Published in final edited form as:

Res Autism Spectr Disord. 2008 April 1; 2(2): 320–331. doi:10.1016/j.rasd.2007.08.002.

Genetic and Environmental Influences on Symptom Domains in Twins and Siblings with Autism

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Abstract

Clarifying the sources of variation among autism symptom domains is important to the identification of homogenous subgroups for molecular genetic studies. This study explored the genetic and environmental bases of nonverbal communication and social interaction, two symptom domains that have also been related to treatment response, in 1294 child and adolescent twins and siblings with pervasive developmental disorders (PDDs) from the Autism Genetic Resource Exchange under the age of 18. Twin/sibling resemblance was assessed through correlations and behavior genetic modeling of Autism Diagnostic Interview (ADI) nonverbal communication and social scores. Variation in these phenotypes was explained by additive genetic, dominant genetic, and unique environmental factors with no evidence for shared environmental factors. Broad heritability estimates were higher for nonverbal communication (45%) than social interaction (28%). Nonverbal communication and social scores were partially accounted for by the same underlying genetic and environmental factors. Gender differences were not supported. These results add to information on familial resemblance of these symptom domains based on correlational methods, and this study is one of the first to apply behavioral genetic modeling to a PDD population. The results have implications for molecular genetics as well as treatment.

Introduction

Pervasive developmental disorders (PDDs) such as autism involve impairment in social interaction, delayed and/or stereotyped communication, and restricted or repetitive behaviors and interests (American Psychiatric Association, 2000). Risk for autism is 60 to 100 times

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higher for siblings of affected individuals than the general population (see Rutter, et al., 1999 for review). In addition, concordance rates for monozygotic (MZ) twins range from 60% to 90% as compared to 2% to 10% for dizygotic (DZ) twins and siblings; it has been concluded that the heritability of autism is over 90% (Rutter et al., 1999). However, despite this strong genetic influence, research suggests significant genetic heterogeneity as well as the influence of environmental factors (Andres, 2002). Studies of possible candidate genes for autism thus far have been remarkably inconsistent (Bacchelli & Maestrini, 2006).

Several different strategies have been utilized in an attempt to select homogenous groups for molecular genetic studies, including choosing participants based on characteristics such as the presence of language delay (e.g. Spence et al., 2006) or a clear history of developmental regression (e.g. Molloy et al., 2005). However, it is unclear whether characteristics that have been used for sample selection are influenced more by genetic or environmental factors. Power would be strengthened if subgroups were chosen empirically—based on behavioral genetic analyses suggesting that variation in a particular characteristic has a strong genetic basis. One potential strategy that, to our knowledge, has not been employed, is selecting participants based on treatment response. It is clear that some children respond well to intensive behavioral treatment and that this intervention impacts the core features of autism (e.g., Birnbrauer & Leach, 1993; Eikeseth et al., 2002; Sallows & Graupner, 2005; Sheinkopf & Seigel, 1998); however, it is equally clear that the success of behavioral treatment in altering the developmental trajectory of children with autism is *not* universal (e.g., Goin-Kochel et al., in press; Rogers, 1998; Lovas, 1987). A possible explanation is that responders and non-responders have different autism etiologies—a premise that assumes that the factors contributing to the development of autism are the same as those regulating responsiveness to treatment. Clarifying whether symptom characteristics found to predict treatment response are largely genetic would begin to answer this question and possibly suggest a more fruitful strategy for molecular genetic subject selection. Two core symptom characteristics have recently been found to predict treatment response (Sallows & Graupner, 2005). Specifically, fewer pretreatment nonverbal communication deficits, as measured by the *Autism Diagnostic Interview—Revised* (ADI; Lord et al., 1994), were positively related to improvement in both IQ and social skills following treatment, and higher pretreatment levels of social responsiveness (lower scores for ADI social dysfunction) predicted post-treatment gains in IQ (Sallows & Graupner, 2005).

Previous studies of familial resemblance for symptom domains among multiplex families have been inconsistent (e.g., MacLean et al., 1999; LeCouteur et al., 1996; Spiker et al., 1994). Three studies have examined familial resemblance of symptom domains as measured by ADI social and nonverbal communication total scores (Kolevzon et al., 2004; MacLean, et al., 1999; Silverman, et al., 2002). Two of these studies did not find evidence of significant sibling resemblance in the ADI social domain among affected siblings (Silverman et al., 2002; MacLean et al., 1999). On the other hand, siblings significantly resembled each other in ADI nonverbal communication domain, with an intra-class correlation (ICC) coefficient of 0.19 for a sample size of 457 (Silverman et al., 2002) and .39 for a sample size of 94 (MacLean et al., 1999). A study that included 33 MZ twins with autism also found evidence for familiarity of the ADI nonverbal domain (ICC = .56; Kolevzon, et al., 2004). Kolevzon et al.'s (2004) study was also the only study to date to find evidence for familial resemblance between siblings with autism in the social domain, with an ICC of .75 for MZ twins (Kolevzon et al., 2004).

The present study expands upon this previous work by using behavior genetic analyses based on structural equation modeling (SEM) to examine the sources of variation in ADI nonverbal communication and social scores among affected siblings with PDD. SEM has many advantages, including evaluating the goodness-of-fit of alternative models as well as parameter estimation and significance testing (Posthuma & Boomsma, 2005). To our knowledge, only

three previous studies (Constantino et al., 2006; Sung et al., 2005; Ronald et al., 2006a) applied behavior genetic modeling to PDD-related questions. These studies all used questionnaire data to determine the etiology of autistic traits in the general population (Constantino et al., 2006; Ronald et al., 2006a; Sung et al., 2005). This information may not be generalizable to clinically affected individuals with autism or PDD, given evidence that the domains of functioning affected in autism are more interdependent in autism than in the general population (Dyck, Piek, Hay, Smith, & Hallmayer, 2006).

The present study aimed to clarify the genetic and environmental influences on two symptoms domains measured by the gold-standard structured clinical interview for autism in a population of clinically diagnosed individuals. The structural equation modeling program *Mx* (Neale et al., 2003) was used to analyze data from twins and siblings with PDD diagnoses who participated in the Autism Genetic Resource Exchange (AGRE). It was hypothesized that: (1) the resemblance of siblings affected with PDD in social impairment and nonverbal communication deficits would be best explained by genetic factors; (2) the contribution of genetic and environmental factors would vary by gender; and (3) nonverbal communication and social scores would be explained, in part, by the same underlying genetic and environmental factors.

Method

Participants

All participants were part of the AGRE collection, which is a nationally available, genetically informative sample of individuals with PDDs. AGRE advertisements target multiplex families, but families with a single affected individual are also accepted. Participants were enrolled in AGRE if they had a physician/specialist diagnosis of Autistic Disorder, Asperger's Disorder, or PDD Not Otherwise Specified (PDD-NOS). Diagnoses were confirmed by AGRE staff using the ADI and the *Autism Diagnostic Observation Schedule* (Lord et al., 2000), and 90% met criteria for Autistic Disorder. All available confirmed cases were selected from AGRE for participation in the current study if they were 18 years old or younger ($M = 7$, $SD = 3.4$). The sample included 676 families (943 male siblings and DZ twins, 257 female siblings and DZ twins, 76 male MZ twins, and 18 female MZ twins). The sample was predominantly Caucasian (76% Caucasian, 13% unknown, 8% more than one ethnicity, 2% Asian, 2% African American, <1% Native Hawaiian/Pacific Islander).

Level of functioning among participants was variable, which is representative of the PDD population at large. The mean standard score (SS) for estimates of nonverbal IQ based on the *Ravens Progressive Matrices* was average ($M = 99$; $SD = 20$), but the mean SS for receptive vocabulary based on the *Peabody Picture Vocabulary Scale-III* was low average ($M = 82$; $SD = 27$). Scores on the *Vineland Scales of Adaptive Behavior* indicated that most participants had significantly delayed independence skills (Communication SS: $M = 60$, $SD = 26$; Socialization SS: $M = 56$, $SD = 18$; Daily Living SS: $M = 47$, $SD = 23$; Motor Skills SS: $M = 77$, $SD = 20$); *Vineland* means for this sample were very consistent with published *Vineland* supplemental norms for autism (Carter et al., 1998).

Measures

Parents were interviewed with the *Autism Diagnostic Interview - Revised* (ADI; Lord et al., 1994), a standardized caregiver interview for the diagnosis of PDDs. Item scores were summed in the areas of communication, social interaction, and restricted, repetitive behavior, representing dysfunction in these areas. The ADI has adequate internal consistency (Cronbach's alpha .69 – .95) and interrater reliability (mean kappa of .70; Lord et al., 1994). ADI total scores for the social interaction and nonverbal communication ADI subscales were

used in the current study because they correlate with behavioral treatment response. Items were scored based on the ADI-defined “most abnormal” period of four to five years old, with two exceptions that were scored based on whether they were *ever* present (use of other’s body and inappropriate facial expressions).

Procedure

All data were obtained through AGRE; the authors had no contact with family members or confidential information. AGRE used trained ADI raters who traveled to the families’ homes to conduct the interviews. All AGRE raters were initially checked for reliability and were subsequently checked on a regular basis by an experienced ADI trainer. The interview, with parental permission, was video taped as a quality control performance check.

The SAS computer program was used to recode and organize the data set to be consistent with requirements for behavior genetic modeling. Specifically, all full siblings were identified and the data were reorganized by family identification numbers. In addition, each family was assigned a zygosity code that indicated whether the family had non-twin siblings only, MZ twins, DZ twins, triplets, or quadruplets.

Analyses

Behavior genetic analyses are predicated on the fact that MZ twins share 100% of their genes and DZ twins/siblings share 50% of their genes, on average. Therefore, MZ twins are expected to correlate 1.0 for the cumulative effects of genes (e.g., additive genetic factors, represented by the letter A), whereas this correlation is expected to be 0.5 for DZ twins/siblings. The corresponding coefficients for dominant genetic factors (D) are 1.0 for MZ twins and 0.25 for DZ twins. Environmental effects that are shared among family members (C), and by definition correlated 1.0 between both MZ and DZ twins/siblings, have the effect of making the MZ and DZ/sibling phenotypic correlations more similar to each other. Finally, unique environmental factors (E) that are specific to an individual are, by definition, correlated 0.0 between twin/siblings pairs; thus, they do not contribute to the twin/sibling correlations. When the MZ correlation is greater than the DZ/sibling correlation, the influence of additive genetic factors is suggested. When the MZ correlation is greater than twice the DZ/sibling correlation, dominance genetic factors are expected to contribute to the variance, whereas common environmental factors are expected when the DZ correlation is greater than half of the MZ correlation. When two or more phenotypes are being considered, there is also the possibility of the same underlying factor influencing more than one trait (e.g. common factors).

Structural equation modeling was used to quantify the contribution of these underlying latent variables (A, C, D, and E) to the phenotype based on the variances and covariances within and between twin/sibling pairs. Models were fit to the raw data using maximum likelihood estimation in *Mx* (Neale et al., 2003). We tested for qualitative sex effects by comparing the fit of a model where the covariance between sex pairs was free to vary to the fit of a model in which the covariance was restricted to 0.5. The possibility of quantitative gender effects was tested by comparing the fit of models where parameter estimates are free to vary by gender to the fit of models where they are constrained to be equal between genders. Bivariate Cholesky models also explored the degree of overlap between liability factors (e.g. the possibility of common factors), by testing the degree to which the same genetic and environmental factors influenced both social interaction and nonverbal communication. Nested models were compared with a likelihood ratio test distributed as a chi-square change statistic (χ^2_6), with the degrees of freedom being the difference in degrees of freedom between two models; a χ^2_6 with a non-significant probability value ($p > .05$) indicates that the submodel does not fit the data significantly worse and has superior parsimony compared to the full model. Models were also evaluated in terms of Akaike’s Information Criterion (AIC); more negative AIC values indicate

a better fit. The precision of parameter estimates was further evaluated by calculating 95% confidence intervals.

Results

The polychoric correlations between MZs and DZ/siblings for the nonverbal communication and social dysfunction phenotypes are shown in Table 1. MZ correlations were greater than twice the DZ/sibling correlations for both genders and phenotypes. This suggested a strong genetic influence for these traits, possibly including dominance, and limited, if any, common environmental effects. The MZ correlations of less than 1.0 suggested unique environmental influences were also present. Twin correlations were higher for males than females, particularly for DZs/siblings, though this difference was not statistically significant. The comparison of cross-twin/sibling and within-twin/sibling cross-trait correlations for MZ and DZ twins provides preliminary information on the potential common etiological influences for the two phenotypes. The within-twin/sibling, cross-trait correlation (or the phenotypic correlation) between nonverbal communication deficits and social dysfunction was .70 for males and .75 for females. Comparisons of cross-twin/sibling, cross-trait correlations between MZs and DZs/siblings (e.g. correlation between one twin/sibling's score on nonverbal communication deficits and his or her co-twin/siblings score on social dysfunction) may indicate whether common etiological influences between the two phenotypes are genetic and/or environmental. For males, the MZ:DZ/sibling cross-twin/cross-trait ratio for nonverbal communication deficits and social dysfunction was .39 : .05 and for females it was .34 : .00. The much stronger cross-twin/cross-trait correlation for MZs than DZs/siblings suggests a genetic basis for covariation.

Consistent with the correlational patterns, preliminary univariate analyses indicated that shared environmental effects did not contribute significantly to either phenotype, but both additive and dominant genetic factors did. Univariate analyses also indicated that qualitative sex differences for nonverbal communication and social scores were not significant. However, results on quantitative sex differences suggested that the magnitude of genetic effects was similar between males and females but that there might be a difference in the magnitude of unique environmental effects between genders (results available upon request).

Bivariate Cholesky analyses were conducted for nonverbal communication and social scores (see Table 2). Given that univariate analyses did not indicate the presence of shared environmental effects, bivariate ACE models were not tested. The full ADE model that allowed all parameter estimates to differ between males and females was compared to the saturated model and did not fit significantly worse. Subsequent nested models were compared to the full ADE model with gender effects (model #2). The AE model with gender effects (#3) resulted in a significantly worse fit than model #2, implicating the importance of dominant genetic effects. The E model (#3), which tested the significance of all genetic effects, also did not fit the data. The subsequent analyses tested the significance of gender effects by constraining the ADE model parameters to be equal between genders. Model 5 equated only genetic factors between males and females while model 6 equated all parameters between males and females. Although neither model resulted in a significant loss in fit, model 6 was superior in terms of parsimony. The last two models, 7 and 8, tested the significance of common genetic (additive and dominance) and environmental factors, respectively, between nonverbal communication and social scores and were compared against the best fitting model thus far (#6). Both model 7 and model 8 resulted in a significant loss in goodness-of-fit compared to model 6, which suggested the presence of *common* additive and dominant genetic factors, and unique environmental factors that impact both nonverbal communication deficits and social dysfunction.

Figure 1 shows the best fitting model (model 6), which was the same for males and females and included both unique ADE factors for each phenotype as well as common ADE factors. Based on the best fitting model, broad heritability estimates are 45% and 28% for nonverbal communication and social scores, respectively. Unstandardized parameter estimates and 95% confidence intervals are reported in Table 3. The confidence intervals for both unique and common additive genetic factors included zero in the best-fitting model. This suggests that these paths were not significantly contributing to the overall fit of the model. However, given the significance of the dominance parameters, additive genetic parameters were kept in the models, as models including dominance without additive genetic effects are biologically not plausible. All other paths were significant based on confidence intervals.

Discussion

This study used behavioral genetic structural equation modeling to explore the etiology of nonverbal communication and social dysfunction data from individuals 18 years old or younger who participated in AGRE and had a PDD diagnosis. The analyses suggested that common environmental factors were not influential and that the variation between siblings/twins was better explained by genetic and unique environmental factors for both phenotypes. Dominant genetic effects were stronger than additive genetic effects. Broad heritability estimates were 45% and 28% for nonverbal communication deficits and social dysfunction, respectively. The role of genetic factors is consistent with findings that PDDs themselves are highly genetic (Rutter et al., 1999) and adds to results from correlational studies on the familiarity of specific characteristics. The strong contribution of unique environmental factors, particularly for social interaction scores, highlights the potential importance of treatment.

Unfortunately, because this was only the fourth study to use behavior genetic modeling with a sample that included individuals with PDDs, there is limited basis for comparison of our heritability estimates. The other studies were interested in overall liability of autistic traits and symptoms in the general population; dependent variables were based on parent report questionnaire data; and they included primarily unaffected and subclinical individuals (Constantino & Todd, 2003; Ronald et al., 2006a; Sung et al., 2005). In contrast, the present study focused on only autism-affected individuals and examined liability of clinical characteristics relevant to treatment response from a gold-standard interview measure. In addition, Sung et al.'s (2005) study did not include twins, Ronald et al.'s (2006a) study only included 44 MZ twins with unconfirmed PDD, and Constantino and Todd's (2003) study included 13 twins (no report of how many were MZ) with unconfirmed PDD, whereas our study was based on 94 MZ twins with confirmed PDD. Therefore, differences between studies can be attributed to different aims and thus differing methodologies, as well as power. Sung et al. (2005) found much lower heritability estimates for their scales that were most similar to our nonverbal communication and social measures. This is expected, given that their focus was only on siblings and unaffected family members. Our results are more similar to those in Ronald et al.'s (2006a) study, which also indicated no evidence for shared environmental influences yet somewhat higher heritability estimates for different measures of social and communication impairment (which included impairment in the verbal domain). Constantino and Todd (2003) differed from both our study and Ronald et al.'s (2006a) study in that they found evidence for shared environment for total social responsiveness scores.

Our analyses also tested the degree to which the phenotypes were influenced by the *same* or *unique* genetic and environmental factors. Results indicated a very strong phenotypic correlation between nonverbal communication and social scores that was explained by both common genetic and environmental influences. This finding differs from Ronald et al.'s (2006a) study, which found low correlations between areas of autistic traits and limited evidence for shared etiological factors. This difference may be explained by Ronald et al.'s

(2006a) use of mostly unaffected individuals, given that cognitive, language, and social abilities tend to be more closely correlated in children with PDD than the general population (Carpenter et al., 2002; Dyck et al., 2006). Ronald et al. (2006b) recently completed an additional analysis of their data to examine individuals at the extreme who showed many autistic traits. These results were more consistent with our current findings, in that they found a stronger relationship between domains (correlations of .58 for males and .51 for females) as well as some genetic overlap, in their more extreme sample than the earlier sample comprised of primarily unaffected individuals (Ronald et al., 2006a, 2006b). The fact that our data produced an even stronger correlation in an even more extreme sample (clinically diagnosed individuals), with significant evidence for common genetic and unique environmental influences between social interaction and nonverbal communication, further suggests differences in the interrelatedness and etiology of autistic symptom domains in clinically affected versus unaffected individuals.

Results indicated that the most parsimonious and best-fitting explanation of the data did not include gender differences. This should be considered preliminary because of the fairly small number of female MZ twins, which might have limited our power to detect small differences. However, the pattern of correlations was similar for males and females, so the lack of significant gender effects is consistent with the pattern of data. Our results are different from those in one study, which found that equating genders significantly reduced the fit of genetic models for autistic traits; yet, that study had an even smaller number of female MZs with PDDs and also measured the traits in unaffected individuals (Ronald et al., 2006a).

Our correlational results can be compared to three previous studies that tested ICCs on the same scales among multiplex families. The magnitude of the relationship between MZ twins for ADI nonverbal communication scores found in this study (.57 for males and .47 for females) corroborates a study of 33 MZ twins that found a nearly identical ICC for this same measure (.56; Klevzon et al., 2004). The MZ correlation for ADI social dysfunction was somewhat lower compared to Klevzon et al.'s (2004) findings. The low correlation between DZ twins and siblings found in our study for ADI social scores is consistent with previous research that has found this measure to have low, non-significant correlations between affected siblings (MacLean et al., 1999; Silverman et al., 2002). Our correlations for ADI nonverbal communication scores among affected siblings/DZ twins were somewhat lower than previous studies that found ICCs of .39 and .19 for sample sizes of 94 and 457 respectively, compared to our correlations of .12 for males and .05 for females.

Limitations

Although this study is one of the largest to date of individuals with PDDs, the number of MZ twins was still relatively small for structural equation modeling. Therefore, there was limited power, particularly for gender comparisons. This may be why heritability estimates from the modeling were somewhat lower than would be expected based on the correlation patterns between MZ twins and DZ twins/siblings. In addition, variance for ADI scores was restricted, given that all participants exceeded certain cut-offs on these scales to meet criteria for a PDD. Although restricted variance can reduce power by reducing effect size, it also means that even small to moderate effects are noteworthy.

Aspects of the sample should be considered when interpreting and generalizing findings. The authors recognize that use of a selected sample (e.g. selecting children with diagnoses of PDD as opposed to an unselected population sample) when conducting this type of behavior genetic analysis limits generalizability of findings; estimates can be generalized to the population of children with PDDs/autism but would be biased if generalized to the general population. This is consistent with the study aim to explore the genetic and environmental underpinnings of clinical symptom domains in affected individuals with autism. Studies focused explicitly on

clinically diagnosed individuals are important given accumulating evidence of different etiologic and phenotypic patterns regarding social interaction and communication development in clinically diagnosed individuals. It should also be taken into consideration that the sample included predominantly multiplex families.

We were unable to account for some potential covariates. Given power considerations and the complexity of the data analyses, age corrections were not implemented. The ADI scores were based on responses for when the participant was four or five years old, but there might have been differences in recall of parents based on the participant's current age. Finally, AGRE did not collect data on whether a participant had undergone treatment.

Implications

Despite the aforementioned limitations, this study has several important strengths. We employed a methodology fairly new to PDD studies; and it is, to our knowledge, one of only five studies to investigate phenotypic congruence among AGRE siblings (Constantino et al., 2006; Goin-Kochel, Mazefsky, Riley, & AGRE, under review; Kolevzon et al., 2004; Silverman et al. 2002) compared to over 85 AGRE-based molecular studies. Phenotypic studies are critical in order to clarify how varying patterns of genetic and environmental inheritance correspond to different phenotypes among the population. Such studies are necessary so that more informed, empirically based decisions can be made for sample selection in molecular studies by choosing stratification characteristics with a large genetic influence. Our study begins to address whether ADI nonverbal communication and social domains may be an important endophenotype for molecular genetic studies by demonstrating that the etiology of these phenotypes involves genetic factors as well as the presence of unique environmental factors. Results indicate that nonverbal communication skills may be more genetically driven, and therefore a better stratification choice than social interaction.

These phenotypes are also important because of their relation to treatment response (Sallows & Graupner, 2005). Developing a better understanding of etiological factors related to treatment-response predictors is critical, given that poor post-treatment outcomes are correlated with poor intake measures, suggesting that there is a group of children with autism for whom intensive behavioral treatment is not effective on its own. Developing a better idea of etiological factors and characteristics related to treatment response will also help improve decisions regarding intervention type. The large (72%) unique environmental influence on social interaction that was found in this study suggests that treatment may have a relatively greater impact on social skills than nonverbal communication which is more genetically driven.

Future studies can build on our results by replicating them in samples that include more MZ twins and females. Next steps should also include genetic analyses of subgroups of children who have participated in various treatment programs and have an identified response pattern.

Acknowledgments

We gratefully acknowledge the AGRE Consortium* resources and families. AGRE is a Cure Autism Now program and is supported, in part, by grant MH64547 from the NIMH to Daniel H. Geschwind (PI). Dr. Mazefsky was supported by a National Research Service Award from the NIH, T32MH-20030 (PI MC Neale). We also thank Dr. Michael Neale for this consultation regarding the statistical analyses in this manuscript.

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Figure 1. Standardized variance components expressed as the percent of total variance for each Autism Diagnostic Interview-Revised domain. A = Additive Genetic; D = Dominant Genetic; E = Unique Environmental.

Table 1

Correlations

Variable	MZ		DZ/Sib	
	Males	Females	Males	Females
ADI Nonverbal Communication	.57	.47	.12	.05
ADI Social Dysfunction	.47	.42	.11	.01

Table 2

Fit Statistics for Bivariate Analysis of ADI Nonverbal Communication and Social Dysfunction Total Scores for Males and Females

Model	Model Fit			Model Comparison			
	-2lnl	df	AIC	Model Compared to	χ^2_6	6 df	p value
1. Saturated Model	6247.95	2530	1187.94				
2. ADE with sex differences (Full model)	6264.12	2543	1178.12	1	16.17	13	.240
3. AE with sex differences	6286.48	2549	1188.48	2	22.36	6	.001
4. E with sex differences	6321.15	2555	1211.14	2	57.03	12	.000
5. ADE, with A & D equated males and females	6276.46	2549	1178.46	2	12.35	6	.055
6. ADE, No sex differences	6279.22	2552	1175.22	2	15.09	9	.088
7. ADE model, no sex differences, no Common A or D, Common E only	6291.64	2554	1183.64	6	12.42	2	.002
8. ADE, no sex differences, no common E, Common A and D	6339.19	2551	1237.19	6	59.98	1	.000

Note. Best fitting model is in bold. Sex differences models allowed the estimates to vary by gender.

Table 3
Unstandardized Estimates of Additive Genetic (A), Dominant Genetic (D), and Unique Environmental (E) Influences for ADI Nonverbal Communication and Social Dysfunction Total Scores, With 95% Confidence Intervals in Parentheses

Nonverbal Communication			Social Dysfunction			Common influences on Both Phenotypes		
	Males	Females	Males	Females	Males	Males	Females	
Estimates from the full ADE model, with males and females free								
A	.00 (.00 – .29)	.08 (.00 – .53)	.20 (.09 – .35)	.08 (.00 – .53)	.00 (.00 – .15)	.06 (.00 – .39)		
D	.44 (.25 – .58)	.58 (.07 – 1.02)	.16 (.00 – .34)	.38 (.03 – .96)	.26 (.04 – .43)	.46 (.05 – .75)		
E	.48 (.35 – .71)	.48 (.32 – .71)	.57 (.39 – .77)	.76 (.35 – .98)	.36 (.20 – .51)	.46 (.25 – .80)		
Estimates from the best fitting model, with males and females equal for all parameters								
A	.01 (.00 – .19)		.16 (.00 – .35)		-.02 (-.06 – .15)			
D	.46 (.13 – .64)		.24 (.01 – .56)		.33 (.04 – .50)			
E	.51 (.35 – .71)		.59 (.40 – .80)		.39 (.24 – .57)			