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Co-Occurrence of ADHD and Low IQ Has Genetic Origins

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Previous studies show that the symptoms of attention deficit hyperactivity disorder (ADHD) and lower intelligence quotient (IQ) covary in children. We investigated the aetiology of this association in a large population-based sample of 5-year-old twins. The twins were individually assessed on an IQ test, and data on ADHD symptoms were obtained from mother interviews and teacher ratings. Confirming previous studies, the phenotypic correlation between ADHD symptom scores and IQ was −0.3 and, in a categorical analysis, children with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) ADHD research diagnosis obtained IQ scores nine points lower, on average, than comparison children. We show here that the co-occurrence of ADHD and lower IQ has genetic origins: 86% of the association between ADHD symptom scores and IQ, and 100% of the association between ADHD diagnosis and IQ, was accounted for by genetic influences that are shared by ADHD and IQ. Some candidate genes for ADHD could also contribute to variation in IQ or vice versa. © 2003 Wiley-Liss, Inc.

KEY WORDS: attention deficit hyperactivity disorder (ADHD); hyperactivity; intelligence quotient (IQ); genetics; twin study

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), which affects 5–9% of children [Swanson et al., 1998], consists of a combination of severe overactive, impulsive, and inattentive behaviours. Although ADHD is a categorical diagnosis, several studies support the hypothesis that it represents the extreme of a behaviour that varies continuously throughout the entire population [Biederman et al., 1993; Fergusson and Horwood, 1995; Levy et al., 1997].

Previous research indicates that ADHD and lower intelligence quotient (IQ) covary in the population. The difference between children diagnosed with ADHD and comparison children is about 7–12 IQ points [Mariani and Barkley, 1997; Crosbie and Schachar, 2001; Rucklidge and Tannock, 2001]; in general population samples, the correlation between rating-scale measures of ADHD symptoms and IQ is −0.2 to −0.4 [Fergusson et al., 1993; Goodman et al., 1995; Rapport et al., 1999]. The aetiology of this association has been little explored. For a comprehensive theoretical account of ADHD, it is crucial to investigate whether the co-occurrence of ADHD and lower IQ is due to genetic or environmental causes. If evidence of a shared genetic aetiology was obtained, this could prove valuable in the search for candidate genes, as genes influencing ADHD could also contribute to variation in IQ or vice versa. The association between ADHD and IQ has also wider implications: lower IQ scores predict poor academic and occupational achievement [Kline, 1991], both of which are characteristic of ADHD [Mannuzza and Klein, 2000].

In ADHD and IQ independently, the extent of genetic and environmental influences is well documented. ADHD is highly heritable (60–90%), regardless of whether continuous or categorical criteria are applied [Thapar et al., 1999]. For IQ, a developmental pattern emerges, whereby the extent of genetic influences gradually increases with age: heritability is estimated at 40% at ages 4–6, 50% at ages 6–12, and 80% in adulthood [McGue et al., 1993]. Twin studies also indicate that environmental experiences contribute to both ADHD and IQ, as the heritability for both is short of unity. For IQ in childhood, both environmental experiences that children in the same family share in common

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and those that are unique to each child are implicated [McGue et al., 1993]. Twin analyses of ADHD implicate child-specific environmental influences only [Faraone and Doyle, 2000].

We therefore investigated the contribution of genetic and environmental influences to the specific association between ADHD and IQ, in a large population-based sample of 5-year-old twins. We show here that both ADHD symptom scores in the general population and the categorical diagnosis of ADHD are associated with lower IQ due to a shared genetic aetiology.

MATERIALS AND METHODS

Environmental Risk (E-Risk) Study Sample

Participants are members of the E-risk Longitudinal Twin Study, which investigates how genetic and environmental factors shape children's development. The E-risk sampling frame was two consecutive birth cohorts (1994 and 1995) in the Twins' Early Development Study, a birth register of twins born in England and Wales [Trouton et al., 2002]. The full register is administered by the government's Office of National Statistics (ONS), which invited parents of all twins born in 1994–1995 to enrol. Of the 15,906 twin pairs born in these 2 years, 71% joined the register. Our sampling frame excluded opposite-sex twin pairs and began with 73% of register families who had same-sex twins.

The E-risk Study sought a sample size of 1,100 families to allow for attrition in future years of the longitudinal study while retaining statistical power. An initial list of families was drawn from the register to target for home visits, including a 10% oversample to allow for nonparticipation. The probability sample was drawn using a high-risk stratification strategy. High-risk families were those in which the mother had her first birth when she was 20 years of age or younger. We used this sampling: (1) to replace high-risk families who were selectively lost to the register via non-response and (2) to ensure sufficient base rates of problem behaviours given the low base rates expected for 5-year-old children. Early first childbearing was used as the risk-stratification variable because it was measured for virtually all families in the register, it is relatively free of measurement error, and it is a known risk factor for children's problem behaviours [Maynard, 1997; Moffitt, 2002]. The sampling strategy resulted in a final sample in which two-thirds of Study mothers accurately represent all mothers in the general population (aged 15–48) in England and Wales in 1994–1995 (estimates derived from the General Household Survey) [Bennett et al., 1996]. The other one-third of Study mothers (younger only) constitute a 160% oversample of mothers who were at high-risk based on their young age at first birth (15–20 years). To provide unbiased statistical estimates that can be generalised to the population, the data reported in this article were corrected with weighting to represent the proportion of young mothers in the UK [Birth Statistics, 1996].

Of the 1,203 eligible families, 1,116 (93%) participated in home-visit assessments when the twins were age 5 years. Zygosity was determined using a standard zygosity questionnaire which has been shown to have 95% accuracy [Price et al., 2000]. Ambiguous cases were zygosity-typed using DNA. The sample includes 56% monozygotic (MZ) and 44% dizygotic (DZ) twin pairs. Sex is evenly distributed within zygosity (49% male).

Data were collected within 120 days of the twins' fifth birthday. Research workers visited each home for 2.5–3 hr, in teams of two. While one interviewed the mother, the other tested the twins in sequence in a different part of the house. Families were given shopping vouchers for their participation, and children were given colouring books and stickers. All research workers had university degrees in behavioural science, and experience in psychology, anthropology or nursing. Each research worker completed a formal 15-day training program on either the mother interview protocol or the child assessment protocol, to attain certification to a rigorous reliability standard. With parents' permission, questionnaires were posted to the children's teachers and teachers returned questionnaires for 94% of cohort children.

ADHD Symptoms

Data about children's ADHD symptoms were obtained from mothers and teachers. In the mother interview, children's symptomatology was measured with 18 items concerning inattention, impulsivity and hyperactivity derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [American Psychiatric Association, 1994] diagnostic criteria for ADHD and the Rutter Child Scales (e.g., "inattentive, easily distracted", "impulsive, acts without thinking", "very restless, has difficulty staying seated for long") [Sclare, 1997]. Symptoms were reported for the preceding 6 months and each symptom was scored as "not true" (0), "somewhat or sometimes true" (1) and "very true or often true" (2). Teachers rated each twin using the same set of items. The internal consistency reliabilities of the parent and teacher reports were 0.90 and 0.93, respectively. We formed an ADHD symptom scale by summing the mother and teacher ratings to obtain a highly reliable overall measure. Mother and teacher reports of ADHD symptoms correlated 0.28 ($P < 0.001$), which is typical of inter-rater agreement about behavioural problems [Achenbach et al., 1987]. A square root transformation normalised the distribution. Because boys had more symptoms than girls (r between ADHD symptoms and sex $= -0.19$, $P < 0.001$), we partialled sex from the ADHD symptom scale prior to model fitting analyses.

ADHD research diagnoses were based on DSM-IV criteria. Children received the diagnosis if they had six or more of the hyperactivity-impulsivity symptoms and/or six or more of the inattentiveness symptoms according to either mother or teacher report. In addition, the other rater had to indicate two or more symptoms of either inattentiveness or hyperactivity-impulsivity. Therefore the diagnostic criteria included the presence of symptoms in more than one setting (home and school), as well as onset before age 7 since all children in this study were 5 years old. Symptoms were counted as present only if scored "very true or often true". The prevalence of ADHD diagnoses was 5.7%.

IQ

Each child was individually tested using a short form of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) [Wechsler, 1990] comprising Vocabulary and Block Design subtests. IQs were prorated following procedures described by Sattler [1992]. The children's IQs ranged from 52 to 145, normally distributed ($M = 98$, $SD = 14.41$). Although we used a short form of the IQ test to minimise testing demands on the children, it was nonetheless possible that the IQ and ADHD scores are correlated because children with ADHD are disinterested and inattentive when taking tests. We tested this possibility in a separate sample of 400 boys whose videotaped test sessions were rated by blinded observers (inter-rater agreement = 0.81) [Lynam et al., 1993]. Less than one-quarter (two IQ points) of the association between ADHD symptoms and IQ could be attributed to inattentive test-taking behaviours.

Analyses

All phenotypic analyses were corrected for the non-independence of the twin observations by using tests based on the sandwich or Huber/White variance estimator [Gould and Sribney, 1999].

The structural equation modelling program Mx [Neale, 1997] was used to conduct the genetic analyses on ADHD symptoms as a continuous dimension. The logic behind quantitative genetic analyses of twin data has three parts. First, MZ twins share all their genes but DZ twins, like ordinary full siblings, share on average only half of their polymorphous genes. As such, when the similarity of MZ twins is greater than the similarity of DZ twins, this indicates a genetic contribution to behaviour. In model fitting, this yields a significant variance component called A (additive genetic variance). Second, MZ twins' genetic similarity is twice that of DZ twins', and therefore, if only genes were influencing their behaviour, MZ twins' behaviour should be twice as similar as DZ twins'. If not, this indicates that the environments the children share in common have enhanced their similarity. In model fitting, this yields a significant variance component called C (common or shared environmental variance). Third, if MZ twins, despite sharing all their genes, are not perfectly identical in their behaviour, this indicates that experiences unique to each twin, and not shared with their co-twin, have reduced the twins' behavioural similarity. In model fitting, this yields a significant variance component called E (child-specific environmental variance, which also includes measurement error).

Models are fit to the MZ and DZ covariance matrices. The full ACE model is fitted first. Then, to attain the most parsimonious model, parameters which do not significantly contribute to the fit of the model are dropped. Because E includes measurement error, it is not usually dropped in univariate analyses. The AE and CE models are nested within the full ACE model (i.e., subsets of free parameters in these models are contained in the full model). For nested models, the change in the chi-square value is used to determine which model provides the best fit to the data. For non-nested models, the Akaike's information criteria (AIC) and root mean square error of approximation (RMSEA) values are used to compare the fit of alternative models. For both these indices, lower values indicate less difference between the observed and predicted covariances, and therefore better fit [Williams and Holahan, 1994]. RMSEA is more appropriate as an overall measure of fit for large sample sizes. RMSEA values between 0.00 and 0.05 indicate excellent fit, and the values between 0.05 and 0.08 good fit [MacCallum et al., 1996].

Previous research on ADHD has revealed that the DZ correlations are sometimes less than half of MZ correlations [Thapar et al., 1999]. In the present study, as in others, such sibling contrast was observed in mothers' ratings but not teachers' ratings (suggesting sibling contrast is limited to mothers' ratings and is therefore not a general effect such as genetic dominance). As such, to estimate the ACE parameters free of sibling contrast, we also fitted a contrast-effect model (AE_s) to the ADHD data [see Neale and Stevenson, 1989; Neale and Cardon, 1992 for a full description of the AE_s model]. The AE model is nested within the AE_s model.

In the bivariate twin analysis, MZ and DZ correlations are compared across traits: i.e., one twin's ADHD symptoms are correlated with the co-twin's IQ score. If the cross-trait twin correlations are greater for MZ than for DZ twins, this implies that genetic factors contribute to the phenotypic correlation between the two traits. A genetic correlation (r_A) indicates the extent to which genetic influences on one trait overlap with those on the second trait (regardless of their individual heritabilities). Based on the genetic correlation and the individual heritability of each trait, the extent to which shared genetic influence generates a phenotypic correlation between two traits can be estimated.

We used the Mplus package [Muthén and Muthén, 2002], which has extensive categorical data modelling capabilities, to estimate univariate and bivariate models with a diagnostic classification of ADHD. The bivariate model is based on a Cholesky parameterisation [Loehlin, 1996], using Weighed Least Squares, with the ADHD diagnosis variable treated as a threshold variable [Muthén, 1984].

RESULTS

The phenotypic correlation between ADHD symptom scores and IQ was -0.28 ($t_{1106} = -10.77$, $P < 0.001$). Children with an ADHD research diagnosis had a mean IQ of 89 ($SD = 15.27$) and the comparison children had a mean IQ of 98 ($SD = 14.11$; $t_{1047} = 5.81$, $P < 0.001$).

The MZ and DZ within-pair correlations (Tables IA and IB) provide rough estimates of the extent to which genetic, shared environmental and child-specific environmental factors contribute to ADHD and IQ in childhood. The greater MZ than DZ correlations for IQ (MZ = 0.70 vs. DZ = 0.53), ADHD symptom scores (MZ = 0.64 vs. DZ = 0.20, Table IA) and ADHD diagnosis (MZ = 0.87 vs. DZ = 0.33, Table IB) indicate substantial genetic effects on each phenotype.

TABLE IA. Within-Pair Pearson Correlations: ADHD Symptom Scores and IQ

	Twin 1 ADHD symptoms	Twin 1 IQ	Twin 2 ADHD symptoms	Twin 2 IQ
MZ twins				
Twin 1 ADHD symptoms	1.00			
Twin 1 IQ	−0.26	1.00		
Twin 2 ADHD symptoms	0.64	−0.21	1.00	
Twin 2 IQ	−0.25	0.70	−0.31	1.00
Mean (SD)	15.46 (11.52)[a]	96.81 (13.64)	14.99 (11.12)[a]	97.15 (14.32)
DZ twins				
Twin 1 ADHD symptoms	1.00			
Twin 1 IQ	−0.31	1.00		
Twin 2 ADHD symptoms	0.20	−0.12	1.00	
Twin 2 IQ	−0.12	0.53	−0.27	1.00
Mean (SD)	16.93 (11.86)[a]	98.88 (14.61)	14.30 (11.00)[a]	98.44 (15.07)

[a]Prior to transformation.

For IQ, the ACE model provided the best fit to the data (Table II). The proportion of variance in IQ accounted for by additive genetic effects was 40% (95% confidence interval (CI) 28–54%), by shared-environmental factors 31% (95% CI 18–42%) and by child-specific environmental factors 29% (95% CI 25–33%). For ADHD symptom scores, the contrast-effect (AE_s) model provided the best fit. The proportion of variance in ADHD symptom scores accounted for by additive genetic effects was 72% (95% CI 65–77%) and by child-specific environmental factors 28% (95% CI 23–35%), after contrast effects (s = −0.08, 95% CI −0.13 to −0.03) were removed from the total variance explained. For ADHD diagnosis, the AE model provided the best fit, with genetic contribution estimated at 85% and child-specific environmental contribution estimated at 15%.

As expected based on the univariate analyses of ADHD symptom scores and IQ, the bivariate model that provided the best fit to the data consisted of the AE_s model for ADHD symptom scores and the ACE model for IQ (Table III). The proportion of the phenotypic correlation between ADHD symptom scores and IQ (r = −0.28) that is explained by shared genetic effects can be estimated from the parameter estimates in the bivariate twin model (Table III). Specifically, this estimate (−0.24) is obtained by multiplying the square root of the heritability estimate for ADHD symptom scores (0.72) by the square root of the heritability estimate for IQ (0.40) by the genetic correlation between ADHD symptom scores and IQ ($r_A = -0.45$). Thus, 86% (−0.24/−0.28) of the phenotypic correlation between ADHD symptom scores and IQ was accounted for by genetic influences that are shared by ADHD and IQ (Fig. 1). The remaining 14% of the phenotypic correlation that was not due to genetic effects was accounted for by child-specific environmental influences (and possibly measurement error).

Supplementary bivariate models were carried out to examine the association between IQ and symptom scores of inattention, hyperactivity and impulsivity, separately. In each case the best-fitting model consisted of the AE_s model for the behavioural dimension and the ACE model for IQ. The proportion of the phenotypic correlation between inattention symptoms and IQ (r = −0.31) explained by shared genetic effects was 81% ($r_A = -0.50$); the proportion of the phenotypic correlation between hyperactivity symptoms and IQ (r = −0.25) explained by shared genetic effects was 85% ($r_A = -0.38$); and the proportion of the phenotypic correlation between impulsivity symptoms and IQ (r = −0.10) explained by shared genetic effects was 91% ($r_A = -0.17$).

For ADHD diagnostic data, a bivariate model that consisted of the AE model for ADHD and the ACE model for IQ provided the best fit to the data (Table III). As above, the proportion of the phenotypic correlation

TABLE IB. Model-Estimated* Within-Pair Correlations: ADHD Diagnosis and IQ

	Twin 1 ADHD	Twin 1 IQ	Twin 2 ADHD	Twin 2 IQ
MZ twins				
Twin 1 ADHD	[a]			
Twin 1 IQ	−0.42	1.85[b]		
Twin 2 ADHD	0.87	−0.23	[a]	
Twin 2 IQ	−0.39	0.70	−0.23	2.00[b]
DZ twins				
Twin 1 ADHD	[a]			
Twin 1 IQ	−0.35	2.07[b]		
Twin 2 ADHD	0.33	−0.15	[a]	
Twin 2 IQ	−0.05	0.54	−0.26	2.27[b]

*Based on a threshold model with both a categorical (ADHD) and a continuous (IQ) dependent variable.
[a]Fixed by the model.
[b]Variance.

TABLE II. Fit of Quantitative Genetic Models Examining the Aetiology of IQ and ADHD

	AIC	RMSEA	χ^2	df	*P*	Comparison model	$\Delta\chi^2$	Δdf	*P*
IQ									
1. AE	17.97	0.09	25.97	4	0.00				
2. CE	39.18	0.14	47.18	4	0.00				
3. ACE	0.15	0.04	6.15	3	0.11	1	19.82	1	<0.001
ADHD symptoms									
1. AE	1.60	0.04	9.60	4	0.05				
2. CE	97.42	0.21	105.42	4	0.00				
3. AE_s	−5.17	0.00	0.83	3	0.84	1	8.77	1	<0.01
4. ACE	3.60	0.05	9.60	3	0.02	1	0.00	1	n.s.
ADHD diagnosis									
1. AE	−6.02	0.00	1.98	4	0.74				
2. CE	6.18	0.07	14.18	4	0.01				
3. AE_s	−5.23	0.00	0.78	3	0.86				
4. ACE	−4.02	0.00	1.98	3	0.58	1	0.00	1	n.s.

AIC, Akaike's information criteria; RMSEA, root mean square error of approximation.

(−0.34) that is due to shared genetic effects was obtained by multiplying the genetic correlation (−0.59) by the square root of the univariate heritability estimates for ADHD diagnosis and IQ. Given a model-estimated phenotypic correlation of −0.34 between ADHD diagnosis and IQ, 100% (−0.34/−0.34) of the correlation was accounted for by shared genetic influences (Fig. 1).

DISCUSSION

With a large population-based sample of twins who were individually assessed on an IQ test, we demonstrated that the association between ADHD symptoms and lower IQ is largely due to a shared genetic aetiology: 86% of the phenotypic correlation between ADHD symptom scores and IQ, and 100% of the phenotypic correlation between ADHD research diagnosis and IQ, was accounted for by genes that influence both ADHD and IQ. The data indicate that environmental effects, though linked to IQ and ADHD individually, do not contribute substantially to their covariation in the population.

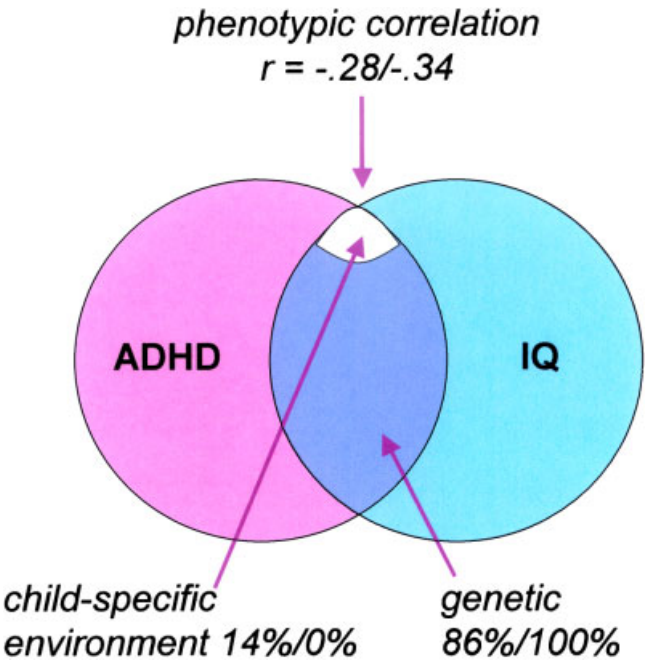

Fig. 1. Genetic and environmental contributions to the negative phenotypic correlation between IQ and both ADHD symptom scores and ADHD diagnosis. [Colour figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

This study is, to our knowledge, the first genetic-epidemiological study of the specific association between ADHD and lower IQ. Two other studies examined the association between cognitive ability and behaviour problems in a sample of preschool twins [Plomin et al., 2002] and twins aged 6–17 years [Jacobs et al., 2002], but were not able to specifically examine ADHD. We focused on 5-year-old children because this is the developmental period during which symptoms of ADHD are first manifest. However, we do not know whether the findings will replicate in other age groups. Although the negative phenotypic association between IQ and ADHD has been observed in samples ranging in age from early childhood through adolescence [Fergusson et al., 1993; Goodman et al., 1995; Mariani and Barkley, 1997; Rapport et al., 1999; Crosbie and Schachar, 2001; Rucklidge and Tannock, 2001], it is possible that this association is accounted for by different factors at later ages than in early childhood. In addition, we did not administer full IQ tests. However, the Vocabulary and Block Design subtests correlate highly with Verbal IQ (0.80) and Performance IQ (0.78), respectively (data from 5-year-olds) [Wechsler, 1990; Sattler, 1992].

Previous research suggests that the association with IQ may be particularly strong for inattentiveness [Chhabildas et al., 2001]. In the current data the association was stronger for both inattention and hyperactivity than for impulsivity, but the genetic relation with IQ was similar across the different symptom dimensions.

Multiple genes of small effect size (called quantitative trait loci (QTLs), or susceptibility genes) are likely to be responsible for the genetic influences on complex traits, such as ADHD and IQ [Plomin et al., 1994]. Molecular

TABLE III. Estimates of Genetic and Environmental Contributions to the Association Between ADHD and IQ

	r_A (95% CI)	r_E (95% CI)	s	Phenotypic r attributable to: Genes	Phenotypic r attributable to: Child-specific environment	AIC	RMSEA	χ^2	df	*P*
ADHD symptoms	−0.45 (−0.57 to −0.36)	−0.15 (−0.22 to −0.07)	−0.04 (−0.06 to −0.01)	−0.24	−0.04	−12.18	0.01	11.82	12	0.46
ADHD diagnosis	−0.59	—	—	−0.34	0.00	0.91	0.05	34.92	17	0.01

The phenotypic correlation between ADHD symptom scores and IQ is −0.28, and between ADHD diagnosis and IQ is −0.34.
r_A, genetic correlation; r_E, child-specific environmental correlation; s, contrast effects; AIC, Akaike's information criteria; RMSEA, root mean square error of approximation.

genetic studies have identified dopamine pathway genes as candidate genes in ADHD, with promising, though not yet conclusive, results emerging for the dopamine D4 receptor (*DRD4*) [Faraone et al., 2001] and the dopamine transporter (*DAT1*) [Curran et al., 2001] genes. Large-scale research programs into the genetics of general cognitive ability are also underway [Plomin, 2001]. The shared genetic aetiology of ADHD symptoms and lower IQ could be due to pleiotropic (multiple different) effects of genes that are implicated in the aetiology of ADHD, or of genes, yet to be identified, related to individual differences in IQ. This has implications for future molecular genetic studies, as a gene that is linked to either ADHD or IQ may also act as a susceptibility gene for the other phenotype. Such pleiotropic effects of a specific QTL have recently been suggested to explain, at least in part, the comorbidity between ADHD and reading disability [Willcutt et al., 2002]. Alternatively, the shared genetic aetiology between IQ and ADHD symptoms may indicate a causal, genetically mediated pathway from one phenotype to the other. For example, ADHD symptoms could interfere with learning, affecting IQ scores, or with performance on intelligence tests [see Goodman et al., 1995, for a further discussion of possible pathways]. Data from a previous study (see "Materials and Methods") suggest, however, that the association between ADHD symptoms and lower IQ cannot be fully attributed to inattentive test-taking behaviours.

That the co-occurrence of ADHD and lower IQ has genetic origins raises the possibility that specific genes may influence brain networks that underlie both ADHD and IQ. This would fit in with two sets of recent data indicating, first, that brain volume abnormalities in ADHD are early emerging and persistent [Castellanos et al., 2002] and, second, that there are shared genetic influences on the association between brain volume and IQ [Posthuma et al., 2002]. The current finding also raises the question of the extent to which the association with lower IQ reflects the specific psychological processes that are hypothesised to be impaired in ADHD. Future research can address these questions by combining cognitive and brain-imaging methods with genetically informative designs. The present study, together with the recent finding on brain volume and IQ [Posthuma et al., 2002], illustrates how the combination of different approaches—genetic, cognitive and brain-imaging methods, along with behavioural or diagnostic assessments—will help to build causal models relating genes, brain, cognition and behaviour.

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