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How to cite:

Hoekstra, Rosa A.; Happé, Francesca; Baron-Cohen, Simon and Ronald, Angelica (2010). Limited Genetic Covariance Between Autistic Traits and Intelligence: Findings From a Longitudinal Twin Study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 153B(5) pp. 994–1007.

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Version: Accepted Manuscript

Link(s) to article on publisher's website:
<http://dx.doi.org/doi:10.1002/ajmg.b.31066>

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LIMITED GENETIC COVARIANCE BETWEEN AUTISTIC TRAITS AND INTELLIGENCE: FINDINGS FROM A LONGITUDINAL TWIN STUDY

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Word Count text: 6,741

Running head title: Genetic covariance between autistic traits and IQ

In press in the American Journal of Medical Genetics Part B: Neuropsychiatric

Genetics. DOI 10.1002/ajmg.b.31066

Abstract

Intellectual disability is common in individuals with autism spectrum conditions. However, the strength of the association between both conditions and its relevance to finding the underlying (genetic) causes of autism is unclear. This study aimed to investigate the longitudinal association between autistic traits and intelligence in a general population twin sample and to examine the etiology of this association. Parental ratings of autistic traits and performance on intelligence tests were collected in a sample of 8,848 twin pairs when the children were 7/8, 9, and 12 years old. Phenotypic and longitudinal correlations in the sample as a whole were compared to the associations in the most extreme scoring 5% of the population. The genetic and environmental influences on the overlap between autistic traits and IQ and on the stability of this relationship over time were estimated using structural equation modeling. Autistic traits were modestly negatively correlated to intellectual ability, both in the extreme scoring groups and among the full-range scores. The correlation was stable over time and was mainly explained by autistic trait items assessing communication difficulties. Genetic model fitting showed that autistic traits and IQ were influenced by a common set of genes and a common set of environmental influences that continuously affect these traits throughout childhood. The genetic correlation between autistic traits and IQ was only modest. These findings suggest that individual differences in autistic traits are substantially genetically *independent* of intellectual functioning. The relevance of these findings to future studies is discussed.

Keywords: Autism; intellectual disability, twins, genetics, childhood

Introduction

Autism is associated with various degrees of intellectual disability (ID). A review of epidemiological studies reported that about 40% of individuals with autistic disorder have severe to profound levels of ID, about 30% have mild to moderate ID, whilst the remaining 30% show intellectual functioning in the normal range (Fombonne, 2006). Conversely, autism diagnoses are common in the intellectually impaired: a recent study suggested an autism prevalence of 28% in adolescents with ID (Bryson et al., 2008). However, the broader range of autism spectrum conditions (ASC), including Asperger syndrome (AS; where there is no cognitive or language delay) and Pervasive Developmental Disorder-not otherwise specified (PDD-NOS; where symptoms are mild or partial) encompass many individuals with average or even above average IQ. Prevalence estimates vary widely between studies, with some studies suggesting that ID may be present in as few as 15% of the ASC population (Gillberg, 1998). Recently it has been suggested that the prevalence of severe ID in ASC may be overestimated due to ascertainment bias (Skuse, 2007). The precise association between ASC and intellectual functioning and its relevance to finding the underlying causes of ASC thus remains unclear.

Studies by independent research groups indicate that characteristics of the autism phenotype can be measured reliably using quantitative scales (Baron-Cohen et al., 2001; Constantino et al., 2003; Hurley et al., 2006) and that autistic traits may follow a continuous distribution in general population samples (Baron-Cohen et al., 2001; Constantino and Todd, 2003; Hoekstra et al., 2008). Using such instruments makes it possible to study the association between autistic traits and intelligence in community-based samples, free of the possible effects of ascertainment bias.

We recently explored the association between autistic traits and intelligence and academic achievement in the extreme groups from a general population-based sample of twins in middle childhood (Hoekstra et al., 2009). Extreme autistic traits (defined as the top 5% scorers of the general population on a parent- or teacher-rated measure of autistic traits) were only modestly related to ID (defined by a score in the bottom 5% on measures of intelligence and academic achievement). The phenotypic correlations between autistic traits and IQ were similar in the extreme scoring groups and in the sample as a whole, suggesting that the association between the traits was independent of mean scores. Moreover, the association was similar for both parent-rated and teacher-rated autistic traits, suggesting that the association between autistic traits and IQ is similar for different raters.

Analyses of individual differences, rather than extremes analyses, permit the use of sophisticated structural equation models that can distinguish continuous influences of genes and environment from temporary influences in longitudinal datasets (Hoekstra et al., 2007a; Plomin et al., 2008). Within the Twins Early Development Study (TEDS), measures of autistic traits and intelligence were assessed at multiple time points in childhood. The current report exploits the longitudinal nature of this dataset and aims to answer the following questions: i) What is the association between parent-rated autistic traits and intellectual abilities at different time points in childhood? ii) What is the longitudinal association between these traits? and iii) To what degree do genetic and environmental influences explain the association?

Materials and Methods

Participants

The participating twin families were part of TEDS, a longitudinal study of twins born between 1994 and 1996 who are representative of the general population in the United Kingdom (Kovas et al., 2007). A detailed description of the sample characteristics of TEDS is presented elsewhere (Oliver and Plomin, 2007). Ethical approval for TEDS was provided by the institutional review board of the Institute of Psychiatry and informed consent was obtained by post or online consent forms. When the twins were 7 (mean \pm SD = 7.12 \pm .24), 9 (mean 9.01 \pm .29) and nearly 12 (mean 11.56 \pm .69) years old the children were administered a general intelligence test. Parent-reported measures of autistic traits were collected when the twins were nearly 8 (mean 7.89 \pm .53), 9 (mean 9.01 \pm .29) and nearly 12 (mean 11.28 \pm .70) years of age.

Exclusion criteria were as follows: no first contact data available (159 families); extreme pregnancy or perinatal difficulties (180 families); unclear zygosity of the twins (317 families); not having English as the first spoken language of the family (162 families); specific medical syndrome (not including suspected ASC), such as Down syndrome or chromosomal anomalies (227 families). After exclusions, data for at least one time point were available for 8,848 twin pairs, of which 1,456 were monozygotic male twin pairs (MZM), 1,478 dizygotic male pairs (DZM), 1,598 monozygotic female pairs (MZF), 1,456 dizygotic female pairs (DZF), 1,437 dizygotic twin pairs of opposite sex with a male firstborn (DOSMF) and 1,423 opposite sex twin pairs with a female first born (DOSFM). Zygosity of the same-sex twins was determined using polymorphic DNA markers or by a parent-report

questionnaire asking questions about twin similarity (Price et al., 2000). At age 9, the invitation for participation in the study was restricted to the children born between January 1994 and August 1995, resulting in a smaller sample size at this time point. Data on IQ and/or on autistic traits were available for 7,681 7/8-year-old twin pairs, for 3,284 9-year-old pairs and for 5,906 pairs at age 12.

Measures

The Childhood Autism Spectrum Test (CAST) is a 31-item questionnaire filled out by parents (Scott et al., 2002; Williams et al., 2008). Each item asks whether the child shows particular behaviors associated with ASC, and item scores are summed additively. A sum score of ≥ 15 is the cut-off for identifying children at risk for ASC (Scott et al., 2002). Items can be subdivided into three subscales based on the DSM-IV criteria (American Psychiatric Association, 2000) for ASC: Social impairments (SIs, 12 items); communication impairments (CIs, 12 items); and restricted repetitive behaviors and interests (RRBIs, 7 items) (Ronald et al., 2006a). The CAST shows good test-retest reliability ($r=.83$) (Williams et al., 2006) and satisfactory internal consistency ($\alpha = .73$ in the TEDS data). Parents filled out the full CAST when the twins were 8 and 12 years old and an abbreviated 20-item version when the twins were 9 years of age (Ronald et al., 2008). All but one of the CAST items relate to current behavior of the child. The single item asking about past behavior was omitted at age 12 to avoid difficulties with recall and to prevent artificial inflation of the phenotypic correlation between the CAST scores at age 8 and age 12. Thus, the questionnaire included 31 items at age 8, 20 items at age 9, and 30 items at age 12.

The large scale of this study did not permit administration of intelligence tests using face-to-face test procedures. However, innovative test administration procedures using telephone testing (at age 7), parental test administration with booklets (age 9) and web-based testing (age 12) have proven both cost-effective and reliable (Oliver and Plomin, 2007). At all time points, a general intelligence composite score was calculated based on the performance on two verbal and two nonverbal tests. At age 7, the subtests Similarities, Vocabulary and Picture completion from the Wechsler Intelligence Scale for Children-III (WISC-III; Wechsler 1992) and the subtest Conceptual grouping from the McCarthy Scales of Children's Abilities (McCarthy, 1972) were adapted for telephone administration. The intelligence composite score derived from the telephone administered test battery was found to correlate 0.72 with the Stanford-Binet Intelligence Scale, indicating this is a valid method to assess intelligence (Petrill et al., 2002). At age 9, IQ was assessed using test booklets that were filled out by the twins under supervision of their parents. This time the intelligence composite score was based on adaptations of the WISC-III Vocabulary and Information subtests and the subtests Figure classification and Figure analogies from the Cognitive Abilities Test: Third Edition (Lohman et al., 2003). Web-based test administration at age 12 comprised adaptations of the WISC-III Information, Vocabulary and Picture Completion subtests, and the Raven's Standard and Advanced Progressive Matrices (Raven et al., 1996).

Children with suspected ASC

Children at risk of ASC were identified either by parental information regarding their twin's diagnoses or from scores above the cut-off on the CAST at age 8. These suspected children were followed up and parents were interviewed by

telephone using the Development and Well-Being Assessment (DAWBA; Goodman et al., 2000). 94 children were identified with the DAWBA as having autism, 11 children as AS and 65 children as ASC other than autism or AS. Parent-rated CAST scores for these diagnostic groups were available for 145 children at age 7 (75 with autism; 10 with AS and 60 diagnosed with other ASC). Information on IQ at this age was available for 51 children. The majority of the children identified with the DAWBA as having an ASC was not invited to take part in the study at age 9 and 12 to avoid over-testing, as these children already participated in another TEDS study at the time. CAST scores were available for 36 children with ASC at age 9 and for 73 children at age 12. IQ data were available for 3 children at age 9 and for none of the DAWBA-identified children at age 12.

Statistical analyses

The effects of sex and age on mean CAST and IQ scores were examined using analysis of variance in one randomly selected member of each twin pair. To correct for these possible effects, subsequent analyses were based on age- and sex-regressed scores. Phenotypic correlations and twin resemblance were estimated in a saturated model using structural equation modeling in the software package Mx (Neale et al., 2006a). The saturated model specifies all possible relations between family members and does not impose any theoretical model on the covariance structure. This model provides information both on the phenotypic correlations within persons (e.g. the correlation between autistic traits and IQ, or the correlation between CAST scores at different time points), on the within-trait twin correlations (e.g. the twin correlation between CAST scores at age 7), and on the cross-twin cross-trait correlations (e.g. the correlation between IQ scores at age 7 in the oldest of the twin with CAST scores at

age 8 in the youngest of the twin). All available data were analyzed, including data from incomplete twin pairs, using the raw data option in Mx.

If IQ and autistic traits are causally related, a change in the one trait should result in increased or decreased expression of the other trait (de Moor et al., 2008). To examine this, within-person difference scores between IQ at different time points and between CAST scores at different time points were calculated and the correlation between these difference scores was examined.

It is conceivable that autistic traits only have an effect on intellectual functioning when the autistic traits are in the severe range, or vice versa, that only the intellectually impaired show increased CAST scores. To examine this possibility, apart from phenotypic correlations in the full-range scores, phenotypic group correlations (PGCs) were calculated for the sample of children who scored in the top 5% range of CAST scores, or in the bottom 5% of IQ scores. PGCs examine the extent to which extreme scorers (or ‘probands’) on trait X *as a group* score above or below the population mean on unselected trait Y (Plomin, 1991). PGCs are calculated by dividing the proband’s standardized score on the unselected variable Y by the proband’s standardized score on the selected variable X. For example, a PGC between autistic traits and IQ for extreme CAST scorers with the value of 1.0 means that the probands’ mean score on IQ is just as extreme as the probands’ mean score on autistic traits; a PGC of 0.0 would mean that the probands selected for extreme autistic traits have a mean IQ score that is no different from the population mean. These correlations are bidirectional: selecting probands for extreme autistic traits and

examining their quantitative IQ score may give different results from selecting probands for extremely low IQ scores and examining their scores on autistic traits.

Genetic model fitting

Monozygotic (MZ) twins are genetically identical at the DNA sequence level, while dizygotic (DZ) twins and non-twin siblings share on average 50% of their segregating genes. By comparing the resemblance in MZ twins with the resemblance in DZ twins, it is possible to decompose phenotypic variance and covariance into genetic and environmental components (Boomsma et al., 2002). Additive genetic influences (A) result from the additive effects of alleles at all contributing genetic loci. Shared environmental influences (C) represent the environmental effects common to both members of a twin pair. Nonshared environmental influences (E) are the effects of the environment that are not shared by the family members, these effects also include measurement error. The relative importance of the components A, C, and E was estimated using structural equation modeling in Mx (Neale et al., 2006a). Genetic modeling was performed following several steps. The influences of A, C, and E on all measures and on their overlap were first examined in a multivariate triangular or Cholesky decomposition (Neale et al., 2008). A Cholesky decomposition yields the best possible fit to the data, as it is a fully parameterized model. First, the significance of sex differences in the relative contribution of A, C, and E was tested. Next, it was tested whether the genetic influences on all measures could be described by a genetic common factor model (see Figure 1a). A good fit of this model would suggest that there is one common set of genes that continuously influences both autistic traits and intellectual functioning throughout childhood. To account for trait and age-specific genetic influences, genetic factors unique to each measure were also specified. Whilst

testing the fit of the genetic common factor model, the influences of C and E were modeled as a Cholesky decomposition.

Subsequently, a genetic common factor model encompassing two factors was fitted to the data (see Figure 1b). In this model, one genetic common factor (A_{CAST}) explains the genetic covariance between CAST scores at the three time points, whilst a second genetic factor (A_{IQ}) captures the genetic covariance between the three measures of IQ. This model fits well if there is one set of genes that influences autistic traits throughout childhood, and another set of genes that affect intellectual abilities in this time period. The genetic correlation between the two genetic common factors indicates the extent to which both sets of genes overlap. To ensure that the results of our analyses are independent of the order of which the variables are entered, the genetic and environmental correlation matrices were constrained to be equal in both sexes (Neale et al., 2006b). Again, trait and age-specific genetic influences were also specified and the influences of C and E were parameterized in a Cholesky decomposition.

Insert Figure 1a and 1b about here

Similar common factor models were applied to examine the covariance structure of the shared and nonshared environmental influences, whilst keeping the remaining variance components unchanged in a Cholesky decomposition. Additionally, a model was tested in which the nonshared environmental influences were constrained to be CAST-specific or IQ-specific (i.e. the nonshared

environmental influences on the overlap between IQ and CAST scores were set to zero).

The fit of the different submodels was evaluated against the Cholesky decomposition using likelihood ratio tests and Akaike's information criterion. The likelihood ratio is the difference between minus twice the log likelihoods ($-2 LL$) of two nested models and follows a χ^2 distribution. The degrees of freedom (df) are given by the difference in the number of parameters estimated in the two models. A high increase in χ^2 against a low gain of degrees of freedom denotes a worse fit of the submodel compared to the full model. The most parsimonious model, with still a limited χ^2 , is chosen as the best fitting model. Akaike's information criterion ($AIC = \chi^2 - 2df$) was used to compare the fit of the models that were not nested. The model with the lowest AIC value shows the best balance between goodness of fit and parsimony and is therefore the preferred model.

Lastly, we explored whether the association between autistic traits and intelligence was different for the three different features of the autism triad. Phenotypic correlations with IQ were estimated separately for SIs, RRBI and CIs at all three time points. After establishing which subscale accounted for most of the variance between autistic traits and intelligence, genetic model fitting was repeated including these items only.

Results

Descriptives

The descriptive statistics for the CAST and IQ scores at all three ages are summarized in Table I. Analyses of variance showed that boys obtained significantly

higher CAST scores than girls at all ages, whilst the effect of age was not significant. At age 7 and age 12, boys obtained somewhat higher scores than girls on the IQ test, this effect was not significant when the twins were 9 years old. At all three ages, there was a positive effect of age on performance on the intelligence test, with higher scores in slightly older children. It should be noted that the sizes of these effects were very small, and mainly reached significance due to the large sample included in this study. All subsequent analyses were corrected for these effects. Although some skewness was observed in the distribution of the CAST scores (skewness statistics were between 1.19 and 1.64), we used the untransformed scores in the genetic analyses. A simulation study by Derks and colleagues (2004) showed that a square root transformation of the data (the most commonly used transformation when data are censored) does not remove bias induced by non-normality of the data.

Insert Table I about here

Children DAWBA-identified as having an ASC for whom autistic traits data were available ($n = 145$ at age 8, $n = 36$ at age 9 and $n = 73$ at age 12) showed CAST scores that were between 3.30 and 3.79 SD higher than the population mean and this effect was significant (age 7: $F(1, 12626) = 2528.685, P < .001$; age 9: $F(1, 6508) = 420.510, P < .001$, age 12: $F(1, 11116) = 1119.248, P < .001$). IQ scores at age 7 in children for whom data were available ($n = 51$) were .72 SD below the population mean, a significant difference ($F(1, 9998) = 26.667, P < .001$). The IQ scores in this group varied widely, ranging from 2.74 SD below the population mean to 2.38 SD above the population mean. Converting these scores using the most common standardized expression of intelligence (with mean=100, SD=15), these scores

correspond to standardized IQ scores of 59 and 136. At age 9 and 12 the available IQ data in the ASC group was too limited to perform these analyses.

Phenotypic associations

Table II displays the phenotypic correlations (r_{ph}) between autistic traits and IQ at the different time points. Autistic traits assessed at different ages were strongly correlated in both boys and girls ($r_{ph} = .59$ to $.69$). The measures of IQ also showed considerable stability (r_{ph} between $.43$ and $.59$), especially given that different methods of assessment were used at the different ages (respectively telephone, booklet and web-administered tests). With cross-sectional r_{ph} ranging between $-.17$ and $-.26$, the negative association between autistic traits and IQ was modest at all time points and similar in boys and girls. Intriguingly, the association was equally strong across time points as within time points and was similar in both directions (i.e. the correlation between IQ 7 and CAST 12 was similar to the correlation between CAST 8 and IQ 12). This result suggests that the association between autistic traits and intellectual abilities is stable throughout middle to late childhood. The stability in the association was confirmed when the difference scores were examined between IQ at different time points and between CAST scores at different ages. A change in CAST scores over time was not associated with a change in IQ scores, neither when the short time intervals were considered (age 7/8-9: $r = -.01$; age 9-12: $r = 0.00$) nor examining the longest time interval (age 7/8-12: $r = -.01$).

Insert Tables II and III about here

To test whether this finding of a consistently modest association between autistic traits and intelligence holds when the extremes of the population are considered, phenotypic group correlations in the 5% extreme groups were calculated (see Table III). Children scoring in the extreme 5% on the autistic traits measure obtained CAST scores ranging between 11 and 30 (mean = 15.43; SD = 3.84). Children with IQ scores in the lowest 5% of the distribution had IQ scores that were 1.68 to 4.68 SD below the population mean, corresponding to standardized IQ scores of 30-75. The mean standardized IQ scores at age 7, 9 and 12 in this extreme group were respectively 67.60 (SD = 6.45); 66.25 (SD = 5.10); and 64.45 (SD = 7.46). Similar to the full-range scores, longitudinal phenotypic group correlations were substantial in high CAST scorers (PGCs ranging from .55 to .67) and in low IQ scorers (PGCs between .36 and .56), indicating that these traits are stable over time. The association between extreme autistic traits and intellectual impairment was modest (PGCs between -.11 and -.27) and similar in magnitude when probands were selected for low IQ scores (top right hand cells of Table III) or when probands were selected for high CAST scores (bottom left corner of Table III). Moreover, the associations between extreme autistic traits and intellectual impairment did not change over time, suggesting that the association between these traits is stable even in the extreme groups.

Twin resemblance within and across traits

The within trait twin correlations for each of the measures are displayed on the diagonal of Table IV. Similar to previous reports on these data (Davis et al., 2008; Davis et al., 2009; Ronald et al., 2006b), the MZ twin correlations were stronger than DZ twin correlations, especially for the CAST scores, suggesting strong genetic

influences on these traits. The DZF twin correlations for CAST scores were somewhat higher than the correlations in DZM twins, suggesting that genetic influences on autistic traits may be stronger in boys than in girls. Few sex differences were seen in the MZ and DZ twin correlations for IQ, indicating that the relative influence of genetic and environmental effects on intelligence were similar in both sexes. The DZ twin correlations for IQ scores were more than half of the MZ twin correlations, suggesting that shared environmental influences play a role in explaining individual differences in IQ.

The cross-twin correlations for each zygosity group are shown on the off-diagonals of Table IV. Within-trait cross-age twin correlations are displayed in the shaded off-diagonal cells, whilst the transparent cells show the cross-trait twin correlations (both within-age and cross-age). The MZ cross-twin correlations were nearly as high as the within-person (phenotypic) correlations. This pattern of correlations suggests that the association between traits is due to influences common to both twins (i.e. genetic or shared environmental influences). The DZ cross-twin correlations were slightly lower than the MZ cross-twin correlations, but not twice as low, suggesting that both genetic and shared environmental influences account for the overlap between traits.

Insert Tables IV and V about here

Genetic model fitting

Table V gives the fit statistics for the different models tested. The fully parameterized Cholesky decomposition was used as a reference model to evaluate the

fit of the more parsimonious submodels. Sex differences in the relative contribution of A, C, and E were highly significant (see model 2 in Table V), constraining these influences to be equal in both sexes resulted in a significant deterioration of model fit. Applying a single common factor model to the different influences on the covariance between CAST and IQ scores did not fit the data well, neither for genetic (model 3), nor for shared (model 5) or nonshared environmental influences (model 7) on autistic traits and IQ. However, a common factor model including two factors, with one factor common to all CAST measures and a second factor common to all IQ data, gave an adequate description of both the genetic (model 4) and the environmental (model 6 and 8) covariance between the traits. The nonshared environmental covariance between CAST and IQ scores was significant; dropping these effects resulted in a significant reduction in model fit (model 9). All together, the variance and covariance in CAST and IQ scores at three measurement occasions in childhood were best described by a model that included a 2 common factor model for both the genetic, shared and nonshared environmental influences (model 10). The low AIC-value confirmed that this model fitted the data well. The trait and age-specific genetic and shared environmental influences could not be dropped from this model without a significant reduction in model fit (not in Table V for space considerations, all $\chi^2(6) > 23.787$, $P \leq .001$), nor could the common factor loadings be omitted (all $\chi^2(6) > 29.147$, $P < .001$). The path diagram including the parameter estimates for the final model is shown in Figure 2, separately for girls and boys.

Insert Figure 2a and 2b and Table VI about here

The relative importance of the contribution of A, C, and E on the variance and in autistic traits and IQ is given on the diagonals in Table VI. In line with previous publications from parts of this dataset (Ronald et al., 2006b; Ronald et al., 2008) as well as in other samples (Constantino and Todd 2003; Hoekstra et al. 2007b), autistic traits were highly heritable, the genetic influences were somewhat more pronounced in boys (estimates between .74 and .77) than in girls (.65 to .69). As shown in Figure 2, most of the genetic effects on autistic traits were common to all ages, whilst the effects of age-specific influences were lower. For instance, the strong genetic influences on CAST scores at age 8 in boys (.76) were composed of a large influence of common genetic effects ($(\sqrt{.59})^2 = .59$) and a modest effect of age-specific influences ($(\sqrt{.17})^2 = .17$). This indicates that most of the genetic influences on autistic traits were stable over time. Shared environmental influences on CAST were slightly more important in girls (.10-.23) than in boys (.02-.08). About half of these influences were continuous throughout childhood, the remaining part of shared environmental influences were age-specific. Nonshared environmental influences explained 12 to 25% of the variance in autistic traits and these effects were similar in both sexes. Part of these effects (.07-.14) were stable over time, the remaining non-shared environmental influences were temporary.

For IQ, both genetic and shared environmental influences accounted for a modest to moderate proportion of the variance at all ages and in both boys and girls. Most of the genetic influences on IQ were stable, whilst shared environmental influences were both continuous and time-specific. Nonshared environmental influences on IQ explained 22 to 35% of the variance and these effects were mainly age-specific. The latter effects also include measurement error.

The relative contribution of A, C, and E on the covariance between autistic traits and IQ are displayed in the transparent cells of Table VI. Genetic and shared environmental influences were both important in explaining the modest association between CAST and IQ scores. Genetic and shared environmental effects were of approximately equal importance in girls, whilst the genetic influences explained most of the association in boys. Nonshared environmental influences on the covariance between autistic traits and IQ were very small. This is also reflected in the small but significant nonshared environmental correlation (r_e) between both traits, estimated at -.13 (95% confidence interval: -.26 to -.02). The shared environmental correlation (r_c) was found to be -1.00 (95% confidence interval: -1.00 to -.88); the genetic correlation (r_g) was modest and estimated at -.27 (95% confidence interval: -.34 to -.22).

Insert Tables VII and VIII about here

Association between IQ and the autism triad

Lastly, we explored the extent to which the association between autistic traits and IQ differed for the different features of the autism triad. As shown in Table VII, the association between autistic traits and IQ was most strongly explained by CAST items assessing communication difficulties. Examination of the individual items of the CIs scale showed that this association is not due to one or two single items (Table VIII). Apart from the item “Does s/he enjoy joking around”, each item contributed significantly to the association with IQ. The CAST CIs items primarily assess difficulties with pragmatic communication (see Table VIII for item content) and do not measure verbal intelligence directly. The genetic analyses were repeated using the

CI subscale only and it was tested whether the best fitting model from the previous analyses using the CAST total also fitted well on the CAST CIs data. Indeed, the model including two common factors describing the influences of A, C, and E fitted the data well ($\chi^2(51) = 45.942$, $P = .674$, $AIC = -56.058$). Genetic influences explained most of the covariance between communication difficulties and intelligence. However environmental contributions were also significant ($r_c = -1.00$ (95% confidence interval: -1.00 to -.57); $r_e = -.42$ (95% confidence interval: -.60 to -.27)). Although higher than between the total CAST and IQ, the genetic correlation between communication impairments and IQ was still only moderate: $r_g: -.40$ (95% confidence interval: -.46 to -.35).

Discussion

This study investigated the association between individual differences in autistic traits and intelligence in a large sample of twins who were followed at multiple time points in childhood. Whilst both autistic traits and IQ were found to be highly stable traits that were influenced by a common set of genes and environmental influences throughout childhood, the negative association between autistic traits and intellectual functioning was only modest, both in the extremes of the population and in the full-range scores. The genetic correlation between the set of genes that influence CAST scores throughout childhood and the set of genes that influences IQ scores throughout childhood was estimated to be -.27. These results suggest that a modest part of the genetic influences on both traits overlap and act to simultaneously increase autistic traits and reduce intellectual abilities (or vice versa). The majority of genetic influences however, are specific to either autistic traits or to intelligence. These results

suggest that most of the genetic influences on autistic traits are *independent* of IQ in the general population.

These findings are in line with studies of the broader autism phenotype that have generally not found evidence for increased prevalence of ID in the relatives of individuals with ASC (Folstein et al., 1999; Fombonne et al., 1997; Szatmari et al., 1996), nor for differences in cognitive development in siblings of children with autism compared to siblings of typically developing children (Yirmiya et al., 2007). Of interest is also that, unlike other severe developmental conditions such as Williams Syndrome and Down Syndrome, there is no ‘capping’ of IQ in individuals with ASC, and measured IQ can be extremely high (Dawson et al., 2007; Scheuffgen et al., 2000). A recent paper reported sex-specific effects on the relationship between verbal IQ and social communicative difficulties in a general population sample (Skuse et al., 2009). High verbal IQ was found to be protective against social and communication impairments in girls only. In line with our findings these sex-specific effects were not found for full-scale IQ.

Clinical studies that examined the association between severity of autism symptoms and intellectual functioning in ASC found mixed results. Modest to moderate negative correlations between measures of intelligence and severity of social and communication impairments have been reported (Georgiades et al., 2007; Hus et al., 2007; Spiker et al., 2002; Snow et al., 2009), while another study of high functioning individuals with pervasive developmental disorders reported no significant association (Szatmari et al., 2002). Regarding RRBI and IQ, Georgiades et al. (2007) reported a positive relationship between IQ and inflexible language and behavior, but in other studies no significant association was found between IQ and

insistence on sameness and circumscribed interests (Lam et al., 2008; Spiker et al. 2002). A moderate negative correlation between verbal IQ and motor mannerisms was reported recently (Lam et al., 2008), while another study found no evidence for an association between IQ and repetitive sensory and motor behaviors (Georgiades et al., 2007). Altogether these studies suggest that intellectual abilities only explain a limited proportion of the variance in severity of autism. An association with IQ is found most consistently for social and communication impairments and less so for repetitive behaviors, circumscribed interests, and insistence on sameness. These findings are in line with our results that show that in the general population intelligence is most strongly related to CIs and shows near-zero association with items assessing RRBI.

Our results contrast with findings from a recent study including 45 twin pairs in which at least one member of the twin pair was diagnosed with an ASC (Nishiyama et al., 2009). This study reported a high genetic correlation between IQ and autistic traits as assessed with the Childhood Autism Rating Scale (CARS). The CARS is a clinical rating scale that is known to correlate substantially with IQ (Perry et al., 2005). Although it is valuable to have these data from a clinical ASC twin study, the study suffers from a small sample size, resulting in wide confidence intervals around the parameter estimates. Moreover, clinical ascertainment bias cannot be excluded when focussing on clinical cases alone. The authors themselves put forward the suggestion that the genetic correlation found in their study may be inflated because of the inclusion of severely intellectually disabled children who only had a mild degree of autism and had received a PDD-NOS diagnosis.

In our study, the association between autistic traits and IQ was mainly due to CAST items assessing communication difficulties. Examination of the individual items showed that nearly all items of the CAST CIs were significantly related to IQ, suggesting that the association was true for a range of communication difficulties and not due to one or two particular items. The finding of a different association with IQ for different aspects of the autism triad fits in with previous work that proposes that the triad of autistic features is largely fractionable (Happé and Ronald, 2008). Our findings suggest that, for as far as there is overlap between the genetic influences on autistic traits and intelligence, these genes will mainly exert their effect on communication difficulties characteristic for autism.

The association between autistic traits and IQ was similar at all three time points. Moreover, changes over time in IQ were unrelated to changes in autistic trait scores. These results suggest that the modest association between autistic traits and intellectual abilities is stable throughout childhood and that the association is established before the age of 7. In a previous study in the extreme scoring 7-year-olds from the current sample, we found modest genetic overlap between extreme autistic traits and intellectual impairment (Hoekstra et al., 2009). In the current analyses we took advantage of the longitudinal nature of this dataset and separated temporary influences of genes and environment on autistic traits and IQ from the genetic and environmental influences that persist throughout childhood. Our results suggest that the set of genes that continuously affects autistic traits only shows a modest overlap with the set of genes that persistently influences IQ, and thus that most genetic influences on autistic traits are independent of IQ. Apart from genetic influences,

environmental influences also had a significant effect on the modest covariance between autistic traits and intelligence.

Strengths and limitations

The current study examined the association between individual differences in autistic traits and intelligence in a community-based sample. Comparisons between the phenotypic group correlation in the extreme 5% of the sample and the correlation found using the full-range scores showed little evidence for a different association between these traits in the general population versus the extreme. However, it should be acknowledged that this sample included few children with severe or profound ID. The children scoring in the lowest 5% of the distribution obtained IQ scores that were between 1.68 and 4.68 SD below the population mean, corresponding to standardized IQ scores of 75 and 30. Most of these children scored in the moderate ID range. It remains unknown whether our findings also apply to the far extreme cases. Moreover, since known medical problems were an exclusion criterion, our results do not generalize to the 10 to 20% of cases in which the ASC etiology can be ascribed to a medical condition, defined mutation or to gross chromosomal abnormalities (so-called ‘syndromic autism’) (Abrahams & Geschwind, 2008).

Autistic traits were measured by parent report. Previous studies have shown that raters can differ substantially in how they rate autistic traits (Posserud et al., 2006; Ronald et al., 2008) and it could be argued that rater effects might influence the strength of the association between autistic traits and IQ. In a previous study in the extremes of the current sample, both parent and teacher ratings were included, and the association was explored with both IQ and a measure of academic achievement

(Hoekstra et al., 2009). All analyses gave remarkably similar results and pointed towards a modest association between the traits.

Intellectual abilities were assessed using different procedures at each age. Strikingly, the association with autistic traits was similar for IQ tests administered over the telephone, using test booklets, and using web-based tests, indicating that this association holds regardless of the test procedure. The large scale of this study made it impossible to explore specific cognitive abilities in more detail. Future studies should explore how the individual components that make up general cognitive ability are associated with autistic traits.

The strengths of the current study include the large general population based sample. The large sample size provided power to detect relatively small effects, and the fact that the participants were representative of the general population in the United Kingdom means the study was free of the possible effects of ascertainment bias. The longitudinal design of the study allowed us to explore the association between autistic traits and IQ over a 5 year period in childhood during which important cognitive development takes place. The longitudinal data also permitted the fit of common factor models that could distinguish continuous influences that persist throughout childhood from temporary effects. Lastly, the sample size in this study was large enough to explore sex differences in the association between autistic traits and IQ and in the genetic and environmental influences on this association.

Implications

Our finding of only a limited association between autistic traits and intellectual functioning contrasts with previous studies reporting a high prevalence of

ID in individuals diagnosed with autism (Fombonne, 2006). Ascertainment bias may inflate the prevalence statistics of ID in ASC in clinical samples (Skuse, 2007). Moreover, milder forms of autism may remain undetected in people with IQ in the normal or high range, as cognitive compensation may mask the autistic characteristics in these individuals. The results from our unbiased sample suggest that the association between autistic traits and IQ may be considerably smaller than clinical studies suggest. Professionals working in health and education should be made more aware that autism can occur without intellectual disability, to ensure that all individuals who warrant a diagnosis will be detected and will receive a diagnosis without long delays.

It is estimated that genetic syndromes, defined mutations, and de novo copy number variations account for 10 to 20% of ASC cases (Abrahams and Geschwind, 2008). The remaining 80 to 90% of cases are 'idiopathic' and it is thought that common genetic variants, each of small effect, may play an important role in the risk for these forms of ASC (Chakrabarti et al., 2009). Our finding that the genetic association between autistic traits and intelligence is limited in a community based sample suggests that many of these common genetic variants affecting the risk for autism do not influence individual differences in IQ. Genetic research into autism has made enormous progress in recent years, several susceptibility genes have now been identified and the field is starting to understand how genes can affect the autism phenotype (Abrahams and Geschwind, 2008). Many of the genes that are identified thus far are involved in neurodevelopment or in synaptic function (Persico and Bourgeron, 2006). A challenge for future research is to understand how autism can develop while general cognitive abilities are preserved. Based on our results, we would encourage scientists who seek to elucidate the pathways from genes to autism

to bear in mind the substantial genetic independence that autistic traits have with general cognitive ability.

Acknowledgements

The Twins Early Development Study is funded by MRC grant G0500079 to Professor Robert Plomin. Dr Hoekstra is financially supported by the Netherlands Organization for Scientific Research (NWO Rubicon). Statistical analyses were carried out on the Genetic Cluster Computer (<http://www.geneticcluster.org>) which is financially supported by NWO (480-05-003). We gratefully acknowledge the twin families for their ongoing participation. We kindly thank Professor Plomin for the use of the TEDS data.

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TABLE I. Descriptive statistics and the effect of sex and age on measures of autistic traits (CAST) and intelligence (composite IQ score)

	N	Mean (SD)	Min	Max	Sex effect	Age effect
CAST 8 total*	12628	5.24 (3.61)	.00	30.00	<.001, $\eta_p^2=.038$	ns
CAST 8 proportion	12628	.17 (.12)	.00	.97		
CAST 9 proportion	6510	.18 (.11)	.00	.87	<.001, $\eta_p^2=.030$	ns
CAST 12 proportion	11118	.16 (.12)	.00	.93	<.001, $\eta_p^2=.029$	ns
IQ 7	10000	.00 (.99)	-4.33	4.91	.034, $\eta_p^2=.001$	<.001, $\eta_p^2=.005$
IQ 9	6194	.00 (.99)	-4.06	2.30	ns	<.001, $\eta_p^2=.006$
IQ 12	8339	.00 (.99)	-4.68	3.01	<.001, $\eta_p^2=.005$	<.001, $\eta_p^2=.048$

Note: ns = ANOVA P-value non-significant; η_p^2 = measure of effect size; CAST = Childhood Autism Spectrum Test. *CAST 8 total = raw CAST scores on the full 31-item CAST at age 8. A 20-item and 30-item version of the CAST was used at age 9 and 12. To enable the comparison of scores at the different ages, the proportion of endorsed items is shown.

TABLE II. Phenotypic correlations between autistic traits (CAST) scores at age 8, 9 and 12 and IQ data at age 7, 9 and 12 in boys (above diagonal) and girls (below diagonal)

	CAST 8	CAST 9	CAST 12	IQ 7	IQ 9	IQ 12
CAST 8	-	.69	.69	-.17	-.21	-.16
CAST 9	.64	-	.68	-.16	-.22	-.18
CAST 12	.61	.59	-	-.17	-.23	-.18
IQ 7	-.21	-.22	-.19	-	.45	.47
IQ 9	-.24	-.26	-.21	.43	-	.59
IQ 12	-.22	-.26	-.21	.48	.56	-

Note: CAST = Childhood Autism Spectrum Test. All correlations significant at the .05 level. The shaded cells contain the within-trait correlations, cross-trait correlations are displayed in the transparent cells.

TABLE III. Phenotypic group correlations in the 5% extreme groups between CAST scores at age 8, 9 and 12 and IQ data at age 7, 9 and 12

	CAST 8 top 5% (n = 625)	CAST 9 top 5% (n = 333)	CAST 12 top 5% (n=552)	IQ 7 bottom 5% (n = 500)	IQ 9 bottom 5% (n = 317)	IQ 12 bottom 5% (n = 406)
CAST 8	-	.62	.55	-.23	-.19	-.11
CAST 9	.66	-	.55	-.23	-.27	-.24
CAST 12	.67	.58	-	-.20	-.16	-.16
IQ 7	-.14	-.11	-.12	-	.36	.40
IQ 9	-.22	-.21	-.16	.47	-	.50
IQ 12	-.12	-.20	-.16	.52	.56	-

Note: CAST = Childhood Autism Spectrum Test. Selected variables in columns, unselected variables in rows. Data from boys and girls are combined to ensure sufficient sample size. The shaded cells contain the within-trait correlations, cross-trait correlations are displayed in the transparent cells.

TABLE IV. Twin correlations and cross-correlations for CAST total and IQ at all ages in all zygosity groups. (cross-correlations in MZM, DZM and DOSMF above diagonals; in MZF, DZF and DOSFM below diagonals)

	CAST 8	CAST 9	CAST 12	IQ 7	IQ 9	IQ 12
MZF/MZM						
CAST 8	.80/.79^a	.57	.60	-.17	-.18	-.15
CAST 9	.58	.88/.82^a	.57	-.15	-.21	-.15
CAST 12	.54	.53	.76/.79^a	-.19	-.20	-.16
IQ 7	-.20	-.21	-.18	.66/.70^a	.43	.46
IQ 9	-.24	-.26	-.20	.42	.78/.76^a	.55
IQ 12	-.22	-.26	-.20	.44	.56	.65/.71^a
DZF/DZM						
CAST 8	.40/.24^b	.20	.15	-.14	-.18	-.15
CAST 9	.29	.53/.44^b	.22	-.12	-.20	-.17
CAST 12	.26	.28	.41/.27^b	-.12	-.19	-.17
IQ 7	-.15	-.18	-.15	.48/.54^b	.32	.32
IQ 9	-.20	-.20	-.17	.27	.64/.56^b	.40
IQ 12	-.19	-.22	-.16	.27	.39	.44/.53^b
DOSFM /DOSMF						
CAST 8	.30/.37^c	.34	.29	-.10	-.15	-.14
CAST 9	.27	.45/.49^c	.30	-.16	-.20	-.20
CAST 12	.20	.25	.30/.36^c	-.11	-.15	-.14
IQ 7	-.17	-.14	-.14	.53/.47^c	.32	.29
IQ 9	-.19	-.19	-.15	.30	.59/.56^c	.36
IQ 12	-.13	-.13	-.13	.28	.35	.40/.41^c

Note: CAST = Childhood Autism Spectrum Test; MZM = monozygotic males; DZM = dizygotic males; MZF = monozygotic females; DZF = dizygotic females; DOSMF = dizygotic opposite sex, male firstborn; DOSFM = dizygotic opposite sex, female firstborn. ^a First figure correlation MZF, second figure correlation MZM; ^b correlation DZF/DZM; ^c correlation DOSFM/DOSMF. The shaded cells contain the within-trait twin correlations. Within-trait within-age twin correlations are in bold, within-trait cross-age twin correlations are displayed in regular font. The cross-trait twin correlations are displayed in the transparent cells.

TABLE V. Model fitting results for longitudinal multivariate analyses of autistic traits and IQ

model	df	-2LL	cpm	χ^2	p	AIC
1 ACE incl. sex differences	54627	132275.808				
2 ACE no sex differences	54690	133073.824	1	798.016	<.001	672.016
3 A 1 common factor C Cholesky E Cholesky	54645	132437.558	1	161.750	<.001	125.750
4 A 2 common factors C Cholesky E Cholesky	54644	132296.395	1	20.587	.245	-13.413
5 A Cholesky C 1 common factor E Cholesky	54645	132348.406	1	72.598	<.001	36.598
6 A Cholesky C 2 common factors E Cholesky	54644	132284.773	1	8.965	.941	-25.035
7 A Cholesky C Cholesky E 1 common factor	54645	132316.676	1	40.868	.002	4.868
8 A Cholesky C Cholesky E 2 common factors	54644	132300.878	1	25.070	.093	-8.930
9 A Cholesky C Cholesky E no covariance CAST-IQ	54645	132306.039	1	30.231	.035	-5.769
10 Best fitting: A 2 common factors C 2 common factors E 2 common factors	54678	132324.964	1	49.156	.547	-52.844

Note: AIC = Aikake's Information Criterion; -2LL = -2 log likelihood; df = degrees of freedom; cpm = compared to model; CAST = Childhood Autism Spectrum Test.

TABLE VI. The contribution of additive genetic (A), shared (C) and nonshared (E) environmental influences to the variance and covariance in autistic traits and IQ at different ages in childhood in girls (below diagonal) and boys (above diagonal).

	CAST 8	CAST 9	CAST 12	IQ 7	IQ 9	IQ 12
A						
CAST 8	.69/.76*	.79	.84	.77	.65	.70
CAST 9	.79	.65/.74*	.80	.63	.49	.55
CAST 12	.77	.79	.65/.77*	.72	.59	.65
IQ 7	.48	.46	.48	.36/.33*	.63	.69
IQ 9	.44	.42	.45	.59	.30/.40*	.54
IQ 12	.51	.49	.52	.60	.60	.47/.41*
C						
CAST 8	.11/.02*	.03	.02	.21	.30	.25
CAST 9	.12	.23/.08*	.04	.36	.46	.40
CAST 12	.10	.11	.10/.02*	.27	.36	.31
IQ 7	.45	.49	.44	.31/.36*	.35	.29
IQ 9	.55	.58	.54	.39	.48/.36*	.37
IQ 12	.47	.50	.46	.30	.39	.19/.30*
E						
CAST 8	.20/.22*	.18	.14	.01	.06	.05
CAST 9	.09	.12/.18*	.16	.01	.05	.05
CAST 12	.13	.10	.25/.21*	.01	.05	.04
IQ 7	.07	.05	.08	.34/.31*	.02	.02
IQ 9	.00	.00	.00	.02	.22/.24*	.09
IQ 12	.02	.01	.02	.10	.01	.35/.29*

Note: Estimates based on the best fitting model. CAST = Childhood Autism Spectrum Test. *the first figure is the relative contribution in girls, second figure for boys. The contributions of A, C, and E to within trait variance are in bold, the contributions to the within-trait cross-age covariance are in the off-diagonal shaded cells. The contributions of A, C, and E on the overlap between CAST and IQ are displayed in the transparent cells.

TABLE VII. Phenotypic correlations between the triad of autistic traits at age 8, 9 and 12 and IQ data at age 7, 9 and 12 in both sexes.

	CAST SIs		CAST RRBIs		CAST CIs	
	girls	boys	girls	boys	girls	boys
IQ 7/8	-0.11 (-.14; -.07)	-0.07 (-.10; -.03)	-0.05 (-.09; -.01)	-0.04 (-.06; -.02)	-0.23 (-.26; -.20)	-0.23 (-.26; -.19)
IQ 9	-0.17 (-.20; -.13)	-0.14 (-.18; -.10)	-0.09 (-.12; -.05)	-0.05 (-.09; -.01)	-0.27 (-.31; -.24)	-0.27 (-.31; -.23)
IQ 12	-0.10 (-.13; -.07)	-0.08 (-.12; -.04)	-0.06 (-.08; -.04)	-0.03 (-.06; -.02)	-0.25 (-.28; -.22)	-0.25 (-.28; -.21)

Note: CAST = Childhood Autism Spectrum Test; SIs = social impairments; RRBIs = restricted repetitive behaviors and interests; CIs = communication impairments; 95% confidence intervals around the estimates are given in parentheses.

TABLE VIII. The significance and effect size of the contribution of individual CAST items assessing communication impairments (CAST CIs) to the negative association between CAST and IQ at age 7/8 and age 12

Item (abbreviated wording)	CAST CIs 8 – IQ 7	CAST CIs 12 –IQ12
Tend to take things literally	p<.001, $\eta_p^2=.021$	p<.001, $\eta_p^2=.022$
Find it easy to interact with other children*	p<.001, $\eta_p^2=.007$	p<.011, $\eta_p^2=.002$
Can keep a two-way conversation going*	p<.001, $\eta_p^2=.013$	p<.001, $\eta_p^2=.007$
Enjoy joking around*	p=.370	p=.415
Difficulty understanding rules for polite behavior	p<.001, $\eta_p^2=.010$	p<.001, $\eta_p^2=.004$
Voice unusual	p<.001, $\eta_p^2=.005$	p=.065
Good at turn-taking in conversation*	p<.001, $\eta_p^2=.010$	p<.001, $\eta_p^2=.006$
Often say things that are tactless or inappropriate	p<.001, $\eta_p^2=.013$	p<.001, $\eta_p^2=.019$
Sometimes say you instead of I	p<.001, $\eta_p^2=.020$	p<.001, $\eta_p^2=.012$
Sometimes lose the listener	p<.001, $\eta_p^2=.022$	p<.001, $\eta_p^2=.016$
Often turn conversations to favorite topic	p<.001, $\eta_p^2=.008$	p<.001, $\eta_p^2=.005$
Odd or unusual phrases	p<.001, $\eta_p^2=.008$	p<.001, $\eta_p^2=.009$

Note: * designates a reversed item. CAST = Childhood Autism Spectrum Test; η_p^2 = measure of effect size.

Figure captions

FIGURE 1. Path diagrams depicting a 1 common factor model including age and trait-specific influences (Figure 1a) and a common factor model with 2 common genetic factors and age and trait-specific influences (Figure 1b). Each genetic effect correlates 1.0 between monozygotic twins and on average 0.5 between dizygotic twins. Similar models can also be applied to environmental effects. A_c = Common genetic factor exerting its influence on all traits; A_{CAST} = Common genetic factor influencing autistic traits only; A_{IQ} = Common genetic factor influencing IQ scores only; A_s = age and trait-specific genetic influences; CAST = Childhood Autism Spectrum Test.

FIGURE 2. Path diagrams depicting the best fitting model with parameter estimates in girls (Figure 2a) and in boys (Figure 2b): a common factor including 2 factors and age and trait-specific influences for genetic (A), shared environmental (C) and nonshared environmental (E) influences. $A/C/E_{CAST}$ = Common A/C/E factor exerting its influence on autistic traits only; $A/C/E_{IQ}$ = Common A/C/E factor influencing IQ scores only; $A/C/E_s$ = age and trait-specific influences of A/C/E; r_g = genetic correlation; r_c = shared environmental correlation; r_e = nonshared environmental correlation; CAST = Childhood Autism Spectrum Test.

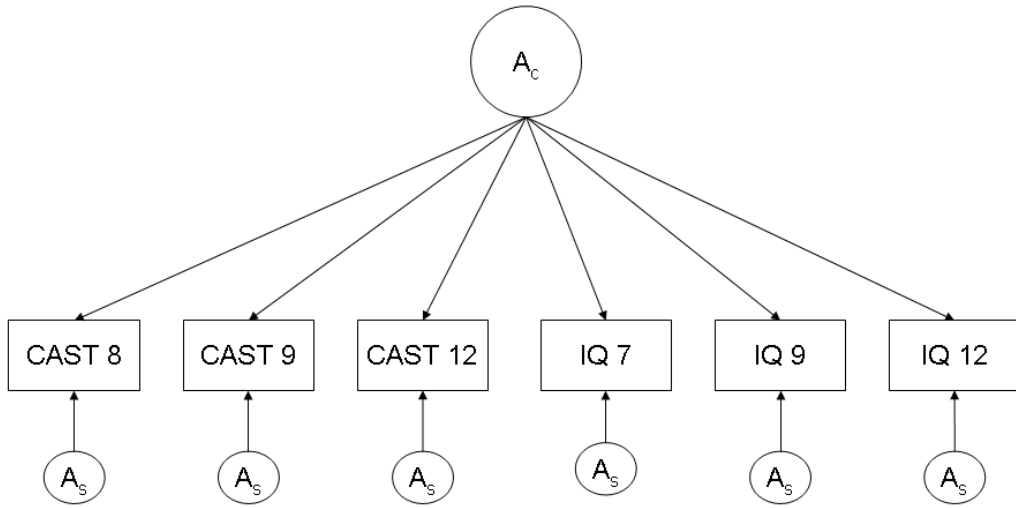


FIGURE 1a.

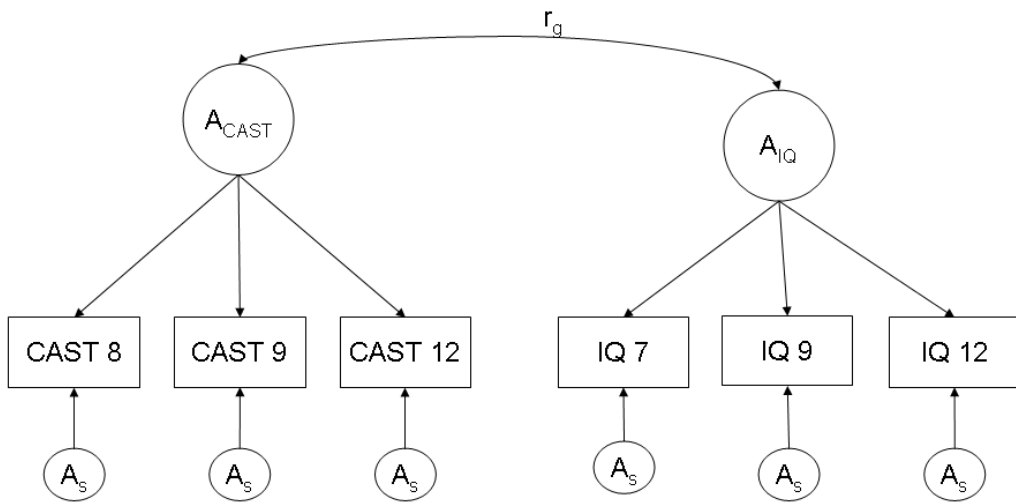


FIGURE 1b.

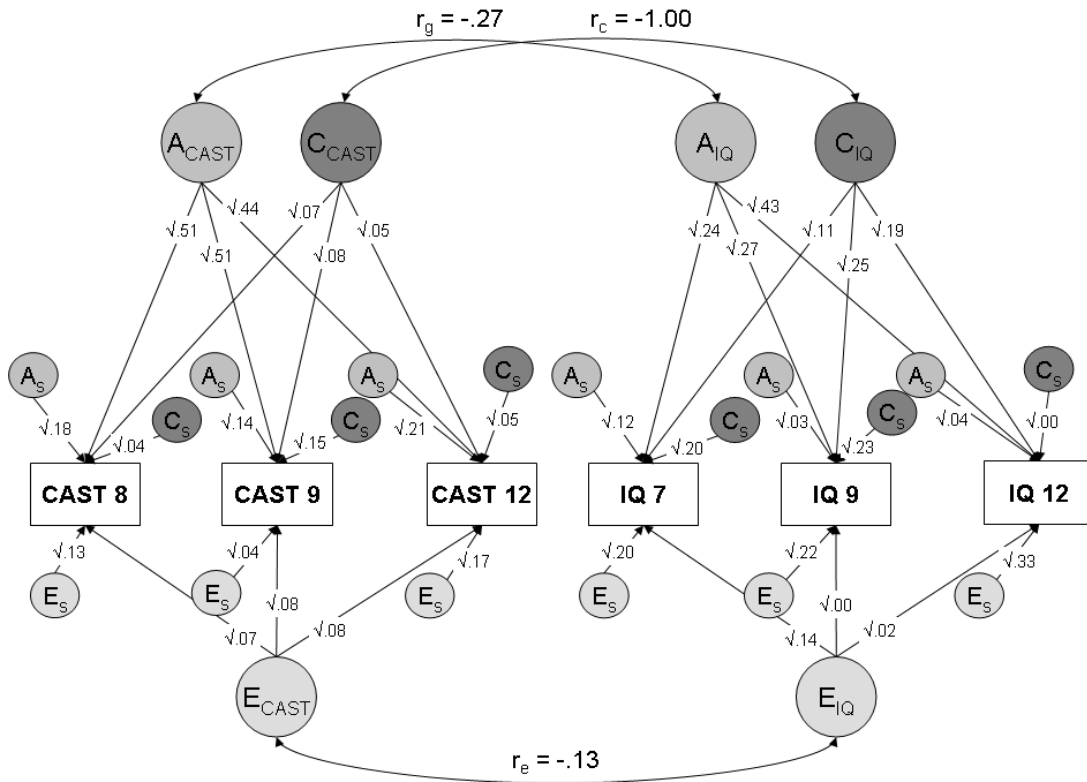


FIGURE 2a.

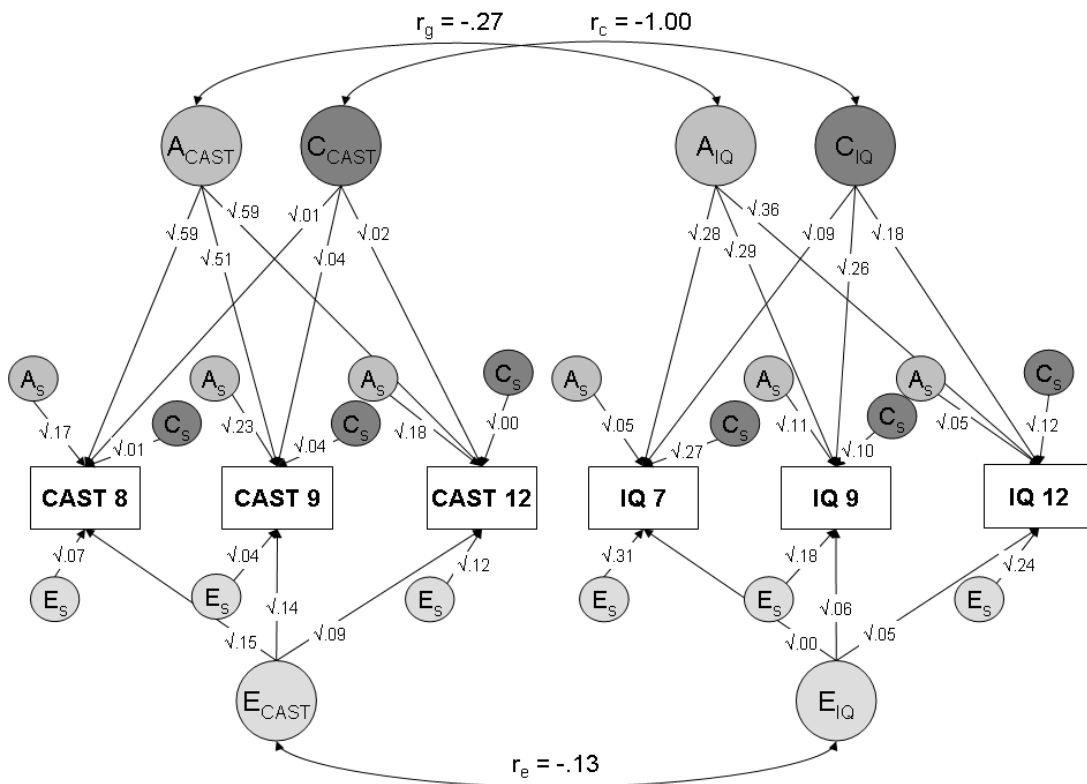


FIGURE 2b.