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A multivariate twin study of autistic traits in 12-year-olds: testing the fractionable autism triad hypothesis

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Abstract

Autistic traits—social impairment, communication impairment, and restricted and repetitive behaviors and interests—are heritable in the general population. Previous analyses have consistently reported limited genetic and environmental overlap between autistic trait domains in samples assessed in middle childhood. Here we extend this research to parent-report data for 12-year-olds. Data from 5,944 pairs in the Twins Early Development Study were analyzed to explore the domain-specific heritability and degree of shared genetic and environmental influences across different autistic traits in the general population and among individuals scoring in the top 5% of each domain. Sex differences in the etiological estimates were also tested in these analyses. Autistic traits were moderately to highly heritable (0.58–0.88) at age 12. Bivariate genetic correlations in the full sample (0.18–0.40) and the extremes (0.24–0.67), as well as even lower unique environmental correlations, all suggested considerable fractionation of genetic and environmental influences across autistic trait domains, in line with previous findings.

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Keywords

autistic traits; autism; twins; genetics; genetic overlap

Introduction

Autism spectrum disorders (autistic disorder, Asperger's disorder, pervasive developmental disorder not otherwise specified; ASDs) are a set of highly heritable neurodevelopmental conditions characterized by substantial phenotypic heterogeneity both within and between subtypes (Bailey et al. 1995; Folstein and Rutter 1977; Ronald and Hoekstra 2011; Rutter et al. 1999; Steffenburg et al. 1989). The behavioral manifestations of ASD are classed into impairments in three domains: 1) reciprocal social interaction (SI), 2) communication (CI), and 3) restricted and repetitive behaviors and interests (RRBI) (APA 1994). When measured in the general population, behaviors falling into these categories are typically referred to as autistic traits (Constantino and Todd 2003; Skuse et al. 2005).

Autistic traits display moderate to high heritability (36–87%) in the general population (Ronald and Hoekstra 2011; Constantino and Todd 2003; Constantino et al. 2000; Constantino and Todd 2005; Hoekstra et al. 2007; Ronald et al. 2006; Ronald et al. 2005; Ronald et al. 2006; Scourfield et al. 1999). Examined independently, social impairment, communication impairment, and restricted and repetitive behaviors and interests display similarly strong genetic influence (Ronald et al. 2006; Ronald et al. 2006; Ronald et al. 2010). When the trait domains are examined separately in the context of a multivariate analysis, one can estimate the degree to which genetic and environmental influences are shared between the three components of the total autism-like phenotype.

Three general population twin analyses have investigated the etiological relationship between different autism-like symptoms. The first study employed a general population sample of twins, the Twin Early Development Study (TEDS), who were assessed at age 7. This study reported modest phenotypic overlap between SI and RRBI and found that the majority of genetic influences were independent between the two domains (Ronald et al. 2005). The genetic correlations, a measure of etiologic overlap ranging from zero to one, between the domains were 0.40 for males and 0.25 for females. Ronald et al. (2006) investigated the etiological relationship between different autistic traits in TEDS again when the twins were age 8, this time using a more comprehensive measure of autistic traits that included an assessment of CI. In the full sample, most genetic influence was impairment specific. In a sub-sample of high-scoring individuals, using a 5% quantitative threshold, genetic correlations ranged from 0.18 to 0.50 between the behavioral domains. This finding suggests that the majority of genetic influences on autism-like behaviors are distinct to each particular phenotypic component. Similar moderate genetic overlap was reported by Ronald et al. (in press) in a Swedish sample of 9- and 12-year-old twins, the Child and Adolescent Twin Study in Sweden (CATSS). Domain-specific influences accounted for 50–70% of genetic variation this study (Ronald et al. 2010).

These observations have contributed to the 'fractionable autism triad hypothesis,' a theory that the phenotypic components of the triad may arise from different genetic or environmental clusters (Happe and Ronald 2008; Happe et al. 2006). Since the hypothesis was initially presented, general population findings have been supported by twin research conducted in clinical samples (Mazefsky et al. 2008; Dworzynski et al. 2009). Population-based quantitative research, however, is uniquely capable of examining certain elements of the hypothesis in detail: through the use of quantitative traits, this study considers symptom severity and sex effects on genetic overlap between ASD trait domains.

The analyses presented here address two research questions about the fractionable autism triad hypothesis using new data from TEDS collected when the twins were 12-years old. 1) Will results for 12-year-olds show limited genetic and environmental overlap between different autistic traits, as has been found in younger children in the same sample? 2) Does the finding of limited etiologic overlap hold for both males and females across the range of impairment?

To our knowledge, this is the first study to examine potential sex differences in genetic overlap among extreme scorers in the general population, those closest to clinical ASD-like behavior. Sex differences in etiologic overlap may be relevant to the probability with which triadic behavior (SI+CI+RRBI), or the clinical phenotype, appears in its entirety. For example, if there is greater etiologic overlap between social and communication impairment in males, SI+CI together could be more likely in males, given equivalent distribution of causal risks. In other words, differences in etiologic overlap may relate to differences in the probability of clustered autism-like behavior. As SI, CI, and RRBI all must be present to obtain a diagnosis of ASD, factors that relate to phenotypic clustering likely relate to prevalence. As males are consistently preponderant among those with both a diagnosis of ASD and extreme autism-like behavior, we hypothesize that etiologic overlap at the extremes of the general population will be greater among males.

Methods

Participants

Participants were from the Twin Early Development Study (TEDS). TEDS is a longitudinal study of twins born in the United Kingdom between 1994 and 1996 (Oliver and Plomin 2007). Twin zygosity was confirmed by DNA in over 75% of cases. A validated questionnaire was employed for the remaining twin pairs (Price et al. 2000).

6,207 families completed the Childhood Autism Spectrum Test (CAST; Scott et al. 2002) for at least one twin and returned the measure at age 12 (mean age 11.3 years, range 9.8–13.5). A complete case method was employed in this analysis—twin pairs were included if their parent completed at least half of the thirty CAST items for both twins. Prorated scores were employed; total scores were adjusted to account for the proportion of items completed. Twin pairs were also excluded for known severe medical syndromes (with the exception of ASD), missing parent consent signature, and extreme pregnancy complications. The final sample included 5,968 twin pairs (11,936 individuals). Of those pairs, 968 were male monozygotic (MZ; MZM, 16.2%), 1,158 were female MZ (MZF, 19.4%), 931 were male dizygotic (DZ; DZM, 15.6%), 1021 were female DZ (DZF, 17.1%), and 1890 were opposite sex DZ (DZOS, 31.7%). Slightly less than half (47.7%) were male, 93.6% were white, and 32.4% of mothers had completed one or more A-levels.

The eligible TEDS participants without valid CAST data at age 12 had lower socioeconomic status (assessed using a combined measure including family income, education, and occupation; $t=19.5$, $df=11028$, $p<0.0001$) and were more likely to contain female twins (47.6% vs. 51.4%, $\chi^2=7.9$, $p=0.01$). There was no difference between those who did and did not respond at age 12 with regard to race or ethnicity (93.5% v. 93.0% white, $\chi^2=0.6$, $p=0.44$). In spite of some socioeconomically-dependent attrition, this sample is highly representative of the United Kingdom as whole. In the general population, approximately 92% of the population is white, 50% of children are male, and 32% of mothers have completed one or more A-levels (Office for National Statistics, 2005).

Measure of Autistic Traits

The parent-rated CAST is a thirty-one item, dichotomous (yes, no) response scale used to screen for autistic traits. A thirty-item version of the scale was used at age 12; an item asking about pretend play was dropped as it was deemed inappropriate for older children. Full psychometric details of the CAST are reported in other publications (Scott et al. 2002). Using a score of 15 as a cut-point, the sensitivity and specificity of the CAST have been reported as 100 and 97 percent respectively, with a positive predictive value of 50 percent (Williams et al. 2005). In this sample, the CAST displayed strong overall internal consistency (Kuder-Richardson 20=0.74). Domain-specific subscales were identified using DSM-IV criteria (as described by Ronald et al., 2006). In this sample the domain-specific subscales exhibited the following internal consistency reliabilities: social impairment, 0.56 (11 items, SI); communication impairment, 0.65 (12 items, CI); restricted and repetitive behaviors and interests, 0.48 (7 items, RRBI). This sample included 80 children with suspected autism spectrum disorders, identified through the Development and Well-Being Assessment (DAWBA; Goodman et al. 2000). The average scores for the suspected ASD group were above the 95th percentile of each subscale distribution and are reported in Table 1. A multivariate subgroup analysis in the diagnosed population was not possible given the limited sample size.

Analyses

Phenotypic analyses—The mean and standard deviation of each subscale was calculated for 1) the full sample, 2) those scoring above the empirically-derived 95th percentile, 3) the ASD individuals, and 4) each sex and zygosity group. Mean scores were compared between the sex and zygosity groups using ANOVA. Dunnett's T3 method was employed for multiple comparisons as homoskedasticity could not be assumed (Field 2002).

Quantitative Genetic Analyses—The analyses within this paper were designed to determine the fractional contributions of genetic and environmental influences on differences between individuals in autistic traits. Genetic contribution (heritability) is defined as that phenotypic trait variation derived from variation in individuals' DNA sequence. Heritability is further divided into additive (A) and nonadditive (D) genetic effects. Environmental effects can be either shared (C) or non-shared (unique, E). Shared environmental effects are defined as all environmental exposures that are shared by the twin pair *and* make twins growing up in the same family more similar. The non-shared environment is defined as features of the environment that do not contribute to the twins' resemblance. Sibling contrast (s) effects are those in which the phenotype of one twin effects the rater's view of the other twin's behavior (Plomin et al. 2008).

Basic analyses were carried out in SAS version 9.2. Structural equation modeling was conducted using the statistical program Mx (Neale 1997). In all cases, the most parsimonious model achieved without a reduction in fit was selected as the best match to the data. The likelihood ratio test (LRT) was employed to compare the fit of nested models. The Akaike information criterion (AIC) was used to compare the fit of non-nested models. All models controlled for age and sex effects on mean trait scores.

Analysis of the Extremes—For each subscale, individuals scoring in the top 5% of the z-score transformed population distribution were identified as extreme scorers. As the extreme scorer label is subscale-specific, it is possible for an individual to be an extreme scorer in one domain (e.g. social impairment) but not in another (e.g. communication impairment).

Twin similarity at the extremes was investigated using probandwise concordances and extreme group correlations. One twin is selected at random as the proband for each of these analyses. The probandwise concordance is calculated by determining the percentage of concordant twin pairs among those in which the proband is identified as an extreme scorer. Extreme group correlations are pearson correlations in which the sample is restricted to twin pairs that contain at least one extreme scorer. The twins' scores are treated continuously (Ronald et al. 2006). In both of these analyses, genetic influence on extreme traits is indicated by greater similarity among MZ twins than DZ twins.

Univariate DeFries-Fulker Extremes Analyses—Univariate DeFries-Fulker (DF) models were examined for each of the subscales (Purcell and Sham 2003). The DF models estimate the degree to which genetic and environmental factors contribute to the quantitative difference in phenotype between extreme scorers and the population as a whole (group heritability). DF models employ the continuous data available, permitting greater comparability with general population analyses (see below) than methods that treat extreme scores categorically (e.g. liability threshold models). The DF technique requires that scores are transformed prior to modeling. First, extreme scoring individuals (probands) are identified based on their position within the population distribution of a trait domain -- in this case, the top 5%. Controls are defined as those who score below the identified threshold ($<95^{th}$ percentile). Both proband and control scores are then expressed as a deviation from the control mean (standardized by sex and zygosity) and divided by the difference between the proband and control means (transformed) (Purcell and Sham 2003; DeFries and Fulker 1988). Within each sex and zygosity group, the mean transformed score of the probands is then 1. Group heritability is suggested when the transformed scores of MZ cotwins are greater than the transformed scores of DZ cotwins. The univariate DF models presented in Table 2 estimated group heritability, shared environmental effects, and unique environmental effects. Quantitative and qualitative sex differences were also examined. Quantitative sex differences reflect sex-based variation in the *magnitude* of genetic or environmental effects on a specific phenotype. Qualitative sex differences indicate that *different* genetic or environmental effects may be influencing a specific phenotype in males and females (Purcell and Sham 2003).

Bivariate DeFries-Fulker Extremes Analyses—A bivariate extension of the DeFries-Fulker regression method was employed to determine the degree of shared genetic and environmental influence between phenotypic domains (Light and DeFries 1995; Stevenson et al. 1993). To estimate differences in genetic overlap (bivariate heritability) between males and females, an interaction term was included between sex and the heritability parameter (DeFries and Fulker 1985). DF models involve a selection variable and are therefore unidirectional. The selection variable indicates the domain from which high scorers were drawn. The outcome variable is the domain of shared influence. For example, the SI→CI (selection→ outcome) model estimates the degree to which the genetic factors driving SI extreme scores also influence trait variation in CI. To permit comparability with the full sample analyses, only same-sex twins were used in the bivariate DF models. All DF models constrained estimates of twin similarity to the sex-specific transformed MZ cotwin mean (TMCM) of the outcome variable. Similar to MZ correlation in a full sample analysis, TMCM is an upper-limit estimate of heritability. Accordingly, estimates of bivariate heritability cannot exceed that empirically derived value.

Genetic correlations at the extremes can be estimated using a formula introduced by Knopik et al. (1997): $r_g(xy) = \sqrt{(H_b\ (x\rightarrow y))(H_b\ (y\rightarrow x))}/(H_g(x))(H_g(y))$, where H_b=bivariate heritability and H_g=univariate group heritability (Knopik et al. 1997). This creates a weighted composite of the two unidirectional bivariate estimates yielding a bidirectional genetic correlation comparable to those derived from full-sample models. Sex-specific

univariate DF estimates, not including DZOS pairs, were calculated to employ this technique.

Twin Correlations in the Full Sample

Within a domain, univariate heritability is suggested by greater similarity within MZ pairs than DZ twin pairs. Quantitative sex effects are suggested when the MZ-DZ difference varies between males and females. Qualitative sex differences are suggested when the DZOS correlation differs from the DZSS correlation.

Multivariate Cholesky Analysis of Autistic Traits in the Full Sample

Bivariate heritability (genetic influence common to two domains) is suggested by greater MZ cross-trait cross-twin (CTCT) correlations than DZ cross-trait cross-twin correlations. The CTCT correlations are presented by sex and, as above, they can be indicative of both quantitative and qualitative sex effects.

Multivariate structural equation modeling was employed to estimate the etiologic overlap between SI, CI, and RRBI in the general population. The following Cholesky decomposition structures were tested: ACEs, ACE, CEs, AEs, CE, AE, and E models. These analyses were restricted to same-sex twin pairs. Including OS pairs in multivariate approaches can induce order-specific fit estimates (e.g., the fit of the model becomes dependent upon the order in which the variables are entered). While methods have been suggested to address this problem (Neale et al. 2006), those solutions are complicated in the presence of sibling contrast effects, which were seen here. DZOS pairs were accordingly excluded to improve the validity of the multivariate estimates. Log-transformed scores were employed in the full sample analysis.

Results

Descriptive Statistics

Table 1 presents the distribution of scores for the full sample as well as for individuals identified as extreme scorers within the 95th percentile of each subscale distribution. On average, parents reported the presence of less than two autism-like behaviors per subscale (mean SI=1.62, mean CI=1.92, mean RRBI=1.42). Each of the subscale distributions was positively skewed (SI=1.50, CI=1.38, RRBI=0.92), as expected given the low means relative to the range of scores (SI 0–11, CI 0–12, RRBI 0–7). Mean differences by sex and zygosity were seen in the full sample subscale scores and are noted in detail in Table 1. Sex and zygosity together accounted for 5% of variation in SI, less than 1% of variation in CI, and 1% of variation in RRBI.

The mean scores for the greater than 95% extreme-scoring groups were 5.91 (SI), 7.08 (CI), and 4.49 (RRBI), highly similar to the means for the 80 individuals with a DAWBA-identified ASD. These 80 individuals (78.75% male) scored within the top three percent of each of the subscale distributions (mean SI= 6.02, mean CI=7.71, mean RRBI=4.51).

Twin Similarity for Extreme SIs, CIs, and RRBIs

Table 2 presents the univariate extreme group results for each of the CAST subscales. Overall, the probandwise concordances and extreme group correlations were high for MZ twins in each domain. The MZ concordances (SI 0.53; CI 0.61; RRBI 0.58) were more than twice the DZSS concordances (SI .12; CI 0.21; RRBI 0.24), suggesting additive and possibly nonadditive genetic influences on extreme scores, and no influence of shared environment. As with the probandwise concordances, MZ extreme-group correlations were much larger than the DZ correlations for each symptom type.

Heritability of Extreme SIs, CIs, and RRBIs

The univariate DF model-fitting results are presented in the lower portion of Table 2. At age 12, extreme scores within each domain were moderately to highly heritable. The best-fitting SI model suggested moderate heritability (0.58) and moderate unique environmental effects (0.42). The best-fitting DF model for CI indicated high heritability (0.72) and modest unique environmental effects (0.28). The best-fitting RRBI model suggested high heritability for both males (0.74) and females (0.71) and modest unique environmental effects. The shared environmental parameter could be dropped without a significant deterioration in fit in each subscale analysis. The magnitude of heritability did not differ significantly between males and females for any of the subscales. The SI and RRBI models, however, suggested an influence of qualitative sex effects on extreme scores. There was no evidence of qualitative sex effects in the best-fitting CI model.

Genetic and Environmental Overlap between Extreme SIs, CIs, and RRBIs

The bivariate DF results are present in Table 3. Each of the six comparisons suggested modest to moderate bivariate heritability of extreme autistic traits. Male estimates of bivariate heritability ranged from 0.28 to 0.49. Female estimates of bivariate heritability ranged from 0.15 to 0.44. Female estimates were lower than male estimates in each of the four comparisons that included social impairment. In the SI→CI and CI→SI comparisons, female estimates of bivariate heritability (0.17, 0.15) were less than half those for males (0.48, 0.49). The female RRBI→SI (0.15) overlap was also approximately half that of the males (0.28). There was a statistically significant interaction between sex and the bivariate heritability parameter in both bivariate SI-CI comparisons (SI→CI, p=0.02; CI→SI, p=0.003). However, after constraining the estimates of bivariate heritability to the MZ transformed cotwin mean, male and female estimates did not differ significantly in magnitude using the confidence interval overlap criterion.

The calculated SI-CI genetic correlation at the extremes was 0.66 for males and 0.24 for females. The male SI-RRBI correlation (0.44) similarly exceeded that for females (0.29). The CI-RRBI correlation was 0.58 for males and 0.57 for females.

Heritability of SIs, CIs, and RRBIs in the General Population

The univariate cross-twin correlations are presented in the top half of Table 4. In each domain, the univariate full sample MZ correlations (0.67–0.78) were more than twice the DZ correlations (0.16–0.40), suggesting additive and possibly non-additive genetic effects, and no shared environment, similar to the results of the extremes analysis (Table 2). MZ correlations less than unity suggested modest unique environmental effects. The differences between the male MZ and DZ correlations, in each domain, were larger than those between the female MZ and DZ correlations, possibly indicative of quantitative sex effects.

Genetic and Environmental Overlap between SIs, CIs, and RRBIs in the General Population

The cross-twin, cross-trait correlations are presented in the lower half of Table 4. The DZ cross-trait correlations (0.02–0.19) were less than those of the MZ (0.16–0.36), suggesting some cross-domain genetic influence on autistic traits. Correlations between the SI and RRBI domains were the lowest for both zygosity groups. The DZSS cross-trait correlations between SI and RRBI were not significantly different from zero (males: r= 0.06, 95% CI −0.001 −0.13; females: r=0.02, 95% CI −0.04 −0.08). For both the SI-CI and RRBI-CI cross-trait correlations, the difference between MZ and DZ males was greater than that between MZ and DZ females, suggesting possible modest quantitative sex effects on bivariate heritability The DZOS correlations were not significantly lower than the combined

DZM/DZF cross-trait correlations, suggesting no qualitative sex effects on multivariate etiology.

The best-fitting Cholesky decomposition model is presented in Table 5. The ACE Cholesky decomposition model with a sibling contrast term presented in Table 5 fit better than the saturated model (LRT= 98.5, df= 85, p=0.15). There was a significant sibling contrast in the SI and RRBI domains for females and the RRBI domain for males. Fit statistics for the other Cholesky models that were tested (as described in the Methods section) are available from the first author upon request.

Each of the three phenotypic domains was highly heritable in males (72%–76%) and moderately to highly heritable in females (58%–74%). There were no significant shared environmental effects in males. Females displayed significant shared environmental influence in the SI (21%) and CI (3%) domains, but not in the RRBI domain. Modest unique environmental effects were suggested for both males and females in each domain (21–28%).

While genetic effects were substantial *within* each domain, there was limited genetic overlap *between* domains. Genetic correlations ranged from 0.23 to 0.40 in males and 0.18 to 0.39 for females. The genetic overlap for both males (r_A=0.40) and females (r_A=0.39) was strongest between the RRBI and CI domains. The genetic correlation between SI and CI was weakest; the SI-CI genetic correlation in females (0.18, 95% CI 0.18 – 0.20) was significantly lower than that for males (0.32, 95% CI 0.29 – 0.34). Unique environmental correlations were modest (0.00–0.22) for both males and females.

Discussion

This study provides further empirical support for the fractionable autism triad hypothesis (Happe and Ronald 2008; Happe et al. 2006). The primary finding of limited genetic and environmental overlap is consistent with previous analyses from the same sample at younger ages (Ronald et al. 2006; Ronald et al. 2005; Ronald et al. 2006) and in other samples (Ronald et al.). Genetic and environmental correlations, which indicate the degree of shared causal influences across different domains, both in the full sample and in the extreme groups, were for the most part low to modest, suggesting fractionation of the total ASD phenotype. The fraction of genetic variance shared between trait domains can be estimated by squaring the value of the genetic correlation between them. Of the 12 genetic correlations estimated (6 sex-specific correlations among both extreme scorers and the sample as a whole), all suggested that more than half of the genetic influences on a particular trait domain were unique to that particular phenotypic component.

Limited etiologic overlap between autistic trait domains suggests that, in many individuals, different components of the ASD phenotype may be associated with different etiologic factors. With regard to the three definitional domains of autism, this means that social impairment, communication impairment, and restricted/repetitive behaviors and interests may be associated with different genetic and environmental influences, even when seen in the same individual. This is supported by recent evidence from clinical ASD samples, which similarly support domain-specific genetic influences (Mazefsky et al. 2008; Dworzynski et al. 2009).

Confirmation in clinical samples suggests a consistency between extreme autistic traits assessed quantitatively and qualitatively-defined ASD. While research in clinical samples is highly valuable, it is limited by the definitional presence of the phenotypic triad (SI+CI +RRBI) in individuals with an ASD diagnosis. General population samples permit the assessment of etiologic overlap as it occurs naturally. Further, sample size limitations in clinical populations often render certain statistical investigations difficult, particularly those

regarding sex-specific phenomena in ASD. Large, general population studies provide a unique opportunity to examine sex differences in autism-like behavior, particularly among those with extreme values.

This study suggests that the fractionable autism triad hypothesis holds in both males and females with extreme scores in autism-like symptom domains at age 12 years. Male and female estimates of genetic overlap were consistent between the non-social (RRBI) and communication domains. The largest sex difference in genetic overlap was seen between the social and communication impairment domains: males displayed greater genetic overlap between SI and CI in both the sample as a whole and among extreme scoring individuals. Of the six calculated genetic correlations at the extremes (three for males, three for females), the largest was the SI-CI comparison among males (0.66); the smallest was the SI-CI comparison among females (0.24).

Among extreme-scoring individuals, male estimates exceeded female estimates of genetic overlap in 4 of the 6 comparisons, each of those involving the social impairment domain. Sex differences in shared etiology between domains may be relevant to male-female differences in the prevalence ASD, a multidimensional, clustered phenotype. Among individuals with a diagnosis of ASD, for which impairment in all three domains is required, males outnumber females by at least 4 to 1 (Fombonne 2003; Fombonne 2005; Yeargin-Allsopp et al. 2003; Bertrand et al. 2001; Chakrabarti and Fombonne 2001). In general population samples of middle childhood or older, the male mean on quantitative measures of autistic traits consistently exceeds the female mean (Robinson et al. ; Constantino et al. 2004; Ronald et al. 2006). Males may be more likely to manifest the ASD phenotype in its entirety if, on average, the effects of ASD-relevant genetic factors are more domain-specific in females. Greater genetic overlap could increase the probability of seeing clustered traits in males, conditioning on the number genetic risk factors present. The degree to which a greater number of genetic risk variants may be required to produce ASD in females has begun to be tested (Gilman et al. ; Levy et al.). This, however, is the first study of autistic traits to investigate sex differences in genetic overlap among general population extreme scorers and the pattern should be reinvestigated in other samples with autistic trait data.

Sex differences were also noted in the relative contribution of genetic and shared environmental effects in the full sample models. A modest shared environmental effect was noted for females only, most substantially in the social impairment domain. The between-domain variation in etiologic structure in females is intriguing given that autistic traits, and the clinical ASD phenotype, are typically investigated as univariate phenomena. The subscale analyses conducted herein suggest that components of the ASD phenotype may be differentially genetically and environmentally responsive and that variation would be missed when the triad is reduced to a single score.

Limitations

This study is subject to the limitations inherent to the twin method (Lynch and Walsh 1998). The analyses conducted among extreme scoring individuals are restricted by a number of methodological challenges common to statistical analyses conducted in small groups. Even with a sample size of nearly 12,000 individuals, the number of females above the 95th percentile in the social impairment domain was limited (54 from MZ pairs, 53 from DZ pairs). Low sample size in those groups limited the ability of this study to test the significance of all but very large differences between males and females with regard to both univariate and bivariate heritability, and eliminated the possibility to consider the modest shared environmental effects noted in the full sample model. The lack of power most substantially influenced the DF model for social impairment, which suggested a large (.42) contribution of the unique environment relative to the other domains since the modest shared

environmental influence in females in the full sample (0.21) was too small to evaluate at the extremes.

The manner in which autistic traits were assessed also introduces limitations. The internal consistency reliabilities (ICRs) of the subscales were modest, as noted in previous applications of the CAST (e.g. Ronald et al. 2006). Sub-optimal ICRs attenuate the association between variables (Fox 1997)—for example, reducing the estimated correlation between twins in a pair. Modest subscale reliability may have accordingly contributed to the estimated ceiling on the heritability estimates (which are capped at the MZ correlation in full sample analyses and the MZ transformed cotwin mean in the DF analyses). However, it is unlikely that the ICRs substantially impacted the estimated relationship *between* MZ and DZ pairs, given equivalent internal consistencies between zygosities. Lastly, this analysis relied solely on parent-rated autistic traits. Future studies should reinvestigate these questions using trained or multiple raters (Ronald et al. 2008).

Conclusions

This study provides evidence in support of the fractionable autism triad hypothesis (Happe and Ronald 2008; Happe et al. 2006): the majority of genetic and environmental influences on autistic traits are unique to each particular phenotypic component in the general population and in extreme scoring groups when assessed by parent ratings in 12-year-olds. The finding of limited genetic overlap between autism-like trait domains was consistent across levels of severity for both males and females. Statistical genetic research has begun to test the fractionable autism triad hypothesis (Liu et al. ; St Pourcain et al. 2010; Ronald et al. 2010) and we encourage future studies to pursue domain-specific research within the total ASD phenotype.

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Table I

Descriptive Statistics

Group	Number of Individuals	SI Mean (SD)	CI Mean (SD)	RRBI Mean (SD)
100%	11936	1.62 (1.52)	1.92 (1.88)	1.42 (1.30)
>95%	596 (SI); 644(CI); 808(RRBI)	5.91 (1.35)	7.08 (1.32)	4.49 (0.74)
ASD	80	6.02 (2.46)	7.71 (2.60)	4.51 (1.77)
Males	5688	1.97 (1.63)	2.05 (1.99)	1.55 (1.36)
Females‡	6248	1.31 (1.34)	1.80 (1.76)	1.30 (1.22)
MZM (1)	1936	1.80 (1.61)	2.02 (1.99)	1.43 (1.33)
MZF (2)	2316	1.25 (1.28)	1.79 (1.79)	1.24 (1.22)
DZM (3)	1862	1.90 (1.56)	2.00 (1.97)	1.48 (1.32)
DZF (4)	2042	1.37 (1.40)	1.80 (1.73)	1.38 (1.24)
DZOS (5)	3780	1.76 (1.59)	1.97 (1.90)	1.51 (1.33)
ANOVA F (df), p		81.10 (4), <0.001	7.91 (4), <0.001	17.94 (4), <0.001
Multiple Comparisons		1,3,5>2,4; 3>5	1,3,5>2,4	1,3,4,5>2

Note: SI=social impairment; CI=communication impairment; RRBI=restricted and repetitive behaviors and interests; SD= standard deviation; ASD=autism spectrum disorder; MZM=monozygotic male; MZF=monozygotic female; DZM=dizygotic male; DZF=dizygotic female; DZOS=dizygotic opposite sex.

‡= Male mean greater than female mean for all subscales ($p<0.0001$ for all comparisons). ANOVAs examine mean differences between the five zygosity groups on subscale scores. Dunnett's T3 method of multiple comparisons employed as equal variance could not be assumed across sex and zygosity groups. Multiple comparisons denote all significant differences between groups.

Table II

Univariate Heritability of Subscales at the Extremes

	>95% Social Impairments	>95% Communication Impairments	>95% Rest./Rep. Behaviors
Probandwise Concordances			
MZ	0.53	0.61	0.58
DZSS/DZOS	0.12/0.12	0.21/0.20	0.24/0.15
Extreme group correlations (no. of probands)			
MZM	0.48*(121)	0.51*(121)	0.44*(147)
MZF	0.62* (54)	0.61* (99)	0.23 (120)
DZM	0.04 (135)	0.03 (123)	−0.12 (133)
DZF	0.16 (53)	−0.07 (83)	0.23 (118)
DZOS	0.18 (233)	−0.02 (218)	0.02 (290)
DeFries-Fulker extremes analysis (95%CI)			
Group heritability	0.58 (0.54, 0.58)**‡	0.72 (0.66, 0.74)**	0.74 (0.65, 0.74)[a]** 0.71 (0.63, 0.72)[b]**‡
Non-shared environment	0.42 (0.42, 0.46)	0.28 (0.26, 0.34)	0.27 (0.27, 0.35)[a] 0.29 (0.29, 0.36)[b]

Note: MZF=monozygotic female; DZM=dizygotic male; DZF=dizygotic female; DZOS=dizygotic opposite sex; CI=confidence interval; a=male estimate; b=female estimate.

* significantly different from zero at $p<0.05$.

** $h_g^2 + c^2$ constrained to the sex-specific MZ transformed cotwin mean.

‡ test for qualitative sex effects significant at $p<0.05$.

Table III

Bivariate Heritability at the Extremes of the General Population

Selection Variable	Sex and Zygosity	N (probands)	Transformed Means					Bivariate Heritability Estimates		>95% Genetic Correlations
			Proband	*Cotwin*	*Proband*	*Cotwin*		*Outcome Variable*		
			CI		*RRBI*					
SI	MZM	121	0.58	0.48	0.44	0.36		CI	RRBI	**SI-CI**
	DZM	135	0.51	0.14	0.41	0.13				
	MZF	54	0.51	0.36	0.36	0.23	Males	0.48* (0.23, 0.48)	0.36* (0.10, 0.36)	0.66
	DZF	53	0.50	0.27	0.41	0.04	Females	0.17 (0.00, 0.36)	0.23* (0.00, 0.23)	0.24
			SI		*RRBI*					
CI	MZM	121	0.61	0.49	0.57	0.47		SI	RRBI	**SI-RRBI**
	DZM	123	0.51	0.15	0.57	0.17				
	MZF	99	0.35	0.24	0.57	0.46	Males	0.49* (0.24, 0.49)	0.47* (0.17, 0.47)	0.44
	DZF	83	0.35	0.16	0.53	0.26	Females	0.15 (0.00, 0.24)	0.40 (0.08, 0.46)	0.29
			SI		*CI*					
RRBI	MZM	147	0.41	0.33	0.51	0.41		SI	CI	**CI-RRBI**
	DZM	133	0.40	0.19	0.52	0.19				
	MZF	120	0.20	0.15	0.50	0.44	Males	0.28 (0.06, 0.33)	0.41* (0.17, 0.42)	0.58
	DZF	118	0.19	0.05	0.43	0.21	Females	0.15* (0.00, 0.15)	0.44* (0.18, 0.44)	0.57

Note: SI=social impairment; CI=communication impairment; RRBI=restricted and repetitive behaviors and interests; MZM=monozygotic male; MZF=monozygotic female; DZM=dizygotic male; DZF=dizygotic female; H^2g=group heritability; see text for description of transformed means; 95% CI= 95% confidence interval; standard errors adjusted for number of twin pairs with 2 probands.

*h_g^2 constrained to sex-specific MZ transformed cotwin mean.

Table IV

Cross-twin correlations

	MZM Pearson r (95% CI)	MZF Pearson r (95% CI)	DZM Pearson r (95% CI)	DZF Pearson r (95% CI)	DZOS Pearson r (95% CI)
Univariate Cross-Twin Correlations					
SI	0.72 (0.69, 0.75)	0.67 (0.64, 0.70)	0.26 (0.20, 0.32)	0.32 (0.26, 0.37)	0.16 (0.12, 0.21)
CI	0.78 (0.75, 0.80)	0.75 (0.72, 0.77)	0.30 (0.24, 0.36)	0.40 (0.35, 0.45)	0.34 (0.30, 0.38)
RRBI	0.73 (0.70, 0.76)	0.71 (0.68, 0.74)	0.23 (0.17, 0.29)	0.33 (0.28, 0.39)	0.22 (0.17, 0.26)
Cross-twin Cross-trait Correlations					
SI-CI	0.34 (0.29, 0.40)	0.24 (0.19, 0.30)	0.07 (0.004, 0.13)	0.19 (0.13, 0.25)	0.12 (0.07, 0.16)
SI-RRBI	0.19 (0.13, 0.25)	0.16 (0.10, 0.21)	0.06 (−0.001, 0.13)	0.02 (−0.04, 0.08)	0.05 (0.01, 0.10)
CI-RRBI	0.31 (0.26, 0.37)	0.36 (0.31, 0.41)	0.12 (0.05, 0.18)	0.19 (0.13, 0.24)	0.19 (0.15, 0.24)

Note: SI=social impairment; CI=communication impairment; RRBI=restricted and repetitive behaviors and interests; CI= confidence interval; MZM=monozygotic male; MZF=monozygotic female; DZM=dizygotic male; DZF=dizygotic female; DZOS=dizygotic opposite sex.

Table V

Genetic and environmental overlap in the general population (multivariate ACEs estimates)

Fit Statistics	*−2LL*	*df*	*Parameters*	*LRT (df)*	*AIC*				
Saturated	34841.33	24360	108						
Best Fitting Model*	34939.83	24445	23	98.50 (85), p=0.15	−71.5				
Genetic and environmental correlations (95% confidence intervals)									
Male Estimates	A Corr			C Corr			E Corr		
		SI	CI		SI	CI		SI	CI
	SI			SI			SI		
	CI	0.32 (0.29, 0.34)		CI	-		CI	0.17 (0.15, 0.21)	
	RRBI	0.23 (0.19, 0.25)	0.40 (0.37, 0.43)	RRBI	-	-	RRBI	0.19 (0.15, 0.23)	0.22 (0.20, 0.27)
Female Estimates	A Corr			C Corr			E Corr		
		SI	CI		SI	CI		SI	CI
	SI			SI			SI		
	CI	0.18 (0.18, 0.20)		CI	1.00 (1.00, 1.00)		CI	-	
	RRBI	0.20 (0.20, 0.25)	0.39 (0.34, 0.39)	RRBI	-	-	RRBI	0.16 (0.13, 0.19)	0.16 (0.15, 0.19)
Variance components estimates (95% confidence intervals)									
	Social Impairment			Communication Impairment			Restricted Repetitive Behaviors and Interests		
	A^2	C^2	E^2	A^2	C^2	E^2	A^2	C^2	E^2
Male Estimates	0.72 (0.70, 0.74)	-	0.28 (0.28, 0.30)	0.76 (0.74, 0.77)	-	0.24 (0.23, 0.26)	0.76 (0.76, 0.78)	-	0.24 (0.22,0.25)
Female Estimates	0.58 (0.52,0.65)	0.21 (0.20, 0.33)	0.21 (0.20, 0.24)	0.73 (0.69, 0.75)	0.03 (0.02, 0.06)	0.25 (0.23, 0.26)	0.74 (0.74, 0.77)	-	0.26 (0.24, 0.28)

Note: SI=social impairment; CI=communication impairment; RRBI=restricted and repetitive behaviors and interests; A Corr= additive genetic correlations; C Corr=shared environmental correlations; E Corr=unique environmental correlations; A^2=fraction of trait-specific variation attributable to additive genetic factors; C^2=fraction of trait-specific variation attributable to shared environmental factors; E^2=fraction of trait-specific variation attributable to unique environmental factors.

* sibling contrasts present for females in SI and RRBI domains and males in RRBI domain.