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Running Head: A TWIN STUDY

A twin study of autism symptoms in Sweden

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Abstract

This study aimed to empirically identify the number of factors underlying autism symptoms -- social impairments, communication impairments, and restricted repetitive behaviors and interests -- when assessed in a general population sample. It also investigated to what extent these different autism symptoms are caused by the same or different genetic and environmental influences. Autistic symptoms were assessed in a population-based twin cohort of >12,000 9- and 12-year-old children by parental interviews. Confirmatory factor analyses, principal component analyses and multivariate structural equation model-fitting were carried out. A multiple factor solution was suggested, with nearly all analyses pointing to a 3-factor model for both males and females and at both ages. A common pathway twin model fit the data best, which showed that there were some underlying common genetic and environmental influences across the different autism dimensions, but also significant specific genetic effects on each symptom type. These results suggest that the autism triad consists of three partly independent dimensions when assessed in the general population, and that these different autism symptoms, to a considerable extent, have partly separate genetic influences. These findings may explain the large number of children who do not meet current criteria for autism but who show some autism symptoms. Molecular genetic research may benefit from taking a symptom-specific approach to finding genes associated with autism. Keywords: autism, triad, twin, behavior, genetics.

Autism spectrum disorders (ASDs) are currently defined by a triad of symptoms: social impairments (SIs), communication impairments (CIs), and restricted repetitive behaviors and interests (RRBIs). Family studies of individuals with ASD have reported that unaffected family members often show some autistic symptoms (termed the ‘broader autism phenotype’) but do not always show all three types of autistic symptoms together, that is, autistic symptoms segregate out in family members, suggesting different autistic symptoms may have different familial influences (1). Recent population-based twin studies have reported that each of these three sets of features is highly heritable but appears to be caused by largely different genetic influences (2).

This evidence from family and twin studies, combined with the lack of theories in cognitive psychology that can explain all three parts of the triad together, has been cited in support of the hypothesis that autism symptoms are largely ‘fractionable’(2). It has been proposed that it might be time for researchers to give up on trying to find single explanations behind the diverse symptoms in autism and focus efforts on identifying explanations for each set of symptoms (3-5).

The fractionable autism triad hypothesis is based on the idea that SIs, CIs, and RRBIs are partly independent dimensions of behavior, and ASDs occur when children show extreme forms of these problems. A contrasting hypothesis is that all three sets of autistic symptoms in the triad are part of a single underlying dimension. Many factor analytic studies have explored whether autistic symptoms fall into one or multiple statistical factors (for reviews see 2, 4). The majority of factor analysis studies report that multiple factors underlie autistic symptoms, but there are some exceptions, most notably two studies on the Social Responsiveness Scale, which report a single principal component (6, 7). A recent factor analysis of parent and teacher ratings of 730 children with Pervasive Developmental Disorder using items that directly matched the DSM criteria reported that a

three-factor solution provided the best fit to the data (8).

To date, most twin studies on this issue have been based on a UK twin sample assessed in middle childhood at ages 7 and 8 on measures of autistic traits (with one exception, see 12). These previous twin studies have reported modest to moderate genetic overlap across different parts of the autistic triad in the general population (9), in extreme-scoring groups (10), and in children with suspected ASDs based on a parent interview (11, 12). These findings suggest that while some genetic influences may confer risk for developing all the symptoms of the autistic triad, others are specific to particular symptoms.

The present paper attempts to test the hypothesis of a fractionable autism triad at the phenotypic level using factor analysis, and at the etiological level using multivariate structural equation twin model-fitting. Data were collected from a Swedish population twin sample. In contrast to the previous twin studies, which used ‘trait’ measures, the present study employed a measure that closely reflected the current diagnostic criteria for autism (13). Our prediction, based on the results of previous factor analyses, was that we would identify three factors underlying autism symptoms. We expected to find genetic effects broadly influencing symptoms across the autism triad but also symptom-specific genetic effects.

Materials and Methods

Participants

The Child and Adolescent Twin Study in Sweden (CATSS) is a nation-wide cohort that focuses on all Swedish twins turning 9 or 12 years since July 2004. CATSS has an 80% response rate, making it a highly representative population sample. Data were available on 12446 children: N = 5944 9-year-olds and 6496 12-year-olds (the two samples

were independent). Data were collected in the month of the child's birthday. 51% of the sample were male. One hundred and thirty children (76 males, 54 females) were excluded from the analyses because they had a known brain injury (N = 118) or a chromosomal syndrome (N = 12).

For 281 twin pairs, DNA was used to determine zygosity based on a panel of 48 SNPs derived for zygosity analyses. For the remaining twins, an algorithm was used based on 5 items concerning twin similarity and confusion (14). In over 85% of the sample, parental interviews were conducted with the twins' mothers; no significant differences were found between mother and father ratings (17).

Measure

Parents were interviewed with the Autism – Tics, AD/HD, and other Co-morbidities inventory (A-TAC; 15, 16), a telephone interview designed for large-scale epidemiological research in neuropsychiatry. Thirteen items were used to assess autistic symptoms. Items were scored “1” (“yes”), “0.5” (“yes, to some extent”) and “0” (“no”).

The ASD items in the A-TAC have shown good test-retest reliability (.83-.94) and have been shown to discriminate clinically diagnosed ASDs (sensitivity = .89, specificity = .78, positive predictive value = .68, area under ROC curve = 0.88) when administered by laymen over the phone (15). All 13 items showed good internal consistency in the CATSS data (Cronbach's alpha was .81 at both ages). A total of 1.43% of the sample (78% of whom were male) were screen positive for an ASD using the A-TAC cut-off of ≥ 4.5 on the total score (see 17). Based on parent tick box information, a total of 0.7% of the sample (N = 87) were reported to have an ASD diagnosis and these children had elevated A-TAC scores, with mean scores of 5.52, 5.36, 4.03, and 4.44 standard deviations above the population mean for the total score, SIs, CIs and RRBIs, respectively. Together these data

support the validity of the A-TAC measure and suggest that the sample is representative of the general population.

Analyses

Factor analyses. The factor structure of the thirteen ASD items was explored using principal component factor analysis. The Kaiser–Guttman criterion for factor extraction was applied, that is, number of factors was selected as the number of factors with eigenvalues of >1 .

Next, confirmatory factor analyses (CFA) were conducted in the Mplus software version 4.0 to explore the adequacy of fit for the models suggested from the principal component factor analysis (18). A robust weighted least squares estimator (WLSMV) was used, an estimation technique appropriate for categorical data (18).

Phenotypic Analyses. Phenotypic correlations were employed to explore the strength of the relationship between the autism subscales. Correlations were estimated using a saturated model in the *Mx* program (see below), and mean and variance differences by sex, zygosity, age and twin order were evaluated in the saturated model.

The number of children who scored at least 1 on each subscale (i.e. either at least one item was rated ‘yes’ or at least two items were rated ‘yes, to some extent’) were identified and the degree of symptom overlap in these children was explored.

The Twin Design. The twin design is based on comparing the within-pair similarity of monozygotic (MZ) and dizygotic (DZ) twins on a measure or trait of interest (19). The design is based on the assumption that MZ twins share all of their DNA and DZ twins share on average half of their DNA.

Heritability refers to the proportion of variation of a trait in a population explained by genetic influences. ‘Environmental influences’ in the twin design refer to all variance that is not explained by genetic influences, and is split into two types, shared and

nonshared. Shared environment refers to experiences that make children growing up in the same family similar; nonshared environment refers to environmental influences that make children growing up in the same family different (19).

Twin Correlations. Twin similarity coefficients (intraclass correlations; 20) were used for an initial examination of the twin data to compare MZ and DZ twin similarity, and were estimated using the *Mx* program (21). A trait is under additive genetic influences (A) when twin similarity is greater for MZ than DZ twins. Shared environment (C) is indicated if DZ twin correlations are greater than half the MZ twin correlations. Nonshared environment (E) is indicated by the extent to which MZ correlations are less than unity. When MZ twins are more than twice as similar than DZ twins, this suggests nonadditive genetic influences (D) such as dominance (interaction of two alleles at the same locus) or rater contrast effects (as described in *Model-fitting Analyses*).

To evaluate genetic and environmental sources of covariance across variables, cross-trait cross-twin (CTCT) correlations were calculated. CTCT correlations examine the covariance between twin 1 on variable 1 and twin 2 on variable 2, separately for MZ and DZ twins.

Model-fitting Analyses. Prior to model-fitting, scales were corrected for sex and interview order using regression. Multivariate genetic models decompose the variance of each phenotype and the covariances between phenotypes into A, C or D, and E. Three standard multivariate models were used to investigate the sources of covariance between the autism subscales: the Cholesky model, the independent pathway model, and the common pathway model. The *Cholesky decomposition model* is the most ubiquitous multivariate twin model; it is based on triangular decomposition and demonstrates the degree to which covariance is explained by genetic and environmental influences. The *independent pathway model* includes etiological influences shared between the variables as

well as etiological influences specific to each phenotype. Finally, the *common pathway model* is the most constrained of the three and hypothesizes that the common variation between behaviors is due to a single underlying and unmeasured latent factor. This latent factor itself can be investigated in terms of genetic and environmental sources of variance. The model also includes specific genetic and environmental sources on the individual measured phenotypes.

In accordance with the assumptions of the classic twin design, A latent variables were fixed to correlate 1.0 and .5 for MZ and DZ twins, respectively; C latent variables were fixed to correlate 1.0 for both MZ and DZ twins (because all twins in the sample were reared in the same family); D latent variables were fixed to correlate 1.0 and .25 for MZ and DZ twins, respectively; and E latent variables were fixed to correlate 0 (21).

Each of the three multivariate models was run with the following combination of variance components: ACE, ADE, AE, ADEs and AEs. “s” refers to another parameter that can be added to the model, representing a form of phenotypic interaction between twins(21). The ACE model is a standard twin model and as such was tested, but the ACEs model was not run in addition to this because the majority of twin correlations suggested that there were no shared environmental effects and negative sibling interaction parameters were present in our data. Therefore the ACEs model was not considered a suitable model to test. When modelling parent report data, a negative phenotypic interaction often occurs because there is a contrast effect in the parental ratings of their behavior (i.e., parents inadvertently exaggerate behavioral differences between the children). Contrast effects are implicated when DZ variance is significantly greater than MZ variance.

Models were fit to raw data using the Mx structural equation modelling software (21). This approach does not yield a χ^2 for assessing the fit of the model, however, the fit of a model can be assessed by calculating the difference between the negative log-likelihood

(-2LL) of the model and that of a saturated model (i.e., a model in which the variance/covariance structure is not estimated and all variances and covariances for MZ and DZ twins are estimated). The difference in -2LL is asymptotically distributed as χ^2 with degrees of freedom equal to the difference in the number of parameters in the full model and that in the saturated model. Akaike's information Criterion (AIC; 22) and Bayesian Information Criterion (BIC; 23) fit indices were also used to compare the fit of alternative models.

Results

Factor Analysis

Principal components analysis of the thirteen A-TAC autism symptom items showed that there were consistently three factors that had eigenvalues >1 . This three factor solution was found when the data were analyzed together, for males and females separately, at ages 9 and 12 separately, and with either Oblimin or Varimax rotations. The only exception was for males at age 12, for whom only two factors had eigenvalues >1 . Table 1 presents the loadings of the items on each factor using Varimax rotation on all the data (combining ages and genders). The items loading on the first factor all represented questions assessing difficulties with social interaction; this factor explained 33% of the variance in all the items. The 'make-believe' item, which falls in the CI domain in diagnostic criteria, did not load with the other communication items but loaded onto factor 1, with the four SI items. The RRBI items loaded most heavily on factor 2 (explaining 9% of variance) and the CI items loaded most heavily on factor 3 (explaining 8% of variance).

Insert Table 1

Next, confirmatory factor analysis was conducted to explore the fit of the suggested three-factor model. The fit indices suggested an excellent fit of this model (comparative fit index (CFI) = .96; Root Mean Square Error of Approximation (RMSEA) = .02). We also considered a one-factor model. The results showed that the three-factor model had a significantly better fit than this model ($\Delta\chi^2(3, n = 12327) = 310.36.40, p < .001$).

Scale Construction

Items were divided into three scales based on the results of the factor analyses. The items in the SI, RRBI and CI subscales (5 items, 5 items and 3 items, respectively) relate directly to the items in Table 1 with underlined loadings for factors 1, 2, and 3, respectively. Items in each of the scales were summed and converted into scores as a proportion of the total possible score given the number of items completed (which was required to be more than half). The internal consistencies of the SI, CI and RRBI subscales, expressed as Cronbach's alpha, were .74, .54 and .71 respectively. All scales were positively skewed and therefore inverse-transformed prior to the model-fitting. Table 2 presents descriptives for the subscales.

Insert Table 2

Phenotypic Relationship

Table 2 presents the phenotypic correlations between the three autism subscales. All correlations were positive and significant ($p < .01$), ranging from .15-.42. Table 3 presents the prevalence of autism symptoms, defined as raw scores of ≥ 1 on each subscale, alone and in combination with other symptoms.

Insert Tables 3 and 4

Data Descriptives

Means could be equated without a significant decrease in the saturated model fit for twin 1 and twin 2, for males and females, and for age 9 and age 12 data, but they could not be equated across MZ and DZ twins. Variances could be equated for twin 1 and twin 2 but could not be equated across gender, zygosity or age. DZ variance was significantly larger than MZ variance for SIs and RRBI, and MZ variance larger than DZ variance for CIs, for both genders ($p < .05$), and therefore sibling interaction paths were included in the models (see below).

Twin Correlations

Univariate twin correlations are presented on the diagonal for each zygosity group in Table 4. MZ twins were rated as more similar than DZ twins on all scales at both ages, suggesting significant genetic influences. In most cases, DZ correlations were half or less than half the MZ twin correlations, suggesting that there were no shared environmental influences on the subscales and that there were nonadditive genetic influences on the scales or rater contrast effects present in the data (because both have the effect of decreasing the DZ similarity to less than half the MZ similarity). MZ correlations were consistently less than unity suggesting that nonshared environment, which includes any variance due to measurement error, influenced all subscales.

Modest differences between male and female same-sex twin correlations suggested that there were some quantitative sex differences, that is, the degree to which genetic and environmental influences affect these traits may vary between the genders. Qualitative sex differences, which refer to different genetic and environmental influences affecting males and females, were not indicated by these univariate twin correlations because for the most

part DZOS twin correlations were not significantly lower than DZ same-sex twin correlations.

Cross-trait cross-twin (CTCT) correlations are presented on the off-diagonal of Table 4 (male CTCT correlations below diagonal, female CTCT correlations above diagonal). Most of the MZ CTCT correlations were greater than their equivalent DZ CTCT correlations, suggesting that genetic influences were to some degree explaining the overlap between different subscales. The MZ CTCT correlations were all lower than the phenotypic correlations, suggesting that nonshared environment explained part of the covariation.

As noted above, the twin correlations did not suggest that qualitative sex differences were present in the data, and significantly different MZ and DZ variances suggested that sibling interaction paths were required in the model. Therefore, in line with previous behavior genetic research, DZOS were excluded from the models because of the presence of sibling interaction paths (it is considered too complex to include both qualitative sex differences and multiple sibling interaction paths in the same multivariate model, see (24).

Insert Table 5

Model Comparisons

Table 5 presents the fit statistics for models at both ages. In all these models, means were equated across twins 1/2 and males/females but not for MZ/DZ groups. Fit statistics for the ACE, ADE, AE versions are available from the first author on request

The best-fitting model was established based on three fit indices: the change in the Chi-square between submodels (smaller changes with the highest number of degrees of

freedom were favored), the lowest AIC, and the most negative BIC value. First, ACE and ADE Cholesky models were run in which all parameters were estimated. Then the AE model was tested (by dropping the C/D paths) and there was no significant decrease in fit compared to the ACE model ($\Delta\chi^2 = 6.34$, (12 *df*), $p = \text{n.s.}$) or the ADE model ($\Delta\chi^2 = 17.58$, (12 *df*), $p = \text{n.s.}$). Sex differences could not be dropped from this model without a significant decrease in fit ($\Delta\chi^2 = 216.08$ (12 *df*), $p < .001$). Next, independent and common pathway AE models with sex differences were compared to the Cholesky model. The AE common pathway gave the best fit compared to the Cholesky and independent pathway models.

Models were run with sibling interaction paths and there was a deterioration in fit when we tested a model without sibling interaction paths ($\Delta\chi^2 = 39.05$ (3 *df*), $p < .001$), but the sibling interaction paths could be equated across gender without a significant deterioration in fit ($\Delta\chi^2 = 1.03$ (3 *df*), $p = \text{n.s.}$).

For the 12-year-olds, very similar results were found and the best-fitting model was also the common pathway AEs model with different estimates for male and females and sibling interaction paths that could be equated across gender.

Testing the Significance of Symptom-Specific Genetic Effects

The lower section of Table 5 shows the fit statistics for the common pathway AEs at both ages when the paths for specific additive genetic influences on each subscale were sequentially dropped from the model. It was not possible to drop the paths for specific additive genetic influences for SIs, CIs, or RRBIIs without a significant decrease in fit in the age 9 data (SIs: $\Delta\chi^2 = 34.93$ (2 *df*), $p < .001$; CIs: $\Delta\chi^2 = 82.51$ (2*df*), $p < .001$; RRBIIs: $\Delta\chi^2 = 27.17$ (2*df*), $p < .001$) or the age 12 data (SIs: $\Delta\chi^2 = 42.74$ (2 *df*), $p < .001$; CIs: $\Delta\chi^2 = 134.62$ (2*df*), $p < .001$; RRBIIs: $\Delta\chi^2 = 93.21$ (2*df*), $p < .001$). It is not possible to drop the specific nonshared environmental influences from the model because these terms include measurement error.

Insert Figure 1

Figure 1 presents the unsquared unstandardized path estimates for the best-fitting AEs common pathway model, for the 9-year-olds (top panel) and 12-year-olds (bottom panel), alongside the percentages of variance explained by genetic and environmental influences.

The heritability of each scale can be derived from summing the percent variance explained by genetic effects in common with other symptoms with the percent variance explained by unique genetic effects in Figure 1. SIs in 9-year-old boys, for example, have a heritability of $31\% + 36\% = 67\%$. Heritabilities for all symptom scales in the 9 and 12-year-old children ranged from 49% (CIs in 9-year-old girls) to 76% (SIs in 12-year-old boys). The remaining variance for all scales was accounted for by nonshared environment.

In 9-year-olds, sibling interaction paths were estimated at $-.14$, $.05$ and $-.04$ for SIs, CIs, and RRBI subscales, respectively, and in 12-year-olds as $-.15$, $-.02$ and $-.09$ for SIs, CIs, and RBIs, respectively.

In terms of the covariance between subscales, the models in Figure 1 divide genetic and environmental influences into those that are common to the three subscales, shown in the top half of each model influencing the common latent factor (L), and those that are specific to each subscale individually, shown in the bottom part of each model.

For the 9-year-olds, using the path diagram, the percentage of genetic influences for SIs that were specific to SIs in males (i.e., not in common with the genetic influences on CIs and RBIs) was calculated as follows: $((.59*.59)/((.59*.59)+(.72*.87*.87*.72))) * 100\% = 47\%$. Conversely, the remaining genetic influences i.e. $((.72*.87*.87*.72)/((.59*.59)+(.72*.87*.87*.72))) * 100\% = 53\%$ of the

genetic influences on SIs, were shared with CIs and RRBIIs via the common latent factor (L). In the bar chart in Figure 1 these values are presented as a percentage of the total variance. Thus, for SIs for 9-year-olds, heritability was 67%, and 47% of this genetic variance was specific. For CIs and RRBIIs an even larger proportion of the genetic influences were specific to that subscale.

For all three subscales, the larger part of the nonshared environmental effect was specific to each subscale (66-96%). Similar results were found at age 12, as shown in Figure 1.

Discussion

This study explored the factor structure of autism symptoms in the general population in 9- and 12-year-old children. At both ages, ASD symptoms split into three factors – social impairments (SIs), communication impairments (CIs) and restricted repetitive behaviors and interests (RRBIs) –, which mirrored the theoretical autism triad as well as previous empirical results of autism symptoms in children with pervasive developmental disorders (8). The only divergence from the DSM-IV division of items was the ‘make-believe’ item, which loaded with SIs rather than CIs (the same was also found elsewhere, (8)). Our results showed that many more children show one part of the ASD triad than all three together.

The twin analyses revealed that SIs, CIs and RRBIs are all highly heritable (49-72%), which agrees with most previous studies of middle childhood onwards, (9, 25-32); a lower heritability estimate has been reported in one twin study of 2-year-olds (28). The ASD subscales shared a substantial degree of genetic influences, but it was also found that each ASD subscale had significant genetic influences that were specific to itself.

Similar to other studies, environmental effects were primarily nonshared and subscale-specific. With a few exceptions (29, 32), these results concurred with previous twin studies in finding negligible shared environmental effects. Small differences were found between ages 9 and 12, for example, heritabilities were on average slightly higher at age 12 than at age 9, but overall the results are noticeable for their similarity across ages. The best-fitting model included different parameter estimates for males and females, in line with previous studies (e.g. (9)), but overall sex differences were modest.

Previous results (9-11, 30) and the present study concur in suggesting that there are a degree of overlapping genetic and environmental influences between different autism behaviors in the general population but also significant genetic and environmental

influences that are specific to each part of the autism triad. One slight difference is that while the results from the UK twin studies found that SIs and RRBI showed the least amount of phenotypic and genetic overlap within the triad, the present study found that this overlap was highest between SIs and RRBI. The methodology and sampling were similar across the two studies. This difference therefore may be a result of the different measures employed: the A-TAC is a shorter measure that aims to directly reflect ASD symptoms, whereas the CAST, used in the previous UK twin studies, has a greater number of items that may be considered more ‘trait-like’.

The present study should be considered in light of its limitations. Although the items used here closely mirrored the DSM-IV criteria, parental interviews are not equivalent to a psychiatrist’s diagnosis (which would not be feasible with a population cohort) and the A-TAC is not currently considered a gold standard questionnaire for diagnosis in the same way as, for example, the longer and more established ADI-R. The scales had skewed distributions, which may lead to bias in parameter estimates if the assumption of multivariate normality is not met (33). Possibly because of the skewed distributions, all the models fit significantly worse than the saturated model, which is another limitation of the data. Parent report contains some bias (34) and shows only modest correlation with other raters when studying autistic symptoms (29). Parental assessment of problem behavior is a practical option for large studies, and parents are familiar with behavior across time and a range of situations. Finally, diagnostic criteria are likely to evolve, and it will be important to explore the genetic architecture of autism behaviors in more detail, for example, including RRBI subcategories and additional symptoms such as hypersensitivity.

This study has important implications for clinicians. First, this study reports that many children showed autism symptoms in part of the triad only, in as severe a form as

might be expected in children with a formal diagnosis of autism or Asperger's disorder. Further research needs to follow up these children in more detail, to explore their clinical needs and underlying cognitive deficits; some may be 'phenocopies' in that their problems are due to different underlying disorders such as anxiety. Further research could address whether RRBI on their own are more common than SIs or CIs on their own, as suggested by the results in Table 3, or if these different frequencies are an artifact of the measuring instrument. Nevertheless, this finding appears to concur with the high prevalence of Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) diagnoses, which make up almost a third of all ASD diagnoses and are given when presentations do not meet the criteria for Autistic Disorder because of late age at onset, atypical symptomatology, or subthreshold symptomatology, or all of these. Diagnostic criteria that attended to the level of impairment of a child on each aspect of the autism triad, rather than just considering a total sum of autistic symptoms, might better classify these heterogeneous clinical groups. A child with ASD with predominantly social impairments could have different educational and clinical needs as compared to a child with predominantly communication and repetitive behavior problems.

Molecular genetic research has begun to explore the possibility of symptom-specific genetic influences in autism, using candidate gene approaches (35), linkage (36) and genome-wide association (37). Complexity continues to be a key feature in the molecular genetics of ASD; the present findings suggest that knowledge about the causal pathways underlying individual symptoms will help to lead the way in this area of research.

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Table 1. Loadings of autism symptom items in principal component analyses.

| Factor/Item | 1 | 2 | 3 |
|--|------------|------------|------------|
| Was his/her language development delayed or doesn't he/she speak at all? | .05 | .03 | <u>.81</u> |
| Does he/she have difficulties sustaining a conversation? | .38 | .13 | <u>.66</u> |
| Does he/she like to repeat words and expressions or does he/she use words in a way other people find strange? | .23 | .39 | <u>.44</u> |
| Has he/she difficulties with games of make-believe or does he/she imitate considerably less than other children? | <u>.70</u> | .04 | .09 |
| Does he/she have difficulties expressing emotions and reactions with facial gestures, prosody, or body language? | <u>.60</u> | .22 | .23 |
| Does he/she exhibit considerable difficulties interacting with peers? | <u>.61</u> | .31 | .24 |
| Is he/she uninterested in sharing joy, interests, and activities with others? | <u>.73</u> | .19 | .10 |
| Can he/she only be with other people on his/her terms? | <u>.63</u> | .28 | .03 |
| Does he/she get absorbed by his/her interests in such a way as being repetitive or too intense? | .19 | <u>.63</u> | .13 |
| Does he/she get absorbed by routines in such a way as to produce problems for himself or for others? | .23 | <u>.67</u> | .03 |
| Has he/she ever engaged in strange hand movements or walking high on tiptoe when he/she was happy or upset? | .04 | <u>.45</u> | .34 |
| Does he/she get obsessed by details? | .16 | <u>.72</u> | .07 |
| Does he/she dislike changes in daily routines? | .21 | <u>.68</u> | .06 |

Note. Varimax rotation with Kaiser Normalization. Genders and age combined. Highest loadings are underlined.

Table 2. Descriptives and phenotypic correlations

| | SIs | CIIs | RRBIs |
|------------------------|--------|--------|--------|
| M | 0.11 | 0.11 | 0.24 |
| SD | 0.43 | 0.35 | 0.59 |
| Skewness | 6.06 | 3.95 | 3.65 |
| Range | 0-5.00 | 0-3.00 | 0-5.00 |
| Age 9 (N = 1517/1426) | | | |
| SIs | - | .21 | .33 |
| CIIs | .27 | - | .14 |
| RRBIs | .37 | .23 | - |
| Age 12 (N = 1651/1566) | | | |
| SIs | - | .30 | .40 |
| CIIs | .31 | - | .24 |
| RRBIs | .41 | .27 | - |

Note. SIs = social impairments; CIIs = communication impairments; RRBIs = restricted repetitive behaviors and interests. Male phenotypic correlations presented below diagonal, female above diagonal. All phenotypic correlations $p < .01$.

Table 3. Prevalence of autism symptoms alone and in combination with other symptoms in the sample.

| | Males (N = 3165) | Females (N = 2991) |
|---------------------|------------------|--------------------|
| SIs only | 41 (1.3%) | 48 (1.6%) |
| CIs only | 155 (4.9%) | 79 (2.6%) |
| RRBIs only | 284 (9.0%) | 166 (5.5%) |
| SIs + CIs, No RRBIs | 17 (0.5%) | 14 (0.5%) |
| SIs + RRBIs, No CIs | 62 (2.0%) | 40 (1.3%) |
| CIs + RRBIs, No SIs | 56 (1.8%) | 18 (0.6%) |
| SIs + CIs+ RRBIs | 63 (2.0%) | 11 (0.4%) |

Note. Sample consisted of one twin per pair selected randomly for birth order. Presence of autism symptom defined as a raw score of 1 or above on a subscale (see text). SIs = Social impairments; CIs = Communication impairments; RRBIs = Restricted repetitive behaviors and interests.

Table 4. Twin correlations.

| | <i>Age 9</i> | SIs | CIIs | RRBIs | <i>Age 12</i> | SIs | CIIs | RRBIs |
|------|---------------|---------|---------|---------|---------------|---------|---------|---------|
| MZ | (N = 410/425) | | | | (N = 484/469) | | | |
| | SIs | .43/.38 | .18 | .21 | SIs | .50/.45 | .23 | .19 |
| | CIIs | .17 | .73/.61 | .15 | CIIs | .18 | .70/.68 | .16 |
| | RRBIs | .27 | .20 | .49/.43 | RRBIs | .30 | .23 | .59/.48 |
| DZSS | (N = 440/370) | | | | (N = 500/418) | | | |
| | SIs | .12/.24 | .10 | .14 | SIs | .15/.12 | .05 | .14 |
| | CIIs | .09 | .37/.23 | .01 | CIIs | .19 | .29/.26 | .09 |
| | RRBIs | .08 | .08 | .22/.28 | RRBIs | .10 | .13 | .23/.24 |
| DZOS | (N = 1000) | | | | (N = 1024) | | | |
| | SIs | .14 | | | SIs | .14 | | |
| | CIIs | - | .24 | | CIIs | - | .22 | |
| | RRBIs | - | - | .26 | RRBIs | - | - | .20 |

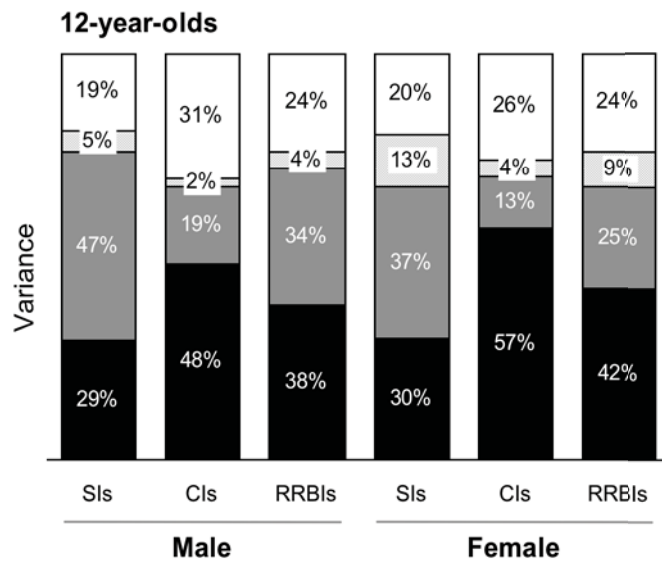
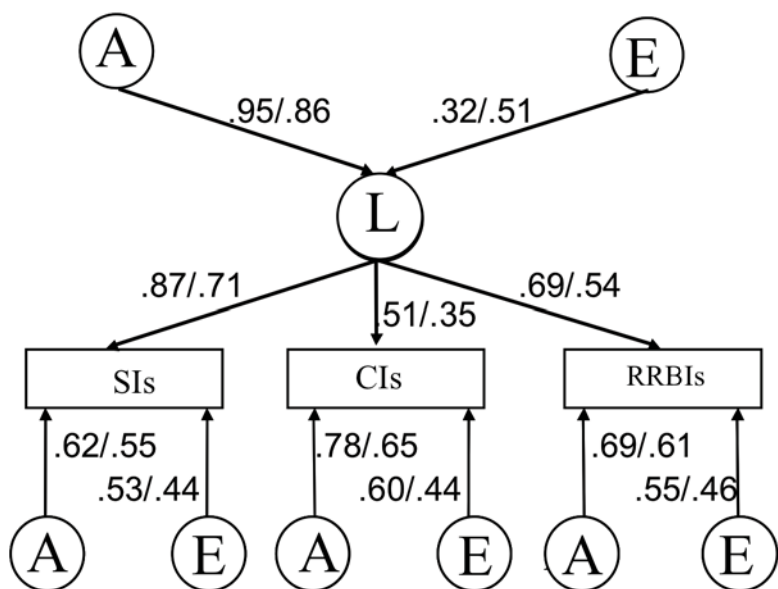
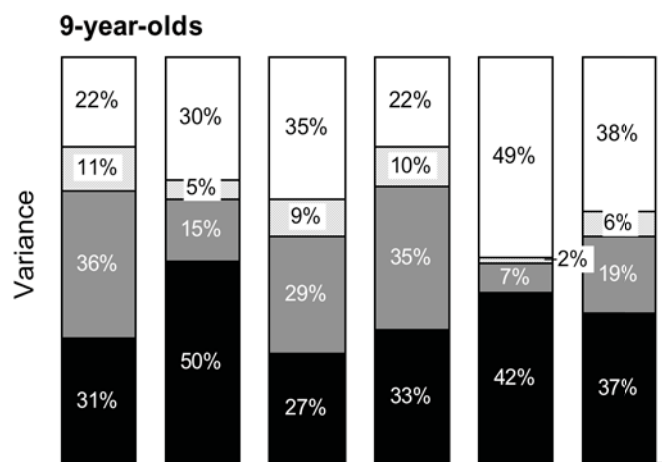
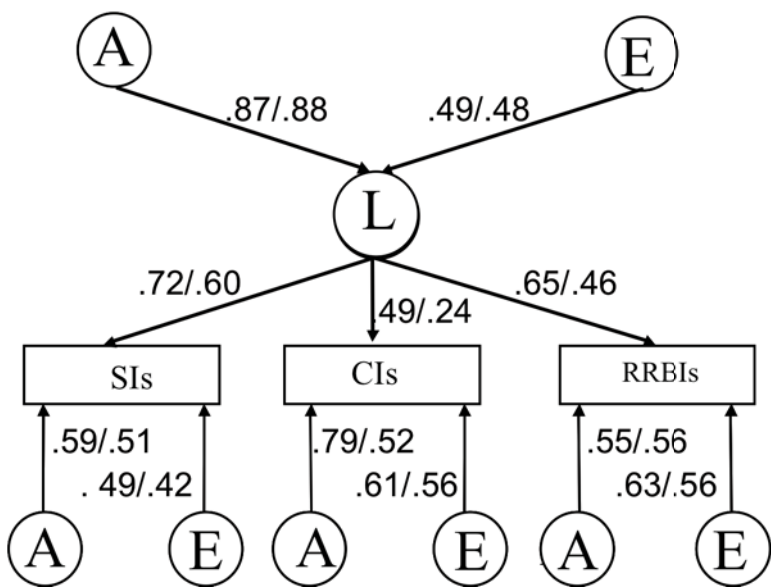
Note. Boys below diagonal, girls above diagonal. MZ=monozygotic; DZ=dizygotic; DZOS=opposite-sex DZ; SIs = social impairments; CIIs = communication impairments; RRBIs = restricted repetitive behaviors and interests.

| | | | | | | | | | | | | | | |
|-------------|----------|------|----|--------|-----------|-------|-----------|----------|-------|----|--------|-------|--------|-----------|
| no specific | 25319.91 | 9832 | 29 | 222.70 | 27.17 (2) | 60.70 | -54244.63 | 29490.48 | 11194 | 29 | 278.31 | 93.21 | 116.30 | -62606.77 |
| A (RRBIs) | | | | (81) | | | | | | | (81) | (2) | | |

Note. Sex = Quantitative sex differences. Sibling interaction paths (s) were equated across gender. ^aBest-fitting model at both ages. $-2LL = \log$ likelihood fit; df = degrees of freedom; par = parameters; $LRT(df) = \text{likelihood ratio } \chi^2 \text{ test with } \Delta df$ comparing model to either saturated model (Model 1) or to best-fitting model (Model 4); AIC/BIC = Akaike's/ Bayesian Information Criterion. A/D = Additive/ nonadditive genetic influences, E = Nonshared environment.

Figure Legend

Figure 1. Path diagrams of best-fitting common pathway model in 9-year-olds (top panel) and 12-year-olds (bottom panel) alongside bar charts for each age showing % variance explained. Path model shown for one twin in a pair. A = additive genetic influences; E = nonshared environmental influences; L = latent factor; SIs = social impairments; CIs = communication impairments; RRBI = restricted repetitive behaviors and interests.



□ Unique nonshared environmental effects
 ▨ Nonshared environmental effects in common with other symptoms
 ▒ Genetic effects in common with other symptoms
 ■ Unique genetic effects