

# Structure of the Autism Symptom Phenotype: A Proposed Multidimensional Model

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## ABSTRACT

**Background:** The main objective of this study was to develop a comprehensive, empirical model that will allow the reorganization of the structure of the pervasive developmental disorder symptom phenotype through factor analysis into more homogeneous dimensions. **Method:** The sample consisted of 209 children with pervasive developmental disorder referred for genetic studies. The 12 subdomains of the Autism Diagnostic Interview-Revised were used in a factor analysis, and the emerged factors were then correlated with independent variables (measures of cognition, adaptive function, and diagnostic subtype). Intraclass correlation coefficients were calculated to investigate any familial relationships between sibling pairs on the derived factors. **Results:** The autism symptom phenotype is indeed made up of three factors or domains that are somewhat different than those used in *DSM-IV*. Rather, domains include social-communication, inflexible language and behavior, and repetitive sensory and motor behavior. For the three factors, only a small amount of variance was accounted for by cognitive and adaptive functioning. Only inflexible language and behavior showed familial correlation between siblings. **Conclusions:** The pervasive developmental disorder symptom phenotype is composed of three domains or factors: social-communication, inflexible language and behavior, and repetitive sensory and motor behavior. Each child with pervasive developmental disorder can be characterized by these dimensions, which give an informative picture of the clinical presentation and a quantitative estimate of the severity of the disability. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(2):188–196. **Key Words:** pervasive developmental disorders, autism, structure of autism phenotype, genetic studies.

The *DSM-IV* defines all pervasive developmental disorder (PDD) subtypes as sharing symptoms from

three symptom categories: impairments in social reciprocity and communication and the presence of repetitive stereotyped behaviors, interests, and activities (American Psychiatric Association, 1994). This conceptualization is based primarily on clinical judgment rather than empirical evidence. An alternative dimensional approach to the autism phenotype that defines the disorder empirically on multiple dimensions ranging from “no impairment, few symptoms” to “severe impairment, many symptoms” may offer several advantages over this conceptualization, including the ability to be more consistent with the variability and complexity of clinical presentation; to measure symptoms quantitatively related to severity of impairment, including those “below threshold” for diagnosis; to incorporate both behavioral symptoms and comorbid developmental impairments; and to draw flexibly from multiple scales in diagnostic decision making.

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However, adoption of a dimensional approach has generated controversy in the autism field about whether variability in clinical expression represents variation in a single underlying dimension (Constantino and Todd, 2003; Constantino et al., 2004) or in a number of different underlying dimensions (van Lang et al., 2006) or whether phenotypic variability is a sign that PDD is a heterogeneous disorder accounted for by independent genetic mechanisms. For progress to be made, a reevaluation of the structure of the symptom dimensions (factors) is warranted.

To date, only a limited number of studies have examined the factor structure of the autism phenotype as a whole. In a study of 98 variables from all three domains of the Autism Diagnostic Interview-Revised (ADI-R), Tadevosyan-Leyfer et al. (2003) concluded that the ADI-R can be described using six factors: spoken language, social intent, compulsions, milestones, savant skills, and sensory aversions. Tanguay et al. (1998) and Robertson et al. (1999) conducted a factor analysis of the ADI-R using 28 items solely from the social and communication domains. Their results indicated that these behaviors can be best described using three factors: affective reciprocity, joint attention, and theory of mind. In a factor analytic study of the three ADI and three Vineland domains, Szatmari et al. (2002) concluded that autistic symptoms and level of functioning independently contribute to the phenotypic variation seen in PDD. More recently, van Lang et al. (2006) concluded that a three-factor model consisting of social-communication, make-believe play, and stereotyped language and behavior was a fairly comprehensive model for the symptom structure of autism. In contrast, using a sample of typical twins and a different instrument (the Social Responsiveness Scale), Constantino and colleagues (Constantino and Todd, 2003; Constantino et al., 2004) identified a single factor that captured all three *DSM* dimensions. Similarly, using cluster analysis, Spiker et al. (2002) and Constantino et al. (2004) concluded that the phenotype could be conceptualized best as a single underlying dimension that differed only in severity. Finally, Ronald et al. (2005) concluded that although individual differences in social and nonsocial behaviors are highly heritable, they appear to be largely independent in terms of genetic influences.

Although all of the studies described above had a similar objective (i.e., to search for the underlying

structure of the autism phenotype), there were notable methodological differences across studies that could account for the varying findings. The most important methodological differences were in sample size (i.e., ranging from 63 to 339), sampling method (i.e., including only affected PDD individuals versus typically developing children or children with other psychiatric disorders), and item pool selected for factor analysis (individual ADI items versus subdomains or another instrument entirely). In addition, it should be noted that the decision on the final number of factors extracted could be influenced by the opinion of different investigators. These methodological differences support the utility of usefully reexamining the PDD symptom phenotype.

The main objective of this study was to develop a comprehensive, empirical model that would allow us to reorganize the structure of the PDD symptom phenotype (through factor analysis) into more homogeneous dimensions. A second objective of this study was to examine the association between the empirically derived factors and other variables such as age, sex, IQ, level of functioning, and familial aggregation that may explain the variation in these underlying domains.

## METHOD

### Sample

Our sample consisted of 209 affected children from multiplex (more than one affected child per family) and simplex (one affected child per family) families with a best-estimate diagnosis of PDD (see below for details) who were participating in a study aimed at identifying genetic causes of autism. The study was approved by the local research ethics board (Hamilton Health Sciences and McMaster University), and all of the participating families gave their written informed consent before entering the study. Only one child per multiplex family was selected. Children with identifiable neurological or chromosomal conditions of any type were excluded. There were no significant sex differences in age or developmental level between affected children from multiplex and simplex families. Descriptive statistics for our sample are presented in Table 1.

### Best-Estimate Evaluation

All participants were initially assessed with the ADI-R and either the original or the newer modular format of the Autism Diagnostic Observation Schedule (ADOS). Further information was collected from the Autism Behavior Checklist, the Arthur Adaptation of the Leiter International Performance Scale (Leiter), and the Vineland Adaptive Behavior Scales (VABS). Raw data from the ADI-R and ADOS; standard scores from the Autism Behavior Checklist, Leiter, and VABS; and any previous clinical notes (including language, psychological, pediatric/psychiatric, occupational therapy, and

**TABLE 1**  
Sample Descriptive Statistics

Characteristics	No.	%	Mean (SD)	Range
Family type				
Multiplex	129	61.70		
Simplex	80	38.30		
Sex				
Male	157	75.10		
Female	52	24.90		
Best-estimate diagnosis				
Autism	165	78.90		
PDD-NOS	21	10.00		
Asperger	23	11.00		
Leiter IQ adjusted <sup>a</sup>			65.55 (26.97)	23–132
Age at ADI-R interview, mo			108.75 (65.30)	28–482
ADI-R level of language (item 19)				
Verbal		56.50		
Nonverbal		43.50		

*Note:* PDD-NOS = pervasive developmental disorder not otherwise specified; ADI-R = Autism Diagnostic Interview-Revised.  
<sup>a</sup> *n* = 183

school records) were forwarded to three raters considered experts in the diagnosis of autism. Each rater made a diagnosis independently using *DSM-IV* criteria. If there was disagreement regarding the diagnosis, then the raters would discuss the case until a consensus diagnosis was reached. The differentiation of PDD subtypes was made by the best-estimate committee using data obtained from the ADI-R, ADOS, and clinical records. Autism was diagnosed according to *DSM-IV* criteria. Asperger disorder was diagnosed in children without clinically significant cognitive and language delay who still demonstrated qualitative impairments in reciprocal social interaction and social-communication and had a pattern of restricted, repetitive behaviors. A diagnosis of PDD not otherwise specified (PDD-NOS) was given when the individual demonstrated fewer than the six behaviors in total needed to receive a *DSM-IV* diagnosis of autism, when the child missed the threshold in one or more of the three domains, or when age of onset was older than 3 years. Further information regarding the consensus best-estimate procedure and its reliability and validity is described in detail in Mahoney et al. (1998).

**Measures**

*Autism Diagnostic Interview-Revised.* The ADI-R (Lord et al., 1994), the most widely used research interview for the diagnosis of autism, is a standardized semistructured interview consisting of three major domains: social interaction, nonverbal and/or verbal communication, and restricted, repetitive behaviors and interests. Each of the 3 domains has 4 subdomains for a total of 12 subdomains. A cutoff point for each of the three domains provides a reliable diagnostic algorithm that accurately discriminates autism from other developmental disorders. The ADI-R is scored using “current” (within 3 months before the interview) and “ever” (throughout the individual’s life) ratings. High scores on the ADI-R indicate more symptoms.

*Autism Diagnostic Observation Schedule.* The ADOS (Lord et al., 2000) is a semistructured direct assessment of communication, social interaction, and play or imaginative use of materials for individuals suspected of having autism or other PDDs. The ADOS consists of four modules, each of which is appropriate for children and adults of differing language levels, ranging from nonverbal to verbally fluent. For the purposes of this study, the ADOS was used only for diagnostic purposes and was not included in the analyses.

*Vineland Adaptive Behavior Scales.* The VABS (Sparrow et al., 1984) is an interview-based measure, completed with the primary caregiver of the target individual, that assesses adaptive behavior in the three domains of communication (receptive, expressive, and written), daily living skills (personal, domestic, and community), and socialization (interpersonal relations, play and leisure time, and coping skills). Low scores on the VABS indicate severe impairment. The VABS has excellent reliability and validity (Sparrow and Cicchetti, 1985) and is sensitive to severity of impairment in autism spectrum disorders (Carter et al., 1998).

*Leiter International Performance Scales.* The Leiter is a standard, nonverbal measure of problem solving and learning ability (Levine, 1986). The Leiter does not require verbal instructions or responses, which makes it appropriate for use in individuals with autism, particularly those with low linguistic levels (Tidmarsh and Volkmar, 2003).

**Data Analysis**

To examine the factor structure of the PDD diagnostic phenotype, all 12 subdomain scores of the ADI-R algorithm were selected for analyses. The normality assumption test and a check for skewness were performed for each domain. Analysis was carried out using principal-components analysis. Principal-components analysis is a statistical technique that transforms an original set of variables into a smaller set of uncorrelated variables, often referred to as factors or components that represent most of the information of the original variables (Dunteman, 1989).

For all principal-components analyses, VARIMAX rotation (Kaiser, 1958) was used to achieve a simpler structure while maintaining independence between the rotated factors. Use of a PROMAX rotation yielded results similar to those reported below. To evaluate the extent to which the obtained factors were correlated with other variables, we calculated scores (Armitage and Colton, 1998) based on each of the derived factors for every participant. Optimally weighted factor scores were automatically generated by SPSS so that the mean factor score for the entire sample was zero and the standard deviation was one. We used Pearson correlation coefficients to examine the association between the empirically derived factors and VABS scores, Leiter IQ score, and age at ADI-R interview. The derived factor model also was examined using confirmatory factor analysis in a different sample consisting of 103 siblings (i.e., the affected siblings of probands from multiplex families) with a PDD diagnosis. Confirmatory factor analysis was carried out using the Mplus statistical software (Muthen and Muthen, 2004).

Linear regression analyses were used to assess the overall variance in factor scores accounted for by differences in cognitive and adaptive function variables on the emerged factors. Variables that had a significant association with the factor scores in the univariate correlations estimated above were used for these analyses.

We also compared means on the emerged factor scores based on best-estimate diagnosis (autism versus Asperger versus PDD-NOS), family type (multiplex versus simplex), and sex using analysis of

variance. Appropriate post hoc testing using Tukey's HSD test was used as needed.

To investigate any familial relationships, we calculated intraclass correlation coefficients (ICCs) between sibling pairs in the multiplex families on the derived factors. Hierarchical linear modeling or multilevel modeling is useful in analyzing data with a hierarchical or clustered structure such as family data with siblings nested within families (Boyle and Willms, 2001). Hierarchical linear modeling allows for nonindependence of units, in this case, multiple siblings per family. In a two-level model, the ICC is calculated as the proportion of variance at the family level and can be interpreted as the expected correlation between two random individuals within the same family (Hox, 2002). This final analysis was carried out on multiplex families (i.e., those with two or more siblings diagnosed with PDD) with complete data on all siblings ( $n = 203$ ; 97 families with 2 siblings, 3 families with 3 siblings).

## RESULTS

The distribution of scores for each of the 12 ADI-R subdomains showed some departure from normal. Even though this may influence the correlations between items/subdomains, it should be noted that principal-components analysis is reasonably robust to departures from normal. Therefore, all 12 subdomains of the ADI-R were used in the factor analysis. A cutoff point for factor loadings of 0.365 was chosen to minimize cross-loading. Four eigenvalues were  $>1.0$ . Two-, three-, four-, and five-factor solutions were examined. In the two-factor solution, the amount of variance explained was only 40%. In the four-factor solution,

one of the factors (fourth) included only one item (D3, stereotyped and repetitive motor mannerisms). Although the five-factor solution accounted for 67% of the variance, one of the factors had only one item, and there were cross-loadings on multiple factors. The selection of the number of factors to extract was based on examination of the first five eigenvalues (2.994, 1.837, 1.208, 1.079, and 0.997) and the screen plot and conceptual interpretability of the emerged factors. As a result, the three-factor solution was selected. Items with moderate to high loadings ( $>0.365$ ) on more than one factor (B4, lack of socioemotional reciprocity; B1, failure to use nonverbal behaviors to regulate social interaction; and D4, preoccupations with part of objects or nonfunctional elements or materials) were included in only one factor on the basis of a higher loading and interpretability. The three extracted components accounted for 50% of the variance. Table 2 presents the factor loadings on the three factors. From these results, we concluded that the domain structure of the ADI-R can best be described using three new distinct factors: social-communication (SOCOM), inflexible language and behavior (ILB), and repetitive sensory and motor behavior (RSMB).

The derived three-factor model also was examined using confirmatory factor analysis in a separate sample of the affected siblings of those included in the primary

**TABLE 2**

Factor Loadings on Social-Communication, Inflexible Language and Behavior, and Repetitive Sensory and Motor Behavior for 209 Individuals With Pervasive Developmental Disorder

ADI-R Subdomain	Factor		
	SOCOM	ILB	RSMB
ADI-R: B2 total, failure to develop peer relationships	<b>0.80</b>		
ADI-R: B3 total, lack of shared enjoyment	<b>0.77</b>		
ADI-R: C1 total, lack of or delay in spoken language and failure to compensate through gesture	<b>0.61</b>		
ADI-R: B4 total, lack of socioemotional reciprocity	<b>0.58</b>		0.53
ADI-R: B1 total, failure to use nonverbal behaviors to regulate social interaction	<b>0.54</b>		0.36
ADI-R: C4 total, lack of varied spontaneous make-believe or social imitative play	<b>0.49</b>		
ADI-R: C3V total, stereotyped, repetitive, or idiosyncratic speech		<b>0.83</b>	
ADI-R: C2V total, relative failure to initiate or sustain conversational interchange		<b>0.82</b>	
ADI-R: D2 total, apparently compulsive adherences to nonfunctional routines or rituals		<b>0.57</b>	
ADI-R: D1 total, encompassing preoccupation or circumscribed pattern of interest		<b>0.42</b>	
ADI-R: D3 total, stereotyped and repetitive motor mannerisms			<b>0.85</b>
ADI-R: D4 total, preoccupations with part of objects or nonfunctional elements or materials	0.35		<b>0.37</b>

*Note:* ADI-R = Autism Diagnostic Interview-Revised; SOCOM = social-communication; ILB = inflexible language and behavior; RSMB = repetitive sensory and motor behavior. ADI-R1 explained variance of 50%. Items with factor loadings  $<0.30$  are not shown. Highest item factor loading is shown in bold.

analysis. Multiple indexes were selected to determine the model goodness of fit: the root mean square error of approximation (Steiger, 1990), the standardized root mean square residual, the Comparative Fit Index (Bentler, 1990), and the Tucker-Lewis Index (Tucker and Lewis, 1973). In general, values >0.90 for the Comparative Fit Index and Tucker-Lewis Index, between 0.05 and 0.08 for root mean square error of approximation, and between 0 and 1 for standardized root mean square residual are considered an indication of acceptable model fit. For the specific model, the root mean square error of approximation value was 0.067, the standardized root mean square residual value was 0.08, the Comparative Fit Index value was 0.92, and the Tucker-Lewis Index value was 0.90. All of these values met the cutoff criteria for acceptable model fit indexes (Williams and Eaves, 2005). For comparison reasons, confirmatory factor analysis also was used to examine the original *DSM-IV* model (as indexed by the three original ADI-R domains). Unlike the proposed model, the *DSM-IV* categorical model failed to meet the main criteria for acceptable model fit (root mean square error of approximation = 0.12, standardized root mean square residual = 0.012, Comparative Fit Index = 0.69, Tucker-Lewis Index = 0.59). In other words, the proposed dimensional model appears to be a better fit to the sample data than the *DSM-IV* model.

The SOCOM factor combines subdomains from the original reciprocal social interaction and communication domains that measure failure to use nonverbal behaviors to regulate social interaction, lack of or delay in spoken language, failure to compensate through gesture, and lack of varied spontaneous make-believe or social imitative play. The ILB factor includes subdomains that measure relative failure to initiate or sustain

conversational interchange; stereotyped, repetitive, or idiosyncratic speech; encompassing preoccupation or circumscribed pattern of interest; and apparently compulsive adherences to nonfunctional routines or rituals. The RSMB factor includes subdomains that measure stereotyped and repetitive motor mannerisms and preoccupations with part of objects or nonfunctional elements or materials and sensory stimuli.

Table 3 presents the zero-order correlations between the emerged factors and other variables of interest. SOCOM is negatively correlated with VABS communication, VABS daily living skills, VABS social, VABS adaptive behavior composite, and Leiter IQ scores. SOCOM is positively correlated with age at ADI-R interview. In other words, the higher the SOCOM, the lower the general functioning level of the child and the older the child is when the ADI-R was conducted. RSMB is negatively correlated with VABS communication, VABS daily living skills, VABS social, and VABS adaptive behavior composite. As with the SOCOM factor, the higher the RSMB, the lower the general functioning level of the child. In contrast, ILB is positively correlated with VABS communication, VABS daily living skills, VABS adaptive behavior composite, and Leiter IQ scores. In other words, the higher the ILB, the higher the general functioning level of the child.

To examine the extent to which the correlated variables predict individual scores on the three emerged factors, we used linear regression analyses. For the first regression, the SOCOM factor was the dependent variable, and the independent variables included the variables with a significant correlation noted above. They were entered as a block. Results indicated that the model significantly predicted the SOCOM factor [ $F_{(5, 177)} = 5.29, p < .001$ ] but

**TABLE 3**

Zero-Order Correlations Between the Three Derived Factors and Vineland Adaptive Behavior Scales Communication, Daily Living Skills, Social Skills, and Adaptive Behavior Composite, as Well as Leiter IQ and Age (at Autism Diagnostic Interview-Revised Interview)

	VABS Communication Standard Score	VABS Daily Living Standard Score	VABS Social Standard Score	VABS Adaptive Behavior Composite	Leiter IQ Score	Age at ADI-R, mo
SOCOM	-0.33**	-0.24**	-0.34**	-0.32**	-0.26**	0.18*
RSMB	-0.27**	-0.32**	-0.29**	-0.32**	-0.14	-0.07
ILB	0.49**	0.34**	0.34**	0.40**	0.43**	0.12

Note: VABS = Vineland Adaptive Behavior Scales; SOCOM = social communication; RSMB = repetitive sensory and motor behavior; ILB = inflexible language and behavior.

\* Correlation is significant at the .05 level.

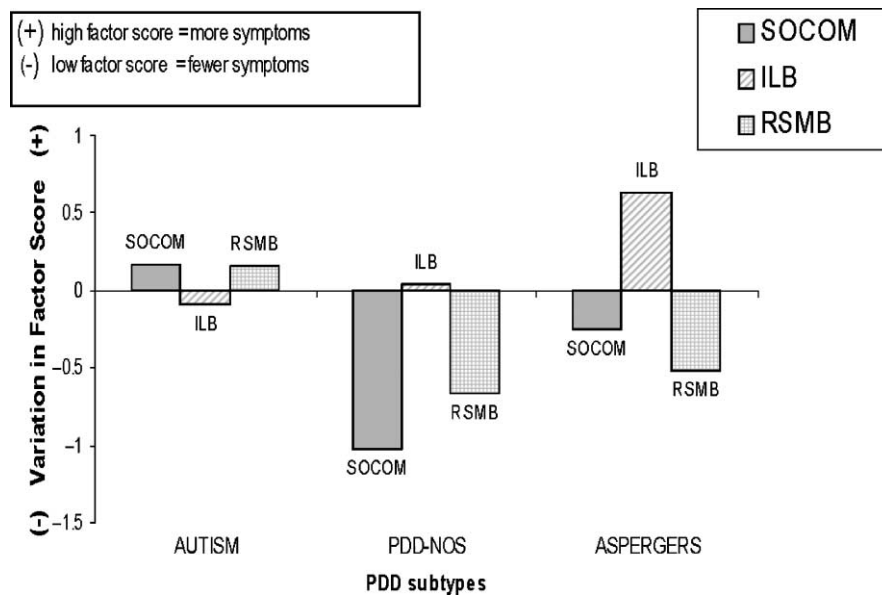
\*\* Correlation is significant at the .01 level.

accounted for only a small amount of the explained variance, with an adjusted  $R^2$  value of 0.13. No variables were independently significantly associated with the SOCOM factor score. For the RSMB factor score, the independent variables included VABS communication, daily living, and social skills scores, which again were entered as a block. The second model significantly predicted the RSMB factor [ $F_{(3, 205)} = 8.20$ ,  $p < .001$ ]. Once again, the low value of the adjusted  $R^2$  of 0.10 meant that the model accounted for only a small amount of the explained variance. The only variable that was significantly associated with the RSMB factor was VABS daily living score [ $t_{(207)} = -2.17$ ,  $p < .05$ ]. For the ILB factor, the independent variables included VABS communication, daily living, and social skills scores, as well as Leiter IQs, which again were entered as a block. This model significantly predicted the ILB factor [ $F_{(4, 178)} = 16.65$ ,  $p < .001$ ]. The amount of explained variance was greater for this factor [ $R^2 = 0.27$ ] than for the other two. The independent association [ $t_{(181)} = 4.45$ ,  $p < .001$ ] of VABS communication scores and Leiter IQ scores [ $t_{(181)} = 2.3$ ,  $p < .05$ ] with ILB is worth noting.

Figure 1 depicts mean scores (i.e., number of symptoms) on derived factors for best-estimate diagnosis (autism versus PDD-NOS versus Asperger). The overall analysis of variance was significantly different for each dimension (SOCOM,  $F = 38.71$ ;

ILB,  $F = 13.97$ ; RSMB,  $F = 31.19$ ;  $p < .001$  for all dimensions). Post hoc testing revealed that for the SOCOM factor, individuals with PDD-NOS score significantly lower (i.e., fewer symptoms) than individuals with autism ( $p < .01$ ) and Asperger ( $p < .05$ ), whereas those with autism and Asperger were not different from each other. For the ILB factor, individuals with Asperger score significantly higher (i.e., more symptoms) than those with autism ( $p < .01$ ). The PDD-NOS group was no different from either on this factor. Finally, for the RSMB factor, individuals with autism score significantly higher (more symptoms) than those with PDD-NOS ( $p < .01$ ) and Asperger ( $p < .01$ ), and the last two were similar. There were no significant differences on any of the three derived factors scores for sex or multiplex versus simplex family type (not shown).

To investigate familial resemblance, we calculated ICCs between sibling pairs on the derived factors using multilevel methods. Results indicate that there is little or no variation in the measures of SOCOM (ICC = 0.06,  $p > .05$ ) and RSMB (ICC = 0.09,  $p > .05$ ) between families and hence low ICCs. Thus, families were similar in their measures of SOCOM and RSMB, and most of the variation observed is between siblings within families. There is significant variation between (relative to within) families for ILB, with ICCs equal to 0.23 ( $p < .01$ ). In other words, siblings tend to be more



**Fig. 1** Mean factor scores (mean = 0, SD = 1) on social-communication (SOCOM), inflexible language and behavior (ILB), and repetitive sensory and motor behaviors (RSMB) for best-estimate diagnosis (autism, pervasive developmental disorder-not otherwise specified [PDD-NOS], Asperger).

similar to one another on this symptom domain than unrelated probands. This suggests that the ILB domain is to some extent under familial, presumably genetic, control.

## DISCUSSION

The results of these analyses suggest that the autism symptom phenotype (as indexed by the ADI-R) is indeed made up of three factors or domains, but they are somewhat different than those in the *DSM-IV*. Instead of separate impairments in social reciprocity and in verbal and nonverbal communication and a preference for repetitive stereotyped activities, we found that the structure of the PDD symptom phenotype is composed of SOCOM, ILB, and RSMB symptoms (Table 2). In essence, the *DSM-IV* phenotype of communication is heterogeneous, made up of items that reflect behaviors that regulate social interaction (both verbal and nonverbal) and items related to flexible use of language in the formulation of complex utterances and in conversation. Consistent with findings from other studies (Cuccaro et al., 2003; Shao et al., 2003; Szatmari et al., 2006), we conclude that the *DSM-IV* phenotype of repetitive stereotype behaviors also is heterogeneous and is composed of insistence on sameness (i.e., inflexible behavior) and RSMB. The proposed dimensional model provides a better fit based on both exploratory and confirmatory factor analysis than the traditional *DSM-IV* categorical model for capturing the structural relationship between autistic symptoms.

It is interesting to find that for verbal children, the ILB items fall in the same domain, suggesting that lack of flexibility, possibly an aspect of executive dysfunction or weak central coherence (Hill and Frith, 2003), may underlie both. The clustering of items in this factor may be driven by the tendency of nonverbal children to have lower scores on insistence on sameness. Thus, the correlation between the language-specific items and insistence on sameness items is confounded by nonverbal IQ and language ability. The key finding, however, is that the autism phenotype is not composed of a single symptom domain. Although the three domains we identified accounted for only a moderate amount of the variance in the PDD phenotype (50%), this is a substantial amount compared with other studies in this area. For example, although Tadevosyan-Leyfer et al. (2003) provided a six-factor solution, the

variance explained by this solution was only 41%. More recently, van Lang et al. (2006) reported a three-factor structure explaining only 34% of the variance. Whether this low explained variance is due to possible unreliability in the ADI-R measures when measured in this context or to the fact that the subdomains are missing an important aspect of the phenotype is unclear at this point and deserves further investigation.

Our results most closely resemble those of van Lang et al. (2006), who also identified a social-communication domain, a stereotyped language and behaviors domain, and a make-believe play domain. The first two are almost identical to ours in terms of the number of items that make up the factors; the third one is substantially different. It is worth pointing out, however, that the sample assessed by van Lang et al. (2006) is quite different from our sample; their sample was composed of quite cognitively impaired individuals, only roughly half of whom were on the autism spectrum. In addition, our findings appear to be in line with those reported by Ronald et al. (2005) providing further evidence that social (i.e., SOCOM) and nonsocial (i.e., ILB) symptoms are largely independent in terms of genetic influences. It is worth noting that Ronald et al. (2005) did not include items related to repetitive motor mannerisms and behaviors in their analyses.

The key issue now is what these three domains represent. Are they independent clinical phenomena, or are they proxy measures for level of functioning or developmental stages? We were able to explain only a small amount of the variance in these three domains by measures of level of functioning or age. Except for ILB, <20% of the variation in SOCOM and RSMB could be explained by nonverbal IQ, age, and communication. It is true that the amount explained was greater for ILB, largely because of the inclusion of the variable "difficulty initiating and sustaining a conversation," which is closely tied to language level and the ability to speak. These data continue to support the notion that variation in autistic symptoms is not simply a reflection of developmental level but rather may represent variation in some other underlying etiological factor.

The most obvious factor to investigate was familial mechanisms as a reflection of underlying genetic mechanisms, but here, the data were not supportive of the possibility that familial factors account for variation among affected children alone in all three

domains. This is probably the result of the subjects being selected on the basis of being affected with PDD, so we are dealing with a truncated part of the distribution. If both affected and unaffected sibs were included, then it is likely that there would be some correlation (at least on SOCOM) within families. On RSMB, there was little variation between families and much more variation within sibships. This may indicate that there is little genetic heterogeneity between families on this measure; that parents were emphasizing contrasts, not similarities, between affected sibs; or that our sample of affected children represents in some way a narrow segment of the population of children with PDD. A larger sample size or a different sampling scheme may give a different result. For now, we must conclude that there is little evidence that using quantitative traits of SOCOM and RSMB among affected children alone may be useful in quantitative linkage analysis. Instead, ILB may be more fruitful in this context because there is less variation within sibships than between them on this domain. Indeed, insistence on sameness (part of the larger ILB factor) has been fruitfully used as a quantitative measure in linkage analysis (Buxbaum et al., 2004).

#### Limitations

This study has several strengths that ensure confidence in the results. The sample size was large; only participants with PDD were used; there was no restriction on PDD subtype or level of functioning; we used primarily a genetically loaded subset of cases to perhaps ensure that this was a more etiologically homogeneous sample; and we looked at the relationship between the three factors and other variables to try to understand what the factors mean.

As always, there are limitations. Factor analysis as a statistical technique is sensitive to sample size and method of ascertainment, and even slight variations in sample composition and/or factor extraction criteria may give different results. The distribution of scores for each of the 12 ADI-R subdomains showed some departure from normality (although principal-components analysis is reasonably robust to departures from normality). The amount of variance explained in our study, as well in all other studies in this area, is only moderate. The ADI-R domains were not constructed to be used as quantitative measures to measure dimensions or severity. Finally, the estimate of familial aggregation of ILB is

low and may not be large enough to be useful as a quantitative trait alone. Measurement bias may be a real problem and may explain why there is more variation within than between families for SOCOM; parents may exaggerate differences between their affected children.

#### Clinical Implications

We conclude that the PDD symptom phenotype (as indexed by the ADI-R) is composed of three domains or factors: SOCOM, ILB, and RSMB. Each child with PDD can be characterized by these dimensions, which give an informative picture of the clinical presentation and a quantitative estimate of the severity of the disability. If warranted, these dimensions can be used to empirically represent the three *DSM-IV* PDD subtypes of autism, Asperger syndrome, and PDD-NOS. Children with autism and Asperger syndrome have the highest scores (i.e., most symptoms) on the SOCOM domain; those with PDD-NOS have the lowest. Children with Asperger syndrome are distinguished by having high scores on ILB and low scores on RSMB; those with autism, by high scores on RSMB; and those with PDD-NOS, by lower scores (i.e., fewer symptoms) on all three. This clearly defined profile for children currently assigned with a PDD-NOS diagnosis suggests that the term atypical autism would be more appropriate for describing children with low scores on all three dimensions instead of on one or the other as is currently stated. The term PDD-NOS could then be used only to describe children who do not fit any of the three subtype profiles (i.e., autism, atypical, Asperger). In this way, perhaps the differential diagnoses of these PDD subtypes may be done in a more empirical and systematic way. If we add IQ and language assessments to these descriptions, then new phenotypes may also be generated for genetic studies as well.

The empirical approach to understanding the underlying structure of the PDD phenotype (whether by factor or cluster analysis) has, generally speaking, generated one of three alternatives: a single underlying normally distributed factor (i.e., spectrum) in the general population, two categorical subtypes of high- and low-functioning PDD, or a series of different dimensions/factors (e.g., those identified in these results, perhaps adding nonverbal IQ and language to fully capture the phenotype) among affected children. We think the third alternative is most consistent with the data and may be useful for clinical purposes.

However, this conclusion cannot be made with certainty until the genes that confer susceptibility to autism (or to these dimensions/factors) are finally discovered. At the same time, the converse may also be the case; in other words, the potential significance of particular genes may not be apparent until putative dimensions/factors are taken into account.

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