Association between extreme autistic traits and intellectual disability: insights from a general population twin study

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Background
Autism is associated with intellectual disability. The strength and origin of this association is unclear.

Aims
To investigate the association between extreme autistic traits and intellectual disability in children from a community-based sample and to examine whether the association can be explained by genetic factors.

Method
Children scoring in the extreme 5% on measures of autistic traits, IQ and academic achievement were selected from 7965 7/8-year-old and 3687 9-year-old twin pairs. Phenotypic associations between extreme autistic traits and intellectual disability were compared with associations among the full-range scores. Genetic correlations were estimated using bivariate DeFries–Fulker extremes analyses.

Results
Extreme autistic traits were modestly related to intellectual disability; this association was driven by communication problems characteristic of autism. Although this association was largely explained by genetic factors, the genetic correlation between autistic traits and intellectual disability was only modest.

Conclusions
Extreme autistic traits are substantially genetically independent of intellectual disability.

Declaration of interest
None.

Intellectual disability (here defined as IQ < 70) is common in autism. Historically, the prevalence of intellectual disability in autism is estimated at 70%, but recent studies encompassing all autism-spectrum conditions, including Asperger syndrome and pervasive developmental disorder – not otherwise specified, suggest that the prevalence of intellectual disability in autism-spectrum conditions may be considerably lower. It has been suggested that the association between autism and intellectual disability may be inflated because of clinical ascertainment bias. It has been suggested that the prevalence of intellectual disability in autism-spectrum conditions may be considerably lower. If this hypothesis holds true it has implications for studying the causes of autism-spectrum conditions. A strong genetic link between autism-spectrum conditions and intellectual disability would argue for a search for genes influencing both traits. A limited association would argue for separate genetic influences on each trait. A possible ascertainment bias for intellectual disability in autism-spectrum conditions limits the investigation of this association in clinical samples. Instruments that assess autistic traits on a quantitative scale enable studying the relationship in population samples. This study reports on the association between autistic traits, IQ and academic achievement in the extreme 5% scorers of a large community-based twin sample. The genetic informative design allowed for exploration of the genetic and environmental origin of the association.

Participants
Participants were part of the longitudinal Twins Early Development Study (TEDS), a child twin sample representative of the general population in the UK. The sample characteristics of TEDS are described elsewhere. Zygosity in same-sex twins was determined using polymorphic DNA markers (75% of participants) or a parent-report questionnaire that has a reported accuracy of 95%. Participants’ IQ and academic achievement were assessed at ages 7 and 9. Measures of autistic traits were collected when the twins were nearly 8 (parent report) and 9 (teacher report) years.

Exclusion criteria were as follows: no first contact data available (153 families); extreme pregnancy or perinatal difficulties (165 families); unclear twin zygosity (300 families); not having English as the spoken first language (146 families); specific medical syndrome (not including suspected autism-spectrum conditions) such as Down syndrome (225 families). After exclusions data were available for 8104 twin pairs, of which 1340 were monozygotic male pairs, 1325 dizygotic males, 1496 monozygotic females, 1354 dizygotic females and 2589 dizygotic twin pairs of opposite sex. At age 9, only twins born between January 1994 and August 1995 were contacted, resulting in a smaller sample size. Data on IQ, academic achievement and/or autistic traits were available for 7965 7/8-year-old twin pairs and for 3687 pairs at age 9.

Measures
The Childhood Autism Spectrum Test (CAST) is a 31-item questionnaire asking about behaviours associated with autism-spectrum conditions. A CAST score of ≥ 15 is the cut-off for identifying children at risk for autism-spectrum conditions. Items can be divided into three subscales, based on the DSM–IV criteria for autism: social impairments (12 items); communication impairments (12 items); and restricted repetitive behaviours and interests (7 items). The CAST shows good test–retest reliability (r = 0.85) and satisfactory internal consistency (α = 0.73 in TEDS) for the full CAST and moderate α-values for the subscales (social impairments: α = 0.57; communication impairments: α = 0.66; restricted repetitive behaviours and interests: α = 0.50). Parents rated the child’s autistic traits at age 8. If the families gave consent, teachers were asked to complete an abbreviated version of the CAST (20 items) when the twins were 9 years.

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A battery of IQ tests was administered by telephone at age 7. Two verbal (similarities and vocabulary) and two non-verbal subtests (picture completion and concept grouping) from the Wechsler Intelligence Scale for Children–III (WISC–III) and the McCarthy Scales of Children’s Abilities were modified for telephone administration. The IQ composite score derived from the telephone-administered test battery correlates 0.72 with the Stanford–Binet Intelligence Scale. At age 9, IQ was assessed using test booklets completed by the twins under parental supervision. A composite score was derived from two verbal (adaptations of the WISC–III vocabulary and information subtests) and two non-verbal tests (adaptations of the subtests figure classification and figure analogies from the Cognitive Abilities Test). Teachers were asked to assess the twin’s academic achievement using a 5-point rating scale following the UK national curriculum achievement goals. A composite score was used at both ages, based on achievement in English and mathematics at age 7 and in English, mathematics and science at age 9.

Children with autism-spectrum conditions

Children at risk for autism-spectrum conditions were identified from parents informing TEDS about their twins’ diagnoses or from scores above the cut-off on the CAST at age 8. These children were followed up and were administered the Development and Well-Being Assessment (DAWBA). Based on the data available at the time of the present analyses, 85 children were identified with the DAWBA as having autism, 11 children with Asperger syndrome, and 64 children with autism-spectrum conditions other than autism or Asperger syndrome. Parent-rated CAST scores were available for 145 of these children (75 with autism; 10 with Asperger syndrome; 60 with other autism-spectrum conditions). Data on IQ and academic achievement were available for 51 and 84 children at age 7 respectively. Most children with autism-spectrum conditions were not invited to participate at age 9 to avoid over-testing, as these children were enrolled in another project during this time.

Data analyses

Children scoring in the top 5% of the distribution of autistic traits and/or in the bottom 5% of the distribution of IQ and academic achievement scores were defined as extreme cases (proband). This cut-off was chosen as the best balance between the need for a sufficient sample size and the aim of studying extreme groups. All analyses were based on age- and sex-regressed scores.

To examine whether children with extreme autistic traits were at increased risk for intellectual disability (as indexed by low IQ/academic achievement), chi-square tests were performed for one randomly selected twin from each pair. The phenotypic correlations across the full-range scores were examined using structural equation modelling in Mx for Windows, taking into account the genetic relatedness between the twins. Phenotypic correlations indicate whether variation in trait X covaries with individual differences in trait Y. Phenotypic group correlations examine the extent to which extreme scorers on trait X as a group score above or below the population mean on unselected trait Y. Phenotypic group correlations are calculated by dividing the proband’s standardised score on the unselected variable Y by the proband’s standardised score on the selected variable X. A phenotypic group correlation of 1.0 indicates that the probands’ mean score on Y is as extreme as the probands’ mean score on X, a phenotypic group correlation of 0.0 means that the probands’ score on Y is no different from the population mean. Phenotypic group correlations are bidirectional: selecting probands for extreme autistic traits and examining their IQ score could yield different results from selecting probands for extremely low IQ and examining their CAST scores.

Genetic analyses

DeFries–Fulker extremes analysis is a regression analysis of twin data in which the co-twin’s mean score is predicted by their proband’s score, taking into account the genetic relatedness between the twins (1.0 for monzygotic (MZ) twins; on average 0.5 for dizygotic (DZ) twins). Rather than assessing a dichotomy (e.g. intellectual disability present or absent), DeFries–Fulker extremes analysis assesses the continuous distribution directly and thereby provides a powerful test of the aetiology of extreme scores on a continuous dimension.

Sex differences are reported for autism. To maintain the comparability of the MZ and DZ pairs, DeFries–Fulker extremes analyses were carried out on data from same-sex DZ twins only. Prior to the regression analysis all scores were standardised (i.e. expressed as a deviation from the population mean) and then transformed (i.e. divided by the difference between the proband and general population means, specific for each zygosity). Comparing the regression to the population mean for MZ and DZ co-twins of probands gives insight in the genetic influences on extreme traits. If the mean scores of MZ co-twins resemble the proband scores more closely than DZ co-twin scores do there is evidence for genetic effects on the extreme trait.

The following regression equation is used in DeFries–Fulker extremes analyses:

\[
C = B_1P + B_2R + A,
\]

in which C is the predicted score for the co-twin, P is the proband score, R is the coefficient of the genetic relatedness between the twins and A is the regression constant; B_1 is the partial regression of the co-twin’s score on the proband’s score and is an index of average MZ and DZ resemblance independent of zygosity and B_2 is the partial regression of the co-twin’s score on R and is equivalent to twice the difference between the standardised transformed means for MZ and DZ co-twins. The value of B_2 provides a direct estimate of group heritability \((h^2_g)\); the extent to which genetic factors account for the mean difference between probands and the population.

The aetiology of the association between extreme autistic traits and low IQ/academic achievement was studied using the bivariate extension of DeFries–Fulker analysis. Bivariate DeFries–Fulker analysis selects the probands on trait X, but compares the quantitative scores of their co-twins on unselected trait Y. In the bivariate DeFries–Fulker regression equation:

\[
C_Y = B_3P_X + B_4R + A,
\]

C is the predicted score of the co-twin on unselected variable Y, P is the proband’s score on selected variable X, B_3 is the partial regression of the co-twin’s Y score on the proband’s X score, and B_4 is the partial regression of the co-twin’s Y score on the coefficient of the genetic relatedness. The value of B_4 indicates the extent to which the proband’s deficit on trait X can be ascribed to genetic factors that also influence trait Y. Dividing B_4 by the corresponding phenotypic group correlation provides a measure of the proportion of the covariance that can be attributed to genetic factors, called bivariate heritability.

Since bivariate DeFries–Fulker extreme analyses are bidirectional, the analysis for the opposite direction has to be examined separately. The genetic correlation (the extent to which deficits on trait X and deficits on trait Y are affected by the same set of genes) can be derived as:

\[
t_g(XY) = \sqrt{(B_2(XY))(B_2(YX))}/(B_2(X))(B_2(Y))
\]
A genetic correlation of 1.0 suggests complete genetic overlap; a correlation of 0.0 indicates that the traits are affected by two separate sets of genes.

If the transformed DZ co-twin means are less than half the MZ co-twin means, non-additive genetic effects might play a role (although sibling interaction effects could also apply). Because the power in DeFries–Fulker analyses is limited to distinguishing non-additive from additive genetic influences, only broad heritability is examined in this study. When the data suggested non-additive effects (when the estimate for $h^2$ or $B_1$ exceeded the estimate of the transformed MZ co-twin mean), $h^2$ or $B_2$ were based on the estimated value of the transformed MZ co-twin mean.

**Results**

The distributions of the IQ and academic achievement scores were approximately normal; the CAST scores were slightly skewed (skewness statistics were 1.00 (parent ratings) and 1.47 (teacher ratings)). The untransformed scores were used in subsequent analyses, since previous DeFries–Fulker extremes analyses using the CAST showed that data transformation did not affect the results.\(^7\) The 5% with the most extreme (highest) scores on the parent-rated CAST obtained scores $\geq 1.83$ standard deviations above the population mean, equivalent to CAST scores $\geq 1.183$. The 5% with the most extreme (lowest) scores on the measure of IQ scored $\leq 1.68$ standard deviations (age 7) and 1.85 standard deviations (age 9) below the population mean. Mean CAST scores in children with autism-spectrum conditions were well above the clinical cut-off (mean 19.17, s.d. = 5.11), and CAST total and subscale scores were significantly higher than the population mean (all $P < 0.001$). Scores for IQ (mean $-0.69$, s.d. = 0.12) and academic achievement (mean $-1.51$, s.d. = 1.60) were significantly lower than the population mean ($F(1,9986) = 26.86$, $P < 0.001$ and $F(1,11217) = 213.80$, $P < 0.001$), although these descriptive statistics should be interpreted with care since IQ and academic achievement data were only available for 51 and 84 children with autism-spectrum conditions respectively.

The highest-scoring 5% on the parent-reported CAST were more likely to perform in the bottom 5% on the IQ test ($\chi^2(1) = 42.985$, $P < 0.001$, odds ratio (OR) = 4.32) and to show low academic achievement ($\chi^2(1) = 60.876$, $P < 0.001$, OR = 4.44). These odds ratios increased to 6.32 and 7.51 respectively in children who scored at or above the CAST cut-off. Extremely high scorers on the teacher-reported CAST were not significantly more likely to have low IQ scores ($\chi^2(1) = 1.718$, $P = 0.083$, OR = 1.76) but did show an increased risk for poor academic achievement ($\chi^2(1) = 78.979$, $P < 0.001$, OR = 6.76).

The phenotypic correlations between parent- and teacher-rated autistic traits and IQ and academic achievement were all negative and ranged between $-0.07$ and $-0.24$ for the full-range scores and between $-0.01$ and $-0.40$ for the phenotypic group correlations in the 5% extremes, suggesting that the association between number of autistic traits and intellectual disability (as indexed by low IQ/academic achievement) was modest. Both the full-range correlations and the phenotypic group correlations were similar in boys and girls (difference in $r$ < 0.05, online Table DS1), yielding no evidence for a gender effect on the association. To maximise power, all subsequent analyses were conducted for both genders combined. Phenotypic group correlations were also calculated for 15%, 2% and 1% cut-offs (online Table DS1). All associations between autistic traits and IQ were similar, suggesting that the magnitude of the relationship was linear across the sample. For academic achievement, there was a trend in which the phenotypic group correlations were somewhat stronger, with more extreme cut-offs for academic achievement.

Univariate DeFries–Fulker analyses (Table 1) showed high group heritability for parent- and teacher-rated CAST scores ($h^2 = 0.71$ and 0.65 respectively) and academic achievement ($h^2 = 0.85$ at both ages), and moderate group heritability for IQ ($h^2 = 0.31$ (age 7) and 0.44 (age 9)). Univariate DeFries–Fulker analyses have been reported previously\(^2\,\,^23\) and are therefore not discussed in detail here. In the bivariate models, transformed DZ co-twin scores consistently showed a stronger regression to the population mean than MZ co-twin scores, suggesting genetic effects on the overlap between extreme traits. The $B_1$ estimates were negligible for the association between IQ and teacher-rated CAST and modest for all other associations. Dividing each $B_2$ estimate by the corresponding phenotypic group correlation (bivariate heritability) showed that the modest phenotypic association between extreme autistic traits and intellectual disability was mainly accounted for by genetic effects. For example, in the group selected for extremely low IQ, 86% of the association with parent-reported CAST scores was explained by genetic factors ($-0.19/-0.22 = 0.86$). The bivariate heritability estimates were high for all measures, apart from the analyses between extremely low IQ and teacher-rated autistic traits. However, the genetic correlations were only modest. The genetic correlations between extreme parent-rated autistic traits and low IQ or poor academic achievement were 0.44 and 0.31. The genetic correlations using teacher-rated CAST scores were 0.04 and 0.38. What these results mean is that although genetic factors are largely responsible for the phenotypic association between autistic traits and low IQ/academic achievement, most of the genetic effects on autistic traits and on IQ/academic achievement are independent.

Next we explored whether the relationship between extreme autistic traits and intellectual disability varied for the different features of the autism triad. Both the full-range phenotypic correlations and the phenotypic group correlations indicated that the association between extreme autistic traits and intellectual disability is mainly explained by CAST items assessing communication difficulties (online Table DS2). Examination of the communication impairments items suggested that the observed association was not simply due to overlapping item content. The communication impairments items primarily assess difficulties with pragmatic communication (e.g. ‘Does s/he tend to take things literally?’) and do not directly assess (verbal) IQ. Repeating the DeFries–Fulker extremes analyses using just the communication impairments subscale yielded similar results to the CAST total analyses (online Table DS3). The genetic correlation between parent-rated communication impairments and intellectual disability was 0.48 when assessed using IQ scores and 0.33 using academic achievement scores. The genetic correlations between these measures and teacher-rated communication impairments were 0.22 and 0.50 respectively.

Lastly, we explored whether a discrepancy between IQ scores and academic achievement is related to number of autistic traits. Difference scores between IQ and academic achievement were correlated with parent and teacher CAST scores. Higher IQ scores relative to academic achievement correlated significantly with parent-reported communication impairments ($r = 0.06$, $P < 0.01$) and teacher-reported CAST total ($r = 0.14$, $P < 0.01$), social impairments ($r = 0.13$, $P < 0.01$) and communication impairments scores ($r = 0.17$, $P < 0.01$).

**Discussion**

**Modest genetic correlation between extreme autistic traits and intellectual disability**

This paper reports the first population-based study testing the association between extreme autistic traits and intellectual
disability (defined in terms of low IQ/academic achievement). Although the risk of showing poor performance on tests of IQ and academic achievement was significantly increased in children with extreme autistic traits, our results suggest that the association between extreme autistic traits and intellectual disability is only modest. There was a degree of genetic overlap between extreme autistic traits and intellectual disability, as indicated by modest to moderate correlations between social impairments and measures of IQ.36–38 Results for symptoms of restricted repetitive behaviours and interests varied, depending on the sample under investigation and the type of restricted repetitive behaviours and interests studied.36–8 Several family studies indicated an increased rate of social and communication deficits in relatives of individuals with autism.39 There is evidence to suggest that relatives who show communication difficulties.

These results are in line with our finding that the association between autistic traits and intellectual disability was mainly driven by communication difficulties.

### Academic achievement v. IQ in children with extreme autistic traits

Our phenotypic analyses suggested that the association between poor academic achievement and autistic traits became stronger the more stringently the cut-off for extreme groups was set. This trend was not observed in the analyses between autistic traits and IQ, for which the magnitude of the full-range phenotypic correlations and phenotypic group correlations was similar regardless of the cut-off. Analyses exploring discrepancies between IQ scores and teacher-rated academic achievement suggested that teachers and teacher-rated academic achievement are significantly increased in children with extreme autistic traits.
and communication difficulties. Children with such problems may struggle to show their full cognitive potential in the classroom. These results mirror findings from clinical studies that report attenuated academic achievement relative to IQ in individuals with autism-spectrum conditions.2

Methodological considerations

The current study defined extreme autistic traits as the highest-scoring 5% of a large community sample assessed on a continuous measure of autistic traits. This selection included children scoring ≥11.83 on the parent-reported CAST. Children with a diagnosis of autism-spectrum conditions typically4 obtain parental CAST scores ≥15 and our extreme group is therefore likely to include less extreme cases than a clinical sample. Similarly, the lowest-scoring 5% on a measure of IQ and academic achievement were selected. Although the IQ and academic achievement scores in these extreme groups were markedly low (mean academic achievement scores were 2.20–2.60 standard deviations below the population mean; IQ scores were 2.12–2.26 standard deviations below the population mean, corresponding to standardised IQs of approximately 67), it should be acknowledged that this sample included few children with severe intellectual disabilities. Our results cannot therefore be generalised to individuals with severe or profound intellectual disability, in whom the aetiology of autism may be different.4 In about 10–20% of cases, autism-spectrum condition can be accounted for by known medical conditions, defined mutations or gross chromosomal abnormalities41 and the affected individuals are likely also to have intellectual disability. Our results are only informative for the idiopathic cases (accounting for the remaining 80–90%) in which the risk for autism may be influenced by common genetic variants.

The large scale of this study did not permit detailed investigation of the relative strengths and weaknesses in cognitive functioning. The IQ tests were administered by telephone at age 7. Children with many autistic traits, particularly children with communication difficulties, may find it hard to perform well using this assessment procedure. However, similar correlations were found using the academic achievement data and at age 9 (when test booklets were used), strengthening our confidence in the validity of the IQ measure at age 7. At age 9 data were available for a smaller number of twins, and most children with autism-spectrum conditions were excluded at this age to avoid over-testing. We feel that these data are still valuable as the results show remarkable consistency between raters and across age, indicating that these findings are neither rater- nor age-specific.

Implications

This study has implications for future genetic studies of autism. Our results indicate that in a community-based sample the liability to extreme autistic traits is substantially genetically independent of the vulnerability to impaired intellectual functioning. In so far as there is genetic overlap, this link is likely to be found in genes affecting communication abilities. Genes involved in neurodevelopment are probably important in certain forms of autism-spectrum conditions,92 particularly in individuals with severe intellectual disability. However, these genes are unlikely to be the sole explanation of the complex aetiology of autism. Our study suggests that genetic variants that do not affect general intellectual abilities also play a role.

Our finding of a limited association between autistic traits and intellectual disability contrasts with clinical studies reporting a high prevalence of intellectual disability in autism.1 This discrepancy may be explained, in part, by clinical ascertainment bias.4 Individuals with extreme autistic traits and intellectual disability may be more likely to be referred to the clinic. The number of individuals with autism-spectrum conditions with normal IQ may thus be underreported. Health and education professionals may need to be made more aware that autism-spectrum conditions can occur without intellectual disability to ensure that all individuals warranting a diagnosis are detected.

References


Global warming

H. Steven Moffic

Much scientific consensus has developed that global warming is a major threat to the well-being of our planet and ourselves. This danger includes mental health. Violence, trauma and anxiety are all projected to increase. Psychology has also contributed to the genesis and delayed responsiveness to global warming, given the use of denial, narcissism, and fear of change on the part of politicians and citizens. Given the importance of psychiatry for this social problem, psychiatrists should be at the forefront of ‘going green’ in terms of advocacy, modelling and solutions. We are not yet, but our ethical duty requires more.


