated for use in ASD. Available evidence does, however, support clinical impressions that psychiatric co-morbidity is the rule rather than the exception in autism (Gillberg & Billstedt, 2000).

Unfortunately, previous studies have generally focused on *either* family history *or* psychiatric co-morbidity. One previous study found that children with autism and diagnoses of co-morbid depression were more likely to have a family history of depression than children with autism who were not depressed (Ghaziuddin & Greden, 1998). These results must be considered cautiously because diagnoses were based on clinical impressions only. Standardized documentation of the presence of psychiatric disorders in *both* first degree relatives and probands is needed to further clarify whether the genes for affective disorders contribute in some way to the genetic liability to autism or are important to a subset of the population with autism with co-morbid mood and anxiety disorders. This study explored patterns of concordance in affective disorders between 17 adults with autism and their first degree relatives using a sub-sample from the Baltimore Family Study of Autism (BFSA). It was hypothesized that individuals with autism who have first degree relatives with affective disorders would have higher rates of mood and anxiety disorders than those without a positive affective disorder family history.

METHOD

Participants were part of the BFSA; ascertainment, inclusion/exclusion criteria, clinical description, and representativeness of the autism sample are described elsewhere (Lainhart et al., 1997). The BFSA involved measurement of traits and conditions that may illuminate the genetics of autism in the family members of 90 probands with autism and 40 probands with Down Syndrome. Briefly, participants were recruited from parent groups and local schools. All participants provided informed consent following procedures approved by the Johns Hopkins University Institutional Review Board. Proband participants met *DSM-IV* criteria for autistic disorder, confirmed by parent interview with the Autism Diagnostic Interview (LeCouteur et al., 1989) and direct observation using the Autism Diagnostic Observation Schedule (Lord et al., 1989). No participants had known possible non-idiopathic medical causes of autism based on history, physical examination, and karyotype for fragile X.

The 90 autistic subjects ranged in age from 3 to 32 years (mean age = 12.1 years), and included 34 adults with autism. A simple random sample of 26 of the 34 adults was selected, using a random numbers table, for more detailed psychiatric assessment. Seventeen of the 26 subjects in the random sample, half of the total sample of 34 adults with autism, had additional psychiatric assessment. Table 1 shows the characteristics of the probands who had

the additional psychiatric assessment and those who did not. There were no significant differences in mean age, IQ, total ADI algorithm score, parental occupational level or years of education, the male:female ratio, or in the proportion with a history of seizures between the 17 adults who had the additional psychiatric assessment, the 7 non-respondents, and the entire group of 17 adults who did not have additional psychiatric assessment. At the time of the additional psychiatric testing, the adults with autism ranged in age from 18 to 32 (mean = 24). Three (17.6%) of the adults who had the additional psychiatric assessment were nonverbal. A higher proportion of subjects (62.5%) of the 7 non-respondents were non-verbal ($p = .021$), but the proportion of subjects who were nonverbal did not significantly differ between the 17 adults who had additional psychiatric testing and the 17 (including the non-respondents) who did not. The groups also did not differ in quantitative ratings of overall mood and a composite score of anxiety, misery, and inappropriate cheerfulness at the time of study entry. Approximately 70 percent of the adult probands had mental retardation (nonverbal IQ < 70). Of the 17 who had additional psychiatric assessment, 7 were living in their parents' home; 8 were living in group homes; 2 lived in residential institutions; 3 were students, 8 had semi-skilled or unskilled jobs, and 5 worked in sheltered workshops.

Parents and adult siblings were interviewed directly about themselves with The Schedule of Affective Disorders and Schizophrenia – Lifetime Version (SADS-L; Spitzer & Endicott, 1978) to determine history of mood and anxiety disorders. Parents served as informants for the adults with autism (the mother for 10, father for 2, and both parents together for 5 of the probands). The utility of an informant-based SADS-L interview in detecting moderate to severe mood disorders in adults with autism has previously been shown by 5 outpatients with autism who had clinically diagnosed, treatment-responsive mood disorders (Lainhart, 1993). Co-morbid diagnoses in the adults with autism were based on observable behaviors and required increased and sustained impairment over the baseline level. Diagnoses were initially made using Research Diagnostic Criteria (RDC; Harrington et al., 1988) but are reported using *DSM-IV* criteria. Autism diagnostic measures and SADS-L data were collected by experienced clinician researchers who trained until they had nearly excellent inter-rater agreement for the diagnoses of autism, mood disorder, and anxiety disorder. Data on the probands with autism were collected blind to data on family members and vice versa. In an effort not to overanalyze a small data set, the within-family analyses excluded siblings and focused only on the presence of *any* mood disorder or anxiety disorder rather than analyzing by subtype.

RESULTS AND DISCUSSION

Table 2 shows the rates of mood and anxiety disorders in probands and their first degree relatives. Nearly 90% of probands had at least one mood or anxiety disorder diagnosis in addition to autism. Rates of depression and phobias in the adults with autism replicated results from a study of children with autism that was based on a modified child-version of the SADS-L (Leyfer et al., 2006). Phobias were the most prevalent co-morbid disorder in probands (59%), followed by generalized anxiety disorder (41%), and major depressive disorder (24%). Mood disorders were most prevalent in family members, with nearly 60% of families having at least one parent (not including the proband) with major depressive disorder. The vast majority of parents with mood disorders (70%) had the onset of their first episode prior to the birth of their child with autism, which suggests that the burden of raising a child with autism cannot fully account for the elevated rates in parents.

Rates of affective disorders in both probands and family members were higher than published national averages (Kessler et al., 2005). Lifetime prevalence rates from National Comorbidity Study were 28.8% and 20.8% for any anxiety disorder and any mood disorder respectively across all adults aged 18 and older (Kessler et al., 2005). A follow-up study

with a typically-developing control sample would be necessary to determine if the rates in our sample are actually higher than expected in a statistically significant sense; nonetheless, the pattern of higher rates is consistent with previous autism family history research (e.g. Bolton et al., 1998; Piven et al 1991; Piven & Palmer, 1999)

It is difficult to conclusively determine whether the risk of proband mood disorder was greater if a parent had a mood disorder history due to the small sample size. Table 2 shows rates of mood disorder occurrences *within* families, including the relative risk (odds ratio) of a mood disorder in probands based on parental mood disorder status. No clear pattern was present, with the exception of a possible relationship between mood disorder in mothers and mood disorders in probands; 80% (4 of 5) of probands with a mother who had a mood disorder history had a mood disorder themselves, versus only 16% (2 of 12) of probands without a maternal mood disorder history. Rates of anxiety disorders in probands were fairly even between families who did and did not have a parent with a mood disorder (specific data available upon request). The number of parents with anxiety disorders was low ($n = 3$), so we were unable to determine any potential relationship between parental anxiety and proband anxiety or mood disorders.

To our knowledge, this is only the second study to describe the presence of affective disorders in both probands with autism and their parents. Ghaziuddin and Greden (1998) described 23 children who had autism spectrum disorders, confirmed by the Autism Behavior Checklist, who were inpatients at a psychiatric hospital. They also found a much higher occurrence of family history of depression in the group of children who had co-morbid depression based on clinical judgment (10 of 13, 77%) than the children without co-morbid depression (3 of 10, 30%). Our findings extend this earlier work, by demonstrating a similar pattern using more stringent diagnostic criteria, a non-clinical sample, and adults.

Results should be considered preliminary given the small sample size. In addition, examination of the confidence intervals limits the conclusions one can draw. Confidence intervals are broad and span one in some cases, which may be due to both the small sample size and the possibility of measurement error. One potential source of error is non-independent sources of data, in that parents reported both on themselves and on their adult children with autism. Bearing these precautions in mind, this study raises an important issue requiring further research attention. Co-morbid mood disorders appear to be more common in families with a mother with a mood disorder history, which could infer increased risk if this finding was supported in larger studies. This has implications for prevention and treatment efforts, as well as genetics. If our initial findings that family history of mood disorders is most common among probands with co-morbid affective disorders are replicated in larger studies, this may suggest an affective disorder-related genetic pathway for a sub-population of autism. Although too preliminary at this stage to determine, future research exploring this possibility with larger samples and a control group would help clarify whether stratifying autism samples based on family history of mood disorders or proband co-morbidity may increase the likelihood of replicable and meaningful molecular genetic findings. Other possibilities to explain the elevated rates of affective disorders should also continue to be explored in larger studies, including: first, that affective disorders and symptoms are part of the autism syndrome but are separately identified from the perspective of *DSM-IV* criteria; second, that affective disorders occur independently of autism; and third, that affective disorders may be a phenotypic manifestation of the genetic liability to autism. When doing so, it will be critical to consider the assortive mating of parents with autism-related traits and the effects of parenting and living with a child with autism.

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Table 1

Characteristics of Adult Probands with Autism with and without Mood and Anxiety Disorder Assessment

	Probands with mood and anxiety assessment	Probands without mood and anxiety assessment	p-value[a]
	Mean (sd)	Mean (sd)	
Age at Study Entry	21.2 (4.5)	20.2 (7.0)	.611
Age at Psychiatric Assessment	24.8 (4.5)		
	Range 18–32		
ADI algorithm score (social + communication + stereotyped/ repetitive)	43.2 (8.1)	41.2(7.1)	.463
Males:females	16:1	13:3	.335
% IQ ≥ 70	29.4%	23.5%	.697
% nonverbal	17.6%	37.5%	.259
% history of seizures	11.8%	23.5%	.628
Overall distress (mood) at Study Entry	.27 (.59)[b]	.25 (.45)[c]	.937
Any anxiety, misery, abnormal cheerfulness at Study Entry	.50 (.76)[b]	.50 (.67)[c]	1.000
Parent occupation: % professional	70.6%	76.5%	.574
Father education (years)	15.7 (3.3)	16.5 (2.5)	.444
Mother education (years)	15.0 (2.6)	14.7 (2.1)	.713

[a] Statistic: t-test, Fisher's exact test, or X^2 used as appropriate;

[b] n = 14;

[c] n = 12

Table 2

Frequency of Mood and Anxiety Disorders

	Person Affected											
	Proband *n* = *16*		**Either Parent *n* = 17**		**Mothers *n* = 17**		**Fathers *n* = 17**		**Any Sibling[a] *n* = 11**		**Any Family Member *n* = 17**	
Disorder	#	%	#	%	#	%	#	%	#[b]	%	#	%
GAD	7	41.1	3	17.6	1	5.9	2	11.7	1	9.0	4	23.5
Panic	0	0.0	0	0.0	0	0.0	0	0.0	1	9.0	1	5.9
Phobia	10	58.8	1	5.9	0	0.0	1	5.9	1	9.0	2	11.7
Social Phobia	0	0.0	1	5.9	0	0.0	1	5.9	1	9.0	2	11.8
MDD	4	23.5	8	47.1	2	11.8	7	41.1	5	45.5	10	58.9
Minor Depressive Disorder	3	17.7	3	17.7	2	11.8	0	0.0	5	45.5	8	47.1
Dysthymic Disorder	0	0.0	1	5.9	1	5.9	1	5.9	2	18.2	3	17.7
Bipolar I	1	5.9	1	5.9	0	0.0	0	0.0	0	0.0	0	0.0
Bipolar II	0	0.0	1	5.9	0	0.0	0	0.0	1	9.0	1	5.9
Any Mood	6	35.3	9	59.9	5	29.4	7	41.1	7	63.6	12	70.5
Any Anxiety	13	76.5	3	17.7	1	5.9	2	11.8	2	18.2	5	29.4
Any Mood or Anxiety	15	88.2	9	59.9	6	35.3	7	41.1	7	63.6	12	70.5

[a] Only 11 probands had adult siblings for a total of 22 siblings;

[b] These numbers represent the number of families with at least one affected sibling;

[d] Information was available on 17 probands regarding major depression

Table 3

Within-family Concordance Rates for Mood Disorders

			Percent of Probands With a Mood Disorder[a]	Odds Ratio (95% CI)
Presence or Absence of Mood Disorder in Parents	Either Parent	Yes	44% (4/9)	2.4 (0.3 – 19.0)
		No	25% (2/8)	
	Father	Yes	25% (2/8)	0.50 (0.1 – 4.1)
		No	44% (4/9)	
	Mother	Yes	80% (4/5)	20.0 (1.4 – 287.6)
		No	16% (2/12)	

[a]Note. This column shows the percentage of probands who met criteria for a mood disorder, broken down by whether or not the proband had at least one parent, a mother, or a father with a mood disorder history themselves. The first number in the ratio in parentheses is the number of probands positive for a mood disorder in that category; the second number in the ratio is the total number of families in that category (e.g. 4/9 means that of the 9 families with a positive family history of mood disorder in at least one parent, 4 of those families had a proband with a mood disorder).