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Autism Spectrum Disorders as a Qualitatively Distinct Category From Typical Behavior in a Large, Clinically Ascertained Sample

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Abstract

The present study evaluated the hypothesis that autism spectrum disorders (ASDs) are best represented as a discrete category distinct from typical behavior within autism-affected families. The latent structure, categorical versus dimensional, of ASDs informs future diagnostic revisions, clinical assessment, and the design of future research. Data were obtained from Interactive Autism Network, a registry that preferentially recruits families with at least one ASD-affected child. Caregivers reported autism symptoms for affected and unaffected children using the Social Responsiveness Scale and Social Communication Questionnaire. Taxometric and latent variable models examined whether dimensional or categorical models best fit the data. Taxometric and latent variable model comparisons consistently indicated two-group mixtures for all indicator sets, even in participants designated as unaffected by caregivers. The identified category was associated with external indicators of disability, supporting its validity. Results indicated that ASD is best characterized as a category, distinct from typical behavior within ASD-affected families.

Keywords

autism, pervasive developmental disorder, *DSM*, diagnosis, mixture models, taxometrics, autism spectrum disorder

Many psychiatric disorders are etiologically heterogeneous and, therefore, carving nature at its joints has become a particularly important task for modern-day psychopathology research (Meehl, 1995; Meehl & Golden, 1982). The notion that categorical discontinuities will be more clearly linked to basic biological processes has driven the creation, refinement, and increased use of statistical approaches for determining the latent structure of psychopathology (Lenzenweger, 2004). Understanding the latent structure of pathology informs the development and implementation of clinical assessment methods, specifies the design of future research, and guides future diagnostic conceptualizations. As a result, empirical evidence is accumulating regarding the latent structure of psychiatric conditions (Haslam, 2003; Ruscio, Haslam, & Ruscio, 2006; Schmidt, Kotov, & Joiner, 2004).

At the broadest diagnostic level, use of the term *autism spectrum disorder* (ASD) and the presence of diagnostic categories imply that ASDs are distinct from typical social communication and perseverative/repetitive behavior. The present study provides an empirical examination of this hypothesis using a clinically ascertained sample. Recommended statistical methods for identifying categorical versus dimensional latent structure are used to determine whether ASDs represent a distinct phenotype from normal functioning (Ruscio et al., 2006; Waller & Meehl, 1998).

Prior Research

Previous studies have examined several aspects of the latent structure of ASDs, including understanding the factor structure of ASD symptoms (Constantino et al., 2004; Frazier, Youngstrom, Kubu, Sinclair, & Rezai, 2008; van Lang et al.,

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2006) or possible qualitative distinctions among ASDs (Ingram, Takahashi, & Miles, 2008; Munson et al., 2008). A related body of literature has examined whether ASDs represent severe end of a quantitative trait or continuum of social behavior (Constantino & Todd, 2000, 2003; Prior et al., 1998; Spiker, Lotspeich, Dimiceli, Myers, & Risch, 2002; Tanguay, 1998). This model implies that ASDs are not qualitatively distinct from typical levels of social communication and perseverative behavior. The evidence cited for this assertion is based on observations of unimodal symptom patterns in the population (Constantino & Todd, 2003), factor or cluster analyses (Constantino et al., 2004; Prior et al., 1998), identification of residual symptoms in unaffected family members (Constantino et al., 2006), the wide range of ASD symptom severity in affected siblings or twins (Bailey et al., 1995; Folstein & Rutter, 1977), and data suggesting additive genetic influences (Constantino & Todd, 2003; Ronald et al., 2006).

The above findings clearly indicate that *observed* ASD symptom distributions tend to be unimodal in population samples. However, they are not strong evidence for a continuous *latent* structure of ASDs, especially within the pathological end of the general population distribution. This is because factor analyses assume the existence of a continuum and therefore do not distinguish between categories or continua. Similarly, cluster analytic algorithms frequently identify one or more categories when none exist (Cleland, Rothschild, & Haslam, 2000; Grove, 1991). The wide range of ASD symptoms, even in identical twins, does not preclude a categorical model, as this model may include dimensional substructures. Previous structural equation modeling findings supporting genetic heterogeneity (Ronald et al., 2006) may also be consistent with a model incorporating a large number of genetic influences across individuals with ASD, with only one genetic change in each affected individual (private mutations). Furthermore, a categorical model does not assume the absence of symptoms or even negligible symptoms in unaffected individuals. Rather, latent categorical structure may result from a broad observed distribution of symptoms within affected and unaffected groups. Uni- or bimodality of ASD symptoms is neither necessary nor sufficient for establishing the presence or absence of a latent category (Murphy, 1964).

Implications of Latent Structure

The latent structure of ASDs is particularly relevant for future clinical research. If the latent structure of autism is categorical—even within specific subpopulations, then group comparison research is optimized if individuals are accurately sorted into ASD and non-ASD control groups. Alternatively, if a continuum is identified, research performed on subjects comprising that continuum should conceptualize ASD symptoms as quantitative traits. In this scenario, regression-based or latent-factor approaches are likely to be more powerful and informative than group comparison studies, although group comparisons may still be useful in situations where adequate sampling of the continuum is not practical.

Latent structure does not denote a specific genetic or environmental etiology. However the identification of a latent category of pathology is more consistent with threshold models, whereas a continuum is more consistent with graded effects from many minor contributing factors within each individual (Gottesman, 1972; Haslam, 1997; Lenzenweger, 2004; Lykken, McGue, Tellegen, & Bouchard, 1992). Existing data indicate strong genetic influences on ASDs (Bailey et al., 1995), with little support to date for direct environmental causes (Schechter & Grether, 2008). Therefore, identifying a latent category of ASD would indicate a higher probability for threshold genetic effects for subjects within that category. Continuous structure would more likely be a function of poly- or graded-genetic effects within each affected individual, significantly decreasing the probability of single genetic causes within individuals (Haslam, 1997).

Previous genetic studies have identified a large number of regions throughout the genome as being associated with idiopathic ASD (Cuccaro, Lewis, & Pericak-Vance, 2003; Gupta & State, 2007). This has been interpreted as evidence that ASD results from complex, multigenic interactions. However, previous linkage results have been of very small effect, which could be consistent with either (a) the disease being multigenic within individuals or (b) the disease being multigenic at the population level, but with a single gene or a small number of genes resulting in effects in any given individual. A recent study by Zhao et al. (2007), using three independently collected family pedigrees, has provided support for an alternative model. This model specifies that a substantial proportion of ASD cases could be explained by spontaneous mutations, as might arise as a function of advanced paternal age (Reichenberg et al., 2006). The present study will provide an indirect test of the plausibility of alternative (graded vs. threshold) models among individuals in clinically ascertained families.

Identification of the latent structure of psychopathology is also important for determining the appropriate assessment strategy (Ruscio & Ruscio, 2002). If a latent category is supported, the prevalence of the disorder and the most useful diagnostic criteria are defined. In this case, an evidence-based medicine approach to clinical assessment that includes the generation of posttest probabilities of diagnosis is indicated (Kraemer, 1992). This does not imply that an instrument is not helpful but, rather, suggests that the instrument be used to optimize classification rather than to grade severity level. If a latent dimension is supported, additional research is needed to link the continuum to clinically

relevant outcomes, such as functional deficits, prior to setting a diagnostic threshold. This is similar to the assessment strategy for hypertension. In this scenario, diagnostic efforts focus on locating the patient's symptom level on the continuum and relating this symptom level to risk or functional deficit. Specifying the latent structure of ASD will also lead to a more informed revision of the diagnostic criteria and enlighten research regarding comorbidity (Ruscio & Ruscio, 2002) and the boundaries of ASD and other disorders (Tanguay, 1998).

The present study hypothesized that ASDs, as ascertained in clinical samples, are best characterized as a latent category, qualitatively distinct from typical behavior and consistent with the current broad diagnostic conceptualization. A small proportion of siblings designated as unaffected by caregivers were expected to be identified as belonging to the latent ASD category, indicating a broad categorical phenotype.

Method

Participants

Primary data for the present study were obtained from the registry database (IAN Data Export ID: IAN_DATA_2008-07-25) of the Interactive Autism Network (IAN). IAN is an online longitudinal database and research registry maintained at the Kennedy Krieger Institute and supported by funding from Autism Speaks. The registry and associated questionnaires are designed to better understand and track clinical information from ASD-affected families. Any family living in the United States with an ASD-affected family member may volunteer to participate in IAN. To be included in the present study, caregivers (N = 6,621) must have reported ASD symptom data on at least one questionnaire for at least one affected child. This resulted in a total sample size of 11,507 children, with 6,901 affected and 4,606 unaffected siblings. For the majority of affected participants, caregivers reported that an instrument was used to make the diagnosis (79.3%; N = 5,480). Of those caregivers reporting use of a diagnostic instrument, 50.0% (N = 2,739) were administered both the Autism Diagnostic Interview–Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003) and the Autism Diagnostic Observation Scale (ADOS; Lord, Rutter, DiLavore, & Risi, 2002), an additional 23.8% (N = 1,305) reported receiving only one of these scales, and 26.2% did not receive either of these scales. Of the participants not reporting use of the ADI-R or ADOS, 17.9% (N = 511) received the diagnosis from a pediatrician or primary care doctor, 19.6% (N = 558) from a psychiatrist or clinical psychologist, 14.4% (N = 411) from a pediatric neurologist, 17.0% (N = 483) from other sources, and 31.1% (N = 894) chose not to report the source of diagnosis.

Procedures

IAN informants completed all questionnaires via the online portal. These questionnaires included demographic, developmental history, and basic medical information for affected and unaffected children. Informants also completed the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003) and/or the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005). The SCQ is a parent report instrument and consists of 40 questions tapping the three major autism symptom domains: social interaction, communication, and restricted/repetitive behavior. Lifetime ratings, referencing the child's behavior throughout their developmental history, were used for the present study as they permit a wider age range of data collection. Yes/No responses are required for each question. Scoring includes a total score and subscales representing each autism symptom domain derived from the ADI-R domain scores. Subscale scores from the SCQ were used in all subsequent analyses. The internal consistency reliability of these subscales was high (α = .90-.91). The SRS is also a parent report instrument that is intended to approximate interval scaling and has been previously used to evaluate autism symptoms in the population (Constantino & Todd, 2003). It consists of 65 questions tapping traits associated with ASD. Parents report on each question using a 0 (*never true*) to 3 (*almost always true*) Likert-type scale. For the present study, the two SRS subscales most closely linked to ASD diagnostic criteria, social communication (22 items) and autistic mannerisms (12 items), were examined.

To examine SRS subscales, packets of items were created for each subscale. Packets or parcels have important psychometric advantages compared with directly analyzing items scores, including (a) increasing the reliability of the indicator, (b) increasing the variance of the indicator, and (c) improving the subject per indicator ratio to improve model stability and interpretability (Cattell & Burdsal, 1975; Nasser & Wisenbaker, 2003). For the social communication subscale, four item packets were created (2 with six items and 2 with five items). For the autistic mannerisms subscale, three item packets were created (4 items each). In both cases, item packets were created by randomly selecting items from within unidimensional subscales, and the internal consistency reliability of these packets was high (SRS Social Communication α = .83-.89; SRS Autistic Mannerisms α = .79-.87), consistent with each packet focusing on a single construct. Subscale scores, rather than packets, were used for the SCQ as subscales had an insufficient number of items to create packets with sufficient score range. Using subscales is also advantageous for the SCQ as the subscales correspond to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (*DSM-IV-TR*; American Psychiatric Association, 2000) autism symptom domains.

Informed consent was obtained for all participants prior to entry into the IAN data collection. The procedures of IAN were reviewed and approved by the institutional review board of Kennedy Krieger Institute. The procedures of the present study were reviewed and approved by the institutional review board of the Cleveland Clinic (IAN).

Statistical Analyses

The hypothesis that ASD is best characterized as a latent category distinct from typical behavior was evaluated in the IAN total sample and unaffected sibling subsamples. The IAN total sample is significantly biased toward the identification of a pseudo-category as caregivers were asked to provide data for both their affected and unaffected children. The affected versus unaffected designation may induce rater biases that result in spurious identification of a two-group mixture. However, the problem of response bias is circumvented by the a priori prediction that a low base rate category would be identified when only unaffected siblings were analyzed. Thus, we anticipated that the ASD category would include the affected cases and a small proportion of unaffected cases.

The prediction of a low base rate latent category in the unaffected subsample is based on several observations. First, previous data have indicated that presumably unaffected siblings show significant ASD symptoms, particularly in multiple incidence families (Constantino et al., 2006). Second, subtle behavioral manifestations of genetic liability among presumably unaffected relatives are much milder than the application of current diagnostic criteria (Piven et al., 1997). Third, most clinicians and autism diagnostic tools tend to err on the side of high specificity, resulting in decreased sensitivity, to avoid mislabeling. This is particularly true for young children or when only one source of information is used to make the diagnosis (Lord et al., 2008; Risi et al., 2006; Ventola et al., 2006). It was also anticipated that a small number of families with a severely affected child may not yet have identified younger or less affected children because of social comparison processes. The latter position is supported by previous research demonstrating that many young or less affected children may not show obvious stereotypies (i.e., hand and finger or repetitive motor mannerisms; Tanguay, 1998). The prediction of a low base rate latent category in the unaffected subsample was further bolstered by the fact that a substantial proportion of children designated as unaffected by caregivers were rated as having a high symptoms burden on the SCQ (5.1%, $N = 234$ had a score of 15 or greater) and SRS (3.0%, $N = 136$ had a t-score of 70 or greater). Higher scores on these measures suggest that at least some "unaffected" siblings may show sufficient ASD characteristics to represent a low base rate latent category.

Taxometric methods are a set of procedures developed by Meehl and colleagues to identify whether observed data are best modeled as a latent category or a dimension. In contrast, factor analyses examine whether a group of indicators measure a latent dimension, and cluster analyses examine whether individual scores on a set of indicators are grouped or clustered together based on one or more metrics for determining grouping or clustering. Factor analyses are not helpful for examining whether the latent structure of indicators is categorical or dimensional because they assume the existence of a latent dimension, precluding categorical structure. Cluster analyses have been shown to be less effective in determining latent structure as they do not always have clear stopping rule for choosing one or more clusters (Grove, 1991) and often identify one or more categories when none exist (Cleland et al., 2000).

Taxometric methodologists have recommended using multiple taxometric procedures as well as other techniques for identifying latent classes (Schmidt et al., 2004). Thus, hypotheses were examined using two taxometric procedures and a latent variable modeling approach. Taxometric procedures identify whether a set of indicator scores result from the mixing of two latent classes or a single underlying dimension. These procedures also provide a means for estimating the base rate of the latent category *without* predefined specification of category membership. In the present study, the two taxometric procedures were mean above minus mean below a cut (MAMBAC; Meehl & Yonce, 1994) and maximum eigenvalue at the hitmax point (MAXEIG; Waller & Meehl, 1998).

MAMBAC plots are concave when the data are generated from a dimensional latent structure but convex/peaked when the data are categorical. MAXEIG plots are irregular or flat when generated from dimensional structure but convex/peaked when the data are categorical. For MAMBAC and MAXEIG, all pairs of indicators served as input indicators across 75 data windows, using 10 replications to ensure stability at each data partition. For each analysis, 20 simulation data sets (10 categorical and 10 dimensional) were used as a comparison with the research data. This procedure permits computation of an objective index of curve fit, the comparison curve fit index (CCFI). The CCFI has been shown to be highly accurate in determining the true data structure under a wide range of data distribution and validity conditions (Ruscio, Ruscio, & Meron, 2007). CCFI values >.50 indicate stronger fit to simulated categorical data, and CCFI values <.50 indicate greater fit to simulated dimensional data. CCFI values >.60 are considered very strong support for categorical structure. Overlay graphs present the research data overlaying a confidence interval of ±1 *SE* of the simulated data at each data point to provide a visual representation of curve fit. The case removal consistency test and inchworm consistency test were performed

for SCQ indicators in the unaffected sample to ensure that results were not strictly because of skew or difficulties with distinguishing a clear peak on the graph. Participant classifications were computed using the MAXEIG base rate method. These classifications are empirically generated and are not dependent on parent reports or parent designation of affected/unaffected. All taxometric procedures were computed using syntax for the R environment (Ruscio, 2008).

Latent variable models, such as latent class models, are frequently used to identify the latent structure of psychopathology data (Hudziak, Wadsworth, Heath, & Achenbach, 1999; Lenzenweger, McLachlan, & Rubin, 2007; Neuman et al., 1999). Latent class models differ from taxometric procedures in that they implement a maximum likelihood approach to determining whether observed data are derived from a single normal distribution or a mixture of normal distributions. A Monte Carlo simulation study demonstrated that a useful comparison with a two-class model is a one-factor model when ordinal- or approximately interval-scaled indicators are examined (Cleland et al., 2000). This comparison also makes theoretical sense because these models represent the straightforward comparisons of whether data are dimensional (one factor) or categorical (two class). The Bayesian Information Criteria (BIC) was used to determine fit for latent variable models (Yang, 2006). Lower BIC values (in boldface) indicate better model fit. Latent variable models were estimated using Mplus software (Muthén & Muthén, 2007).

Latent variable models are quite accurate for determining the number of latent classes in a data set under favorable data conditions (Magidson & Vermunt, 2002). However, these models typically assume normal within-class distributions and may be less accurate when distributions are nonnormal (Markon & Krueger, 2004), as is common in psychopathology research. Similarly, latent class models assume independence of observations and model comparisons may be less accurate when data are obtained from siblings, as in the present study. Taxometric procedures do not assume independence. Additionally, a large simulation study from our group has recently shown that latent variable model comparisons are less effective at identifying dimensional versus categorical latent structure than taxometric procedures (Frazier, Ruscio, & Youngstrom, 2009). For these reasons, latent variable model comparisons are presented as secondary procedures for determining the generalizability of taxometric findings to other statistical methods. Furthermore, latent variable models were restricted to one-factor versus two-class models, as existing Monte Carlo data indicate that higher class solutions (three-, four-, five-class solutions) are not consistently distinguished from one another and from dimensional solutions (Markon & Krueger, 2006).

Within-sample consistency of taxometric and latent variable models was examined by recomputing analyses in demographic subgroups. The subgroups included age (<7 years and ≥7 years), gender, family type (simplex and multiplex), and gender by family type (multiplex males). These partitions were used based on suggestions that genetic transmission and phenotypic manifestation of autism may differ across genders (Constantino & Todd, 2003) and family types (Virkud, Todd, Abbacchi, Zhang, & Constantino, in press; Zhao et al., 2007), and because autism symptom reports vary across age because of developmental expectations (Lord et al., 2008). Multiplex males were examined as this subgroup may be most likely to show continuous latent structure. All statistical procedures are *blind to diagnostic status*, generating group classifications *empirically*. Taxometric classifications were compared across indicator sets using weighted kappa coefficients to examine the consistency of identified categories.

Follow-up analyses examined the composition and validity of empirical classifications. These analyses were based on MAXEIG classifications generated using the SCQ indicator set in the unaffected subsample, as these were the most complete data and limiting to MAXEIG classifications decreases Type 1 error inflation for these exploratory analyses. Follow-up analyses focused on available developmental milestone and treatment data in unaffected children and included age of walking, age of first words, age of using two to three words to create meaningful speech, age at completion of toilet training, diagnosis of motor delay (presence vs. absence), diagnosis of speech/language disorder, history of speech therapy, and history of special education placement. Pearson's r was used to examine the relationship between empirical MAXEIG classifications and developmental variables.

Results

Sample and Indicator Characteristics

Table 1 reports demographic characteristics for the IAN total sample and affected and unaffected sibling subsamples. Consistent with gender differences in ASD prevalence, male participants occurred more frequently in the affected group versus the unaffected group, $\chi^2(1) = 1185.79$, $p < .001$, and outnumbered female participants by slightly greater than a 3:1 margin in the affected group. Affected siblings were significantly younger than unaffected siblings, $t(8,042) = 8.29$, $p < .001$, consistent with referral bias to IAN or the phenomenon of "stoppage," where parents opt to not have additional children after one is affected by autism. Racial distributions for unaffected and affected subsamples did not significantly differ $\chi^2(6) = 4.62$, $p = .59$). SCQ scores differed significantly as a function of diagnostic method, $F(3, 3861) = 14.92$, $p < .001$. However, significance was largely driven by sample size; the actual differences were trivial (largest mean difference 0.6, $d = .09$).

Table 1. Demographic and Diagnostic Characteristics for the Total Sample and Unaffected Subsample

	Total	Unaffected
N	11,507	4,606
Age (years), *M* (*SD*)	8.17 (4.07)	8.70 (4.28)
Males, *N* (%)	7,871 (68.4)	2,167 (47.0)
Race, *N* (%)		
Caucasian	10,135 (88.1)	4,101 (89.0)
Other races	1,358 (11.8)	501 (10.9)
Unknown	14 (0.1)	4 (0.1)
Diagnosis, *N* (% affected)		
Autism	3,045 (44.1)	—
PDD NOS[a]	2,809 (40.7)	—
Asperger's	1,041 (15.1)	—
CDD	6 (0.1)	—
SCQ total		
N (%)	11,472 (99.6)	4,597 (99.8)
M (*SD*)	15.2 (11.4)	3.5 (5.3)
Skewness (*SE*)	0.02 (.02)	2.9 (.04)
% ≥ 15	55.0	5.1
SRS total		
N (%)	4,400 (38.2)	1,825 (39.6)
M (*SD*)	72.0 (48.6)	25.1 (25.1)
Skewness (*SE*)	0.04 (.04)	2.04 (.06)
% ≥ 70	54.0	7.4

Note: PDD NOS = pervasive developmental disorder not otherwise specified. CDD = childhood disintegrative disorder; SCQ = Social Communication Questionnaire; SRS = Social Responsiveness Scale.
a. PDD and autism spectrum disorder designations were included with PDD NOS.

Taxometric and Latent Variable Modeling Results

Table 2 reports the results of taxometric and latent variable modeling procedures for the total sample and demographic subgroups. *Categorical* structure was supported for all analyses in the total sample. Specifically, CCFI values from both MAMBAC and MAXEIG indicated strong support for categorical latent structure of the total sample and all demographic subgroups (all CCFIs ≥ .570). Figure 1 presents MAMBAC (Panel A) and MAXEIG (Panel B) overlay graphs of the research and simulated data for the total IAN sample based on SRS social communication indicators. Inspection of these figures shows better fit to categorical than dimensional structure—research data show a closer match at most points along the curve to the simulated categorical data and poorer match to simulated dimensional data, particularly at the peak of the curve. The estimated base rate in the total sample (.61-.63 across indicator sets) was slightly higher than the base rate of affected participants (.60 for SCQ and .58 for SRS indicator sets). The BIC from latent variable models also indicated better fit to two-class models relative to one-factor models for the total sample and all demographic subgroups. In most cases, the difference in BIC values was large, supporting better fit of two-class models.

Table 3 reports the results of taxometric and latent variable modeling procedures for the unaffected subsample and demographic subgroups. Taxometric CCFI values indicated strong support for categorical latent structure of the unaffected subsample and all demographic subgroups. Figure 2 presents MAMBAC (Panel A) and MAXEIG (Panel B) overlay graphs of the research and simulated data for the unaffected subsamples based on SRS social communication indicators. Inspection of these figures shows better fit to categorical than dimensional structure and evidence of a low base rate category, peaking to the right of the graphs. SCQ and SRS autistic mannerism indicators are not shown as these graphs demonstrated equivalent or clearer differentiation relative to SRS social communication indicators. Results of the case removal and inchworm consistency tests also supported better fit to categorical structure. Two-class latent variable models showed superior fit to one-factor models for all unaffected subsample analyses consistent with the results of taxometric analyses.

We also investigated higher class solutions (3- to 10-class solutions) across samples and subgroups. Higher class solutions were either inconsistent or minimum BIC were not reached by the 10-class solution. This highlights the problem of violation of normal within-class distributions in latent class modeling, resulting in trivial increases in class number (Markon & Krueger, 2004) and further supports fit of a two-class model.

Category Specification

IAN total sample category classifications showed substantial overlap among indicator sets (Overall agreement = 93% to 94%; κ = .84-.87) and with unaffected subsample classifications (Overall agreement = 93% to 96%, κ = .75-.80). Total sample classifications showed a strong preponderance of male children (80.0%-81.2% male; male risk ratio 4.0:1-4.3:1) consistent with recent epidemiologic estimates (Centers for Disease Control and Prevention, 2007). Total sample classifications had stronger relationships with SCQ total raw scores than caregiver-reported affected versus unaffected designations, SCQ total $t(11{,}469) = 19.51$, $p < .001$. Unaffected subsample classifications were significantly correlated with a history of special education placement ($r = .127$, $p < .001$), speech therapy ($r = .102$, $p < .001$), and diagnosis of motor delay ($r = .102$, $p < .001$), diagnosis of speech/language disorder ($r = .120$, $p < .001$), as well as caregiver-estimated age of walking ($r = .037$, $p = .017$), first words ($r = .084$, $p < .001$), meaningful speech ($r = .080$, $p < .001$). All these results survive a step-down Bonferroni correction, except age of walking. There was no significant relationship with completion of toilet training ($r = .025$, $p = .100$).

Table 2. Taxometric and Latent Variable Modeling Results for the Total Sample and Demographic Subgroups

			MAMBAC		MAXEIG		BIC	
Measure	Subsample/Sample	*N*	CCFI	BR	CCFI	BR	One-Factor	Two-Class[a]
SCQ-Domain Scores		11,472	.897	.63	.782	.63	163,196	**144,780**
	Age <7 years	5,353	.923	.65	.799	.67	76,191	**69,604**
	Age ≥7 years	6,119	.935	.55	.756	.58	86,253	**74,310**
	Males	7,849	.920	.72	.748	.74	112,276	**104,255**
	Females	3,623	.873	.28	.730	.34	48,937	**39,275**
	Simplex	9,948	.938	.60	.804	.62	140,949	**123,988**
	Multiplex	1,076	.887	.80	.708	.78	15,608	**14,902**
	Multiplex males	755	.777	.87	.675	.88	10,860	**10,585**
SRS-Social Communication		4,400	.813	.62	.657	.61	21,294	**16,946**
	Age <7 years	1,805	.804	.65	.691	.66	8,376	**6,989**
	Age ≥7 years	2,595	.826	.58	.698	.57	12,715	**9,728**
	Males	2,999	.838	.70	.675	.70	15,070	**13,295**
	Females	1,401	.826	.32	.614	.34	5,590	**3,215**
	Simplex	3,764	.860	.57	.674	.58	17,918	**13,974**
	Multiplex	467	.737	.78	.594	.79	2,469	**2,346**
	Multiplex males	321	.721	.86	.570	.89	1,727	**1,724**
SRS-Autistic Mannerisms		4,400	.813	.63	.634	.63	21,261	**16,510**
	Age <7 years	1,805	.783	.65	.579	.63	8,750	**7,058**
	Age ≥7 years	2,595	.762	.64	.677	.61	12,524	**9,515**
	Males	2,999	.829	.71	.602	.68	14,866	**13,027**
	Females	1,401	.718	.31	.611	.31	5,755	**3,028**
	Simplex	3,764	.843	.58	.633	.60	18,109	**13,749**
	Multiplex	467	.737	.82	.578	.81	2,303	**2,190**
	Multiplex males	321	.718	.89	.604	.83	1,591	**1,577**

Note: MAMBAC = mean above minus mean below a cut; MAXEIG = maximum eigenvalue at the hitmax point; BIC = Bayesian Information Criteria; BR = Base Rate; CCFI = comparison curve fit index; SCQ = Social Communication Questionnaire; SRS = Social Responsiveness Scale. Lower (two-class) BIC values in boldface indicate better model fit.

a. One-factor and two-class models had 6 and 19 free parameters, respectively, except for Social Communication where one-factor models had 8 free parameters and two-class models had 29 free parameters.

Interestingly, unaffected subsample classifications showed a substantially weaker male predominance (58.7% male; male risk ratio 1.4:1).

Discussion

Results indicate that, within autism-affected families in clinically ascertained samples, ASD is best characterized as a category, distinct from typical behavior. This finding is similar to a large body of findings from clinical and population studies examining the liability to schizophrenia (Haslam, 2003; Schmidt et al., 2004), and the similarity is intriguing given the historical association of the two conditions. Identification of a *latent* ASD category, using a clinically ascertained sample, builds on and clarifies previous literature showing that autism symptoms are continuously distributed at the *observed* score level in the population (Constantino & Todd, 2003). The difference in observed and latent distributions should not be viewed as a discrepancy, as previous researchers have described the numerous reasons why uni- and bimodal observed score distributions do not imply continuous or categorical latent distributions (Meehl, 1995; Murphy, 1964; Ruscio et al., 2006; Waller & Meehl, 1998). Although the difference could be because of sampling, data from other disorders suggest that clinical and population samples tend to show similar latent structure (Frazier, Youngstrom, & Naugle, 2007; Haslam et al., 2006). It is possible, however, that the latent structure of autism symptoms may be different or more complex in population samples (Geschwind, 2008). The present study contributes to understanding of the latent structure of ASD by combining a large clinical sample with more powerful statistical methods for testing the categorical hypothesis. This study is also unique in that it is the first attempt at using an empirically driven approach to determining whether ASD is best conceptualized as a category or continuum using multiple recommended statistical methods.

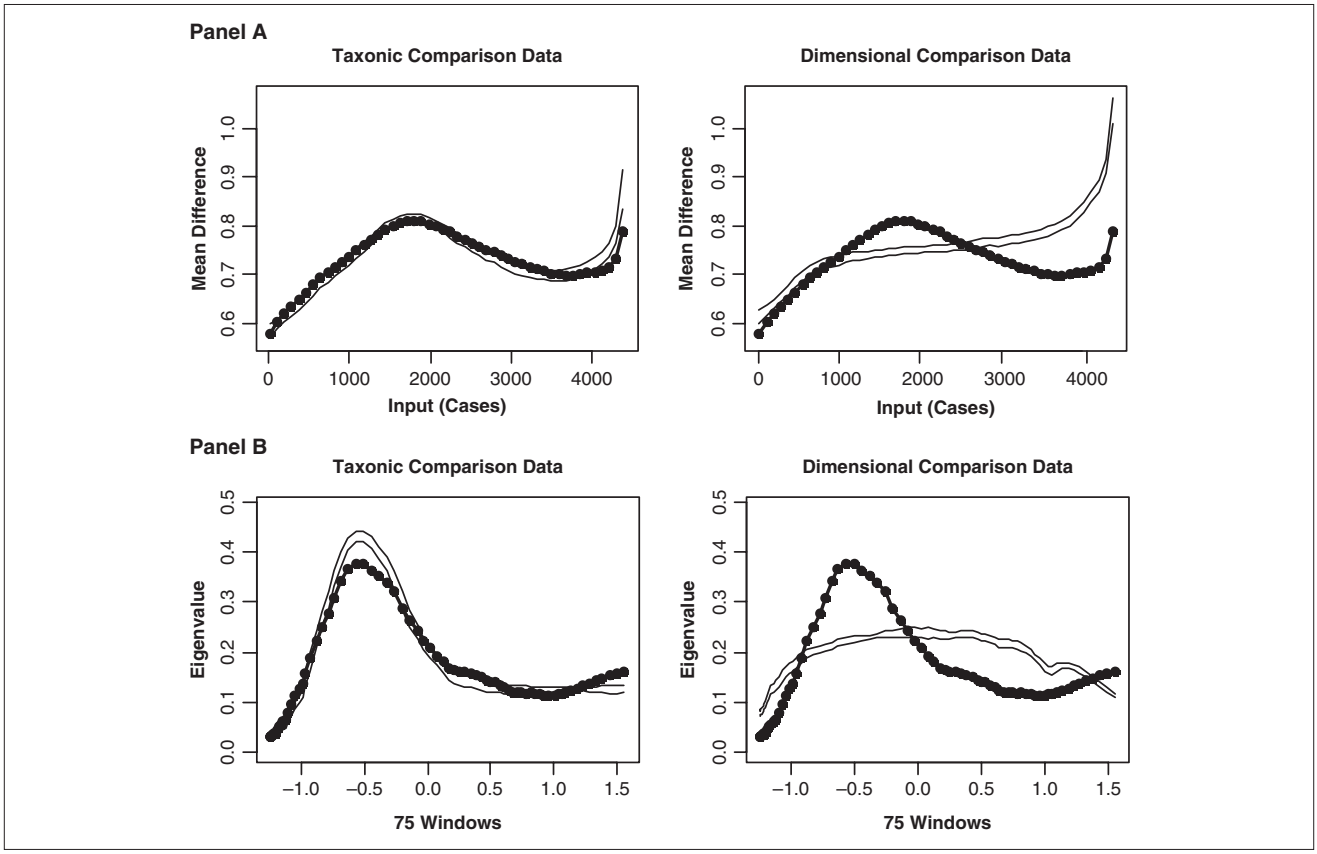

Figure 1. An autism spectrum category is present in the total IAN sample, based on multiple statistical methods and multiple symptom indicators

Note: MAMBAC (Panel A) and MAXEIG (Panel B) graphs present IAN total sample SRS social communication data overlaying simulated categorical and dimensional data.

Table 3. Taxometric and Latent Variable Modeling Results for the Unaffected Subsample and Demographic Subgroups

			MAMBAC		MAXEIG		BIC	
Measure	Subsample/Sample	*N*	CCFI	BR	CCFI	BR	One-Factor	Two-Class
SCQ-Domain Scores[a]		4,597	.891	.07	.660	.05	49,630	**38,739**
	Age <7 years	1,899	.826	.09	.690	.05	20,699	**17,038**
	Age ≥7 years	2,698	.888	.08	.730	.03	28,805	**21,364**
	Males	2,165	.841	.10	.755	.07	24,216	**19,728**
	Females	2,432	.876	.05	.669	.03	25,252	**17,794**
SRS-Social Communication[b]		1,825	.785	.07	.630	.05	3,604	**1,768**
SRS-Autistic Mannerisms		1,825	.736	.06	.610	.04	3,685	**1,436**

Note: MAMBAC = mean above minus mean below a cut; MAXEIG = maximum eigenvalue at the hitmax point; BIC = Bayesian Information Criteria; CCFI = comparison curve fit index; SCQ = Social Communication Questionnaire; SRS = Social Responsiveness Scale. Lower (two-class) BIC values in boldface indicate better model fit.

a. Multiplex subsamples could not be examined for unaffected cases because of low sample size.

b. Demographic subsamples could not be examined for SRS indicator sets because of small sample size.

Classification data supported the validity of the ASD category. Classifications derived from different measures of autism symptoms and across different sampling divisions for examining latent structure showed similar base rates and very strong agreement, with kappas exceeding the thresholds for "excellent" agreement (Cicchetti et al., 2006). Unaffected

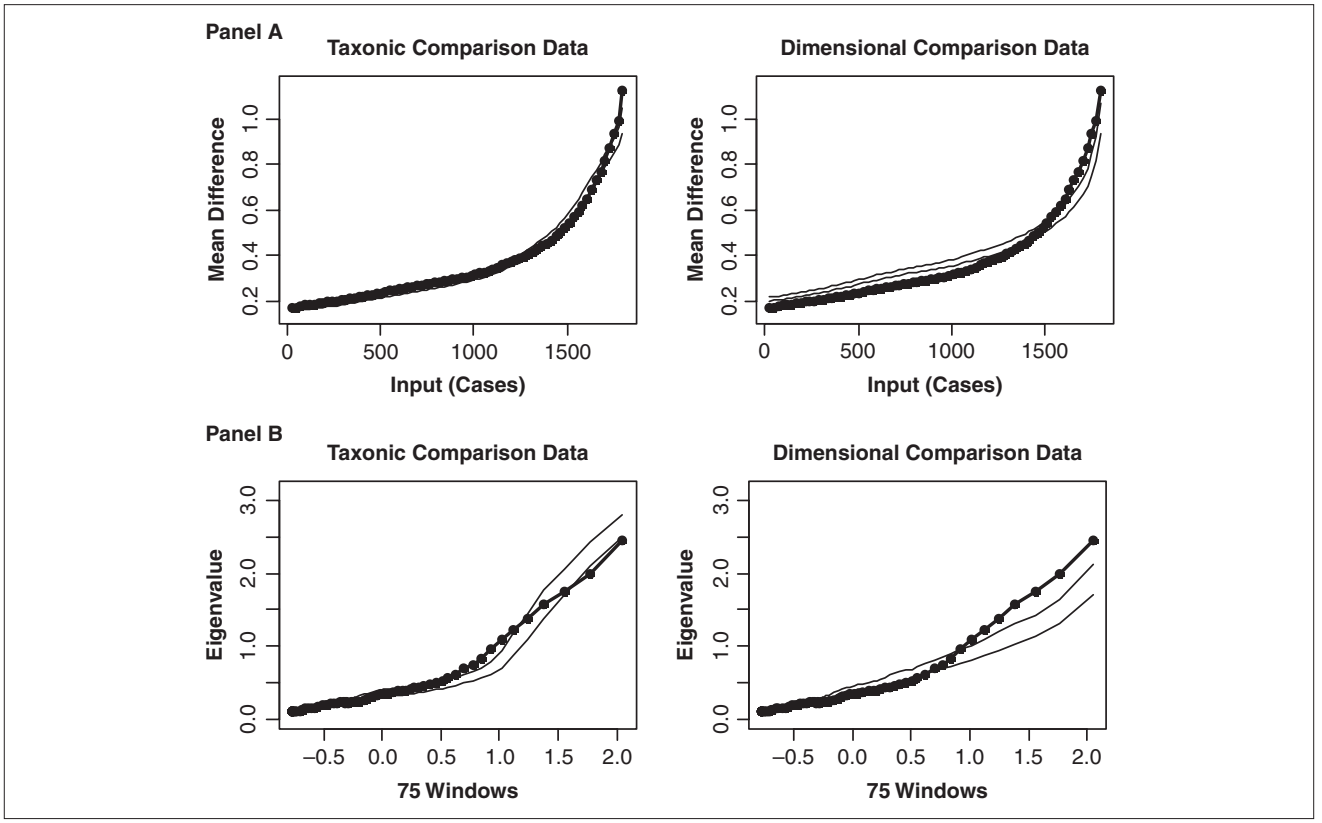

Figure 2. A low base rate autism spectrum category is present in the unaffected sibling sample, based on multiple statistical methods and multiple symptom indicators
Note: MAMBAC (Panel A) and MAXEIG (Panel B) graphs present IAN unaffected subsample SRS social communication data overlaying simulated categorical and dimensional data.

subsample classifications had substantial overlap with total sample classifications and showed significant relationships with independent measures of dysfunction. Thus, this low base rate category appears to represent unidentified or false negative ASD cases. Furthermore, this finding suggests that the ASD category may be broader than the application of current diagnostic criteria, a notion that is supported in this sample by the fact that the observed threshold at which the latent categories were differentiated was only 1.5 *SD* above the general population mean. The higher proportion of females in the low base rate group among subjects designated unaffected by their caregivers indicates that female siblings may be differentially underidentified. Correlations between empirical classifications and developmental variables were significant but modest. The modest magnitude of these relationships is not surprising, because unidentified individuals have less severe overall symptom patterns. However, these correlations support the validity of empirical classifications, suggesting that at least a portion of these unidentified individuals have subtle developmental delays.

Identification of a latent ASD category held for both simplex and multiplex families. This is in keeping with the notion that genetic transmission in multiplex families may be the result of transmission of a single mutation from an unaffected parent carrier to offspring (Zhao et al., 2007). Clearly, additional studies are needed to examine the viability of graded versus threshold genetic effects in simplex and multiplex families and in multiplex males. The current findings of categorical structure for multiplex males were the weakest of all the results reported, and thus the possibility remains that this subgroup shows dimensional rather than categorical structure.

Categorical structure is also consistent with previous family and twin studies that have reported low correlations among autism symptom domains in extreme groups (Ronald et al., 2006). Low correlations were previously interpreted as indicating genetic heterogeneity of autism symptom domains. The present data suggest that this heterogeneity may be across individuals, with a small number of genetic effects contributing to each case.

A qualitatively distinct category of clinically ascertained ASD is consistent with the stability of broad ASD diagnoses (Lord et al., 2008) and a threshold model of etiology (Haslam, 2003; Zhao et al., 2007). The present data are also

consistent with increasing concordance rates when the broader autism spectrum is considered rather than the narrow autistic disorder phenotype (Bailey et al., 1995). These data do not discount the possibility of endophenotypes or subthreshold ASD symptoms in unaffected family members (Constantino et al., 2006; Constantino & Todd, 2005). Rather, it simply indicates that in ASD-affected families, ASD symptoms come in one of two varieties, sub- or suprathreshold.

Future clinical assessment strategies would benefit from evidence-based medicine procedures. This strategy would incorporate multiple, nonredundant measures to generate posttest probabilities of ASD diagnosis (Kraemer, 1992). Evidence-based medicine procedures differ from the continuum model, which attempts to locate patients on a presumed quantitative dimension and then choose a cutoff informed by functional deficits or risk. The present findings indicate that the latter approach may be more useful for understanding differences among cases of ASD rather than between ASD and typical functioning. These data also suggest that SCQ raw scores below 15 and SRS raw scores below 70 may be required to enhance the sensitivity of screening for the higher functioning end of the ASD category in clinical samples.

The present study used a large, Internet-based registry composed of self-referred caregivers' reports of their children. The sample is likely not entirely representative of the larger population of ASD-affected families, particularly those families without Internet access. However, this study, and the Internet registry on which it is based, has several strengths, including sample size, participation of simplex and multiplex families, ease of large-scale data collection, greater access for rural families, representation from across the entire United States, increased access for families that would not otherwise participate in research, and an enriched sample of ASD cases spanning a wide range of severity from mild to severe ASD.

Two distinct measures of autism symptoms were examined in this study, one focused on diagnostic criteria and one measuring a broader range of ASD traits. Inclusion of two measures is advantageous in that it ensures that findings are not because of the reporting instrument. Interestingly, the latent category identified was consistent across two different types of indicator sets, one covering all ASD symptoms (SCQ) and one covering specific symptom domains (SRS social communication and autistic mannerisms). Consistency of the latent category across multifaceted and specific indicator sets supports the notion of pleiotrophic genetic effects, where strong genetic effects influence multiple aspects of the phenotype (social communication and stereotyped/repetitive behavior).

The present study, as with many studies of the latent structure of psychopathology, is limited by use of subjective ratings. Additional studies are needed with more specific biological and behavioral indicators to replicate the present findings. Also, caregiver reports of unaffected siblings' autism symptoms may have been subject to rater contrast effects or biased by initial diagnostic questions. However, these problems were circumvented by the identification of a latent category in the unaffected sample and the use of statistical procedures that are blind to diagnostic status. Inclusion of diagnostic confirmation in future studies would be useful for verifying the nature of identified unaffected cases.

Future studies using representative population samples will be helpful for confirming the present findings and estimating the population base rate and demographic characteristics of ASD. These studies should use different ascertainment procedures to improve representation of low SES families and avoid potential sources of bias by gathering data from individuals without referencing affected or unaffected diagnostic status. Population studies are not without difficulties when applied to answering the question of ASD latent structure. The largest published representative population study to date has approximately 6,000 participants (Ronald, Simonoff, Kuntsi, Asherton, & Plomin, 2008). An autism base rate of 1 in 200 would be needed in this sample to meet the minimum recommended subsample size ($N = 30$) to detect a latent category. The most recent epidemiological estimate of ASD prevalence, 1 in 150, suggests that this sample is adequate for latent structure detection, assuming no ascertainment bias, but subgroup analyses would not be possible. If the actual category base rate is lower, the sample size needed increases dramatically.

Latent structure studies using population samples could be very sensitive to any ascertainment biases influencing the recruitment of low- or high-functioning autism cases. Even a subtle bias in recruitment of low- or high-functioning ASD cases would skew findings toward a dimension, if there is underrecruitment of low functioning ASD, or a pseudocategory, if there is under recruitment of high functioning ASD. It will also be important that population studies of autism latent structure include diagnostic information to ensure that an adequate number and range of ASD cases have been sampled to have sufficient power to detect a latent category. Thus, population based samples should be viewed as complementary, providing data about the latent structure of autism across the entire range of typical social communication presentations, but not replacing enriched or community samples.

If the present findings are confirmed by future studies, next generation diagnostic conceptualizations should emphasize a single ASD category with social communication and repetitive/stereotyped behaviors as the core elements of dysfunction. Additional research using factor mixture models is needed to determine whether subcategories or subdimensions of autism exist. Existing data, coupled with the present findings, suggest that a categorical model with 2-3 subdimensions—social communication,

repetitive/perseverative behavior, and possibly social motivation—may best represent the structure of autism symptoms (Frazier et al., 2008; Snow, Lecavalier, & Houts, 2009).

Conclusions

Results of the present study indicate that, within ASD-affected families in clinically ascertained samples, ASD is best characterized as a category, distinct from typical behavior. If confirmed in future research, categorical latent structure supports molecular genetic approaches searching for major genomic contributions to individual ASD cases and the use of evidence-based medicine approaches to diagnosis. Future studies using population-based or community samples will be helpful for evaluating and generalizing these findings outside clinical samples of ASD-affected families.

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