OPEN ACCESS

KING'S College LONDON

King's Research Portal

DOI:
10.1007/s10802-007-9149-9

Document Version
Peer reviewed version

Link to publication record in King's Research Portal

Citation for published version (APA):
McLoughlin, G., Ronald, A., Kuntsi, J., Asherson, P., & Plomin, R. (2007). Genetic support for the dual nature of attention deficit hyperactivity disorder: Substantial genetic overlap between the inattentive and hyperactive-impulsive components. *Journal of Abnormal Child Psychology*, *35*(6), 999-1008. https://doi.org/10.1007/s10802-007-9149-9

Citing this paper
Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights
Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

•Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
•You may not further distribute the material or use it for any profit-making activity or commercial gain
•You may freely distribute the URL identifying the publication in the Research Portal

Take down policy
If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Download date: 20. Apr. 2025

Europe PMC Funders Group
Author Manuscript
J Abnorm Child Psychol. Author manuscript; available in PMC 2013 October 14.

Published in final edited form as:
J Abnorm Child Psychol. 2007 December ; 35(6): 999–1008. doi:10.1007/s10802-007-9149-9.

Genetic support for the dual nature of attention deficit hyperactivity disorder: Substantial genetic overlap between the inattentive and hyperactive-impulsive components

Gráinne McLoughlin, **Angelica Ronald**, **Jonna Kuntsi**, **Philip Asherson**, and **Robert Plomin**
MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London

Abstract

Objective—Attention deficit hyperactivity disorder (ADHD) is a common, complex and highly heritable disorder, characterised by inattentive, impulsive and overactive behaviour. Evidence for the heritability of ADHD measures in twin population samples has come from the analysis of total scores that combine inattentive and hyperactive-impulsive symptoms subscales. This study investigated, in a community sample, the aetiology of ADHD-like traits and the aetiological overlap between the two dimensions that define the ADHD disorder.

Method—Parents of 6,222 approximately 8-year-old twin pairs from the Twins Early Development Study (TEDS) population sample completed the two subscales of the Conners' 18-item DSM-IV checklist, a screening instrument for ADHD symptoms.

Results—Both subscales were highly heritable (hyperactive-impulsive: 88%; inattentive: 79%). Bivariate genetic modelling indicated substantial genetic overlap between the two components; however, there were significant independent genetic effects.

Conclusions—These findings suggest that many genes associated with the hyperactivity-impulsivity dimension will also be associated with the inattentive dimension but that there is significant genetic heterogeneity as well. These results provide genetic support for combining the two behavioural dimensions that define ADHD, but also suggest that some symptom-specific genes will also be identified.

Introduction

Inattentiveness, impulsivity and overactivity are common behaviours among young children. At extreme, developmentally inappropriate levels, these behaviours may lead to the diagnosis of attention deficit hyperactivity disorder (ADHD). ADHD is a heterogeneous disorder, which represents variations in a dyad of hyperactivity-impulsivity and inattentive behaviours, as suggested by factor analyses (e.g. Pelham et al., 1992) and the DSM-IV conceptualisation of the disorder (Lahey et al., 1994). Clinically, the combined subtype is characterised by both hyperactive-impulsive and inattentive behaviours; the predominantly hyperactive-impulsive and inattentive subtypes have extreme behaviours in only one domain.

Despite the widespread dependence of current candidate gene and genetic linkage studies of ADHD on DSM-IV nosology, little is known about the extent of genetic overlap between

Correspondence and reprint requests to: Gráinne McLoughlin, MRC Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK +44 20 7848 5261+44 20 7848 0866grainne.mcloughlin@kcl.ac.uk.

Europe PMC Funders Author Manuscripts
Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

the hyperactive-impulsive and inattentive behaviours. Although family studies cannot disentangle genetic and environmental sources of familiality, studies using a categorical approach based on family clustering of subtypes, have tested whether the subtypes co-aggregate in families, such that biological family members displaying symptoms of a subtype are at increased risk for that specific subtype and not the other subtypes (Faraone et al., 2000; Levy et al., 2001; Todd et al., 2001; Smalley et al., 2000; Rasmussen et al., 2004). Evidence consistent with the hypothesis of genetic overlap emerged in that there was no specificity for ADHD subtypes (Smalley et al., 2000). Other studies suggested that there is no specificity for the combined and inattentive subtypes with some evidence for specificity in the hyperactive-impulsive subtype (Faraone et al., 2000; Todd et al., 2001). In other studies, however, there was evidence for subtype-specific familiality (Levy et al., 2001; Rasmussen et al., 2004), which indicates that there may be some genes that have unique effects on the different subtypes. The conflicting results from family studies on the DSM-IV subtypes of ADHD prompted a recent meta-analysis, which also indicated some subtype-specific inheritance in families (Stawicki et al., 2006). The evidence for genetic heterogeneity of clinical subtypes from family studies must be considered in light of the fact that one cannot completely extrapolate the subtypes from the behaviours as, for example, the combined subtype has symptoms from both domains.

In addition, a factor analysis in a community sample supported the view that ADHD symptoms are best considered as the extremes of at least two distinct continuously distributed dimensions that roughly correspond to the DSM-IV subtypes (Hudziak et al., 1998). Twin studies, using community samples, can address the genetic and environmental overlap between the hyperactive-impulsive and inattentive components of ADHD as continuous quantitative dimensions rather than diagnostic categories. Previous studies using community twin samples that investigated the genetic architecture of hyperactivity-impulsive and inattentive behaviours yielded similar results. A study of a relatively small sample of male twins aged 11 and 12 years (188 pairs) used teacher ratings on the DSM-III based MTFS Teacher Rating Form (TRF) and parent ratings on the Diagnostic Interview for Children and Adolescents-Revised, Parent version (DICA-R)(Sherman et al., 1997). The DSM-III behavioural scales do not correspond to the two-factor solution of DSM-IV: DSM-III diagnoses ADD with and without hyperactivity -- both share symptoms of impulsivity. The inclusion of impulsivity on both symptom dimensions could inflate the estimate of genetic overlap between the symptom dimensions. For this reason, in the Sherman et al. study, factor analysis was used to create two measures which corresponded to hyperactivity-impulsivity and inattention. In twin analyses, the genetic correlation, which indicates the genetic overlap between the two traits of ADHD, was estimated as .58 for teacher ratings and .60 for parent ratings.

In a second twin study (Eaves et al., 2000), 1376 adolescent twin pairs and their parents were interviewed using the DSM-IIIR based Child and Adolescent Psychiatric Assessment (CAPA). They investigated the genetic overlap between three behavioural dimensions of ADHD, hyperactivity, inattention and impulsivity and found high genetic correlations but fell well short of unity. Their findings varied by gender and also by rater (maternal, paternal and self ratings). The most recent twin study examined genetic influences contributing to the development of hyperactive-impulsive and inattentive symptoms from childhood to adolescence in a sample of 824 twins using DSM-III and DSM-IV based measures (Larsson et al., 2006). As in the other two studies, multivariate genetic analyses pointed to both common genetic effects and some aetiological independence between the two symptoms dimensions (Larsson et al., 2006).

There is a large gender bias in ADHD prevalence rates: boys are more likely to be diagnosed with ADHD than girls, with male to female ratios ranging from 4:1 to 9:1 (APA, 1994).

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Such a difference may be important in the aetiology of ADHD, as it suggests sex-specific genetic and environmental risk factors may play a role in the development of ADHD, although results from a study of twin and sibling pairs suggest that this is not the case (Rhee et al., 1999). It has been shown that the male to female ratio may differ across the DSM-IV subtypes (Lahey et al., 1994), which highlights the importance of investigating sex-specific genetic and environmental risk factors separately for the two dimensions of ADHD. Eaves et al. (2000) did examine sex differences in relation to the genetic architecture of hyperactivity, impulsivity and inattention and they suggest that there is limited evidence to suggest that the genetic basis of the dimensions of ADHD is the same in boys and girls. The other twin studies investigating the genetic architecture of the symptom domains of ADHD did not examine sex differences, most probably due to limitations of sample size (Sherman et al., 1997; Larsson et al., 2006).

Here, we report analyses of parental reports on the DSM-IV based Conners' Rating Scales (Revised). The Conners' rating scale uses a quantitative Likert response scale, which allows testing of DSM-IV ADHD symptoms from a quantitative perspective. The primary aim of the current study is to conduct a bivariate genetic analysis of the inattention and hyperactivity-impulsivity components of ADHD in order to investigate the genetic architecture of these two dimensions in a large community sample of twins. In addition, the large sample and the inclusion of both boys and girls allow the important investigation of sex differences in the aetiology of the two dimensions. A previous study using some of the present sample reported a heritability of 72% for a unidimensional analysis of ADHD symptoms, with no evidence of sex differences (Kuntsi et al., 2005).

Method

Sample

Participants are members of the Twins Early Development Study (TEDS), a birth cohort study of twins born in England and Wales, which invited parents of all twins born in 1994-1996 to enrol. All participants have given informed consent and the study has been approved by the Institute of Psychiatry Ethical Committee (approval number 183/94). Background information regarding pregnancy, birth, and family demographics was obtained when the twins were 18 months old. Zygosity was determined using a standard zygosity questionnaire, which has been shown to have 95% accuracy (Price et al., 2000); 75% have subsequently been confirmed by DNA markers (Freeman et al 2003). The TEDS families are representative of the United Kingdom population with respect to parental occupation, education and ethnicity (Spinath et al., 2004). Twin pairs were excluded from the current analyses if there were extreme pregnancy or perinatal difficulties (112 pairs), specific medical syndromes (not including ADHD), global developmental delay and chromosomal abnormalities (168 pairs), or if zygosity could not be assigned (175 pairs).

The Conners' questionnaire was sent to 13,490 families. Of these 6,677 families returned the questionnaire (49.5%). Comparing participating families at age 8 and families invited to participate but who did not return data: 94% vs. 90% were white, 15% vs. 11% of mothers had A levels as their highest educational qualification (equivalent of college entrance exams), and 47% vs. 38% of mothers worked. Comparing the 8-year sample to data from the UK General Household Survey (Office for National Statistics, 2002), 94% vs. 93% were white, 48% vs. 50% were male, and 37% vs. 32% of mothers had one or more A-levels. Therefore, despite attrition and non-responses, the sample remains relatively representative of the UK population.

After exclusion criteria, the total sample included 6,222 twin pairs. Of these, 1,043 twin pairs were monozygotic male pairs, 998 were dizygotic male pairs, 1,183 were monozygotic

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

(MZ) female pairs, 1,027 were female dizygotic twin pairs and 1,971 were dizygotic (DZ) opposite-sex twin pairs. The twins were aged 7.88 years (SD = 0.5 years; range 6.85-9.98 years) on average when the parents completed the Conners' subscales.

Measures

The hyperactive-impulsive and inattentive DSM-IV symptoms subscales of the Revised Conners' Parent Rating Scale (CPRS-R; Conners' et al 1998) each include 9 items. The rater indicated on a four-point scale how well each attribute described the child (not true at all (0); just a little true (1); pretty much true (2); very much true (3). Items include, for example, "is always 'on the go' or acts as if driven by a motor" and "has difficulty sustaining attention in tasks or play activities." The hyperactivity-impulsivity and inattentiveness scales were computed by obtaining a mean of the scores on the 9 items for each subscale. In the present sample, the internal consistency reliability of the hyperactivity-impulsivity and inattentiveness scales was 0.84 and 0.89, respectively.

Analyses

The structural equation model-fitting program Mx (Neale 1997) was used to conduct the genetic analyses. Models were fitted to age- and sex-standardized scores, using raw data analysis, rather than covariance matrices. The advantage of this approach is that participants with incomplete data can be included in the analyses, as Mx provides a method for handling incomplete data by using raw maximum likelihood estimation, in which a likelihood statistic (−2LL) of the data for each observation is calculated. This implies that there is no overall measure of fit (such as a χ^2-value with corresponding p-value for the number of degrees-of-freedom, as obtained by fitting directly on observed variance-covariance matrices). Instead, with raw data, there are relative measures of fit: by comparing the −2LL (and degrees-of-freedom) of our models with the −2LL (and degrees-of-freedom) of the saturated model – where the maximum number of parameters is estimated to describe the correlational structure between variables. This provides a likelihood ratio chi-square test of goodness of fit.

The difference between the measure of fit of the saturated model and the genetic model is distributed as a chi-square (χ^2) with degrees of freedom (df) equivalent to the difference in the number of parameters between the models (Neale and Cardon 1992). A χ^2-difference test can be performed to compare the fit of nested models. For non-nested models, the Akaike's information criteria (AIC) was used to determine the best-fitting and most parsimonious model. AIC was computed as χ^2 −2df where the χ^2 is the difference in −2LL between the saturated and restricted model and df denotes the difference in degrees of freedom between the two models. The model with the lowest AIC value is considered to be the most parsimonious by this criterion (Akaike, 1987).

Information about the precision of parameter estimates and their explained variance in Mx was obtained by likelihood-based confidence intervals (CIs) rather than by standard errors. In this method a parameter is progressively moved away from its maximum likelihood estimate in either direction (while the other model parameters are optimized) until the difference in fit, distributed as a chi-square with one degree of freedom, is significant. For 95% CI the .05 level of significance is approximately 3.84 chi-square units in each direction (Neale & Miller 1997). One of the assumptions of twin modelling is that the data are normally distributed; because these data were negatively skewed, a log transformation was used which reduced the skewness of the distribution for hyperactivity-impulsivity to 0.02 and for inattentiveness to 0.08. A test of normality was conducted (sktest; Stata Corporation, 1997), which simultaneously tests for skewness and kurtosis and it indicated that the transformed hyperactivity-impulsivity scores met the normality assumption ($p<0.05$), while

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

the transformed inattentiveness scores did not ($p<0.05$). However, tests of normality are extremely robust and our very large sample size will result in a minor departure from normality being significant. Furthermore, the twin analyses are robust to such minor departures of normality.

Univariate models

The basic univariate ACE model apportions the phenotypic variance into three components: additive genetic (A), shared environment (C, which refers to experiences that make children growing up in the same family similar), and non-shared (child-specific) environment (E, which refers to environmental influences that do not contribute to the similarity of children growing up in the same family and also includes measurement error), assuming no effects of nonrandom mating or gene–environment interaction or correlation. The proportion of variation of a trait in a population that is explained by additive genetic influences is referred to as narrow heritability; broad heritability also includes nonadditive genetic influences (D).The full ACE model is fitted first and then the full ADE, where D is estimated instead of C. To attain the most parsimonious model, parameters that do not significantly contribute to the fit of the model are dropped. The AE model is nested within the full ACE/ADE model (i.e., subsets of the AE parameters are contained in the full ACE/ADE model).

To test for the significance of sex differences, a series of hierarchically-related sex-limitation models was fitted to the data (Neale & Cardon, 1992). Sex differences in ACE parameter estimates, called quantitative sex differences, involve the comparison of ACE estimates for boys and girls. Qualitative sex differences can be derived from the comparison between same-sex DZ twins and opposite-sex DZ twins; to the extent that same-sex DZ twins are more similar than opposite-sex DZ twins, qualitatively different genetic or shared environmental influences for boys and girls are implied. Regardless of quantitative or qualitative sex differences, phenotypic variance differences between the sexes are tested in what is called a ‘scalar’ model. in the series of models, the first model fitted allows for all sex differences (full model), then constrains ACE parameters to be equal for boys and girls to test for quantitative sex differences. Next, the resemblance between same-sex and opposite-sex DZ twins is equated to test for qualitative sex differences which could be due to genetic or shared environmental factors. Finally, the scalar model tests whether variance differences between boys and girls exist independent of quantitative and qualitative sex differences.

Bivariate models

Bivariate models begin with the cross-trait phenotypic correlation, which indicates the degree to which two variables covary. Phenotypic covariance between two variables can be decomposed into shared genetic and environmental influences using multivariate genetic analysis (Plomin et al., 2001). Multivariate twin analysis is an extension of univariate twin analysis based on cross-trait cross-twin correlations (i.e., the correlation between one twin’s inattentiveness and the co-twin’s hyperactive-impulsive score). Similar to univariate twin analyses that compare MZ and DZ twin correlations to estimate ACE parameters, multivariate twin analyses compare MZ and DZ cross-trait cross-twin correlations to estimate the extent to which phenotypic correlation is due to genes or environment. The genetic contribution to the phenotypic correlation is called bivariate heritability. From bivariate heritability, a novel statistic, called the genetic correlation, can be derived. The genetic correlation indicates the genetic overlap between two traits and varies from 0, indicating no genetic overlap, to 1, indicating that the same genes affect both traits. Importantly, the genetic correlation is independent of the heritability of the two traits; that is, the heritability of both traits could be high but the genetic correlation between them could be low, and vice versa. Similarly, in the bivariate model there are also shared and child-specific

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

environmental correlations (r_C and r_E), which represent overlap in environmental influences between two phenotypes, and can also vary between 0 and 1. In addition to a bivariate ACE analysis, we also fitted an ADE bivariate model.

Bivariate sex limitation models were also run to test for quantitative, qualitative, and variance sex differences. A recent paper has suggested that multivariate sex-limitation models that include opposite-sex twins may have problems, which can be avoided by constraining males and females to have the same correlation matrix (Neale et al., in press). For this reason, we ran our multivariate sex-limitation analyses again with correlation matrices equated for boys and girls. However, our multivariate genetic results can be seen to be reasonable by inference from the simple level of cross-trait cross-twin correlations.

Results

Table 1 presents the means and standard deviations (prior to transformation) of each dimension for each sex and zygosity group. Two (sex) by two (zygosity) analyses of variance (ANOVAs) were conducted. ANOVAs showed that boys scored significantly higher on both the hyperactivity-impulsivity [$F_{1, 12, 401}$ =11.50, p<0.001] and inattentiveness subscales [$F_{1, 12, 401}$=116.86, p<0.001]. For zygosity, there was a small but significant difference in hyperactivity-impulsivity [$F_{1, 12, 401}$=10.25, p=0.001] with MZs tending to score higher than DZs, but this was not observed for inattentiveness [$F_{1, 12, 401}$=1.40, p=0. 24]. Significant sex by zygosity interaction emerged for inattentiveness [$F_{1, 12, 405}$=9.764, p<0. 001] but not for hyperactivity-impulsivity [$F_{1, 12, 405}$=0.002, p=0. 97]. However, sex and zygosity together accounted for 2% of the variation both hyperactivity-impulsivity and inattentiveness.

Table 1 also indicates that boys are more variable in their scores than girls. Although variance differences are examined more formally in the context of our sex-limitation model fitting, a simple test of heterogeneity of variance indicated that these differences are significant for both hyperactivity-impulsivity ($F_{3, 12, 401}$) = 65.98, p<0.001) and inattentiveness ($F_{3, 12, 401}$= 96.05, p<0.001).

Consistent with previous analyses (Sherman et al,, 1997; Hudziak et al., 1998), a principal components factor analysis confirmed that the 18 items loaded neatly on two factors that corresponded to the hyperactivity-impulsivity and inattentiveness constructs for both boys and girls (Table 2).

Univariate genetic analyses

The univariate twin correlations (presented in the top panel of Table 3) suggest in broad outline the findings that emerge from univariate model-fitting analyses. MZ correlations are consistently and substantially greater than DZ correlations, suggesting substantial heritability (A) for both hyperactive-impulsive and inattentive behaviours, as reported by parents. Some shared environment (C) is indicated for hyperactivity-impulsivity, as the DZ twin correlations are greater than half the MZ twin correlations; however no C is indicated for inattentiveness from the twin correlations. For inattentiveness in girls, the DZ correlations are just slightly less than half the MZ correlations; as such, a small contribution from nonadditive genetic effects (D) is possible. The univariate twin correlations are generally similar for boys and girls, which suggests no quantitative sex differences. Correlations for DZ opposite-sex twins are similar to correlations for DZ same-sex twins, which indicates no significant qualitative sex differences.

As suggested by the twin correlations, the best-fitting univariate model for both hyperactivity-impulsivity and inattentiveness was the AE model, indicating no significant

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

common environment or nonadditive genetic effects (Table 4). For the sex differences models, the model-fitting analyses confirmed the results suggested by the univariate correlations. There were no quantitative or qualitative sex differences. For both dimensions (except for inattention in females), the DZ correlations were not less than half of the MZ correlations, which suggests that there are not rater bias effects. In addition there was not a significant worsening in fit when MZ and DZ variances were equated in the saturated models (Table 4), which further indicates that there were not rater bias effects for either hyperactivity-impulsivity or inattention. As expected from Table 1, significant variance differences were found for boys and girls. The model fit parameters for this model indicate substantial heritability for behavioural dimensions with A for hyperactivity-impulsivity at 0.88 (CIs: 0.87-0.89) and A for inattentiveness at 0.79 (0.71-0.81), and some child-specific environment (hyperactivity-impulsivity: 0.12 (0.11-0.12) and inattentiveness: 0.21 (0.19-0.22) but no common environment or non-additive genetic influences.

Bivariate genetic analyses on Conners' ADHD symptom domains

The MZ and DZ cross-trait cross-twin (CTCT) correlations (twin 1's hyperactive-impulsive score correlated with twin 2's inattentive score, and twin 2's hyperactive-impulsive score correlated with twin 1's inattentive score) are presented in the lower panel of Table 3. MZ CTCT correlations are higher than DZ CTCT correlations, indicating genetic influence on the phenotypic relationship between hyperactive-impulsive and inattentive behaviours. Some modest shared environmental influence on the phenotypic correlation is suggested in that the DZ CTCT correlations are somewhat greater than half the MZ CTCT correlations. Some modest non-shared environmental influence is also suggested because the MZ CTCT correlations are somewhat lower than the cross-trait phenotypic correlations.

CTCT correlations are similar for males and females, which suggests no quantitative sex differences. Finally, CTCT correlations are similar for same-sex DZ and opposite-sex DZ, which suggests no qualitative sex differences. From the univariate analyses, it was expected that an AE bivariate model would provide the best fit for the genetic relationship between hyperactivity-impulsivity and inattentiveness. However, the full ACE bivariate model fitted better than the AE model (see Table 5). Although an AE model was estimated as the best-fitting univariate model for both behavioural dimensions, bivariate model fitting has more power to detect underlying variance; in combination with the very large sample size, this allowed the model to include the small amount of C that is present. Similar to the univariate analysis, and as expected from the CTCT correlations, bivariate sex-limitation models indicated no substantial quantitative or qualitative sex differences.

The ACE parameter estimates from the bivariate genetic analyses are presented in Table 6. The first column refers to bivariate heritability, which is the genetic contribution to the phenotypic correlation. Bivariate heritability is calculated by dividing the phenotypic correlation by double the difference in MZ and DZ CTCT correlations. This was .71 for boys and .65 for girls, indicating that most of the phenotypic correlation is mediated by genetics. The remainder of the phenotypic correlation can be attributed in almost equal measure to shared and non-shared environmental factors, as seen in columns 2 and 3.

As indicated in column 4 in Table 6, the genetic correlation, a measure of how many of the genes are shared between the two symptom domains, was .62 for boys and .57 for girls, suggesting substantial genetic overlap but also trait-specific genetic influences. Although shared environmental influence is modest, the correlation of .99 for both boys and girls (column 5) suggests that the same shared environmental factors affect the two traits. Column 6 shows a non-shared environmental correlation of .42 for both boys and girls, indicating that non-shared environmental factors are in the main specific to each trait.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Discussion

The primary aim of this study was to conduct a bivariate genetic analysis investigating the extent to which hyperactive-impulsive and inattentive behaviours required for diagnosis of ADHD share the same genetic basis. The main finding was that individual differences in hyperactive-impulsive and inattentive behaviours are both highly heritable and have a large genetic overlap. The genetic correlation was estimated as .57 for girls and .62 for boys, which predicts that more than half of the genes found to be associated with hyperactive-impulsive behaviours will also be associated with inattentive behaviours. The genetic correlations are, however, less then 1.0, which indicates that, despite the substantial genetic overlap between hyperactive-impulsive and inattentive behaviours, there is some genetic independence.

The use of the Conners' rating scale which is based on DSM-IV criteria facilitates the extrapolation of the results in this study to DSM symptoms and diagnostic subtypes, although the present study is limited to a community sample unselected for the extremes of these behaviours. This finding provides an aetiological basis for the clinical diagnoses of ADHD including both a homogeneous diagnosis of ADHD, which dominated earlier molecular genetic research, as well as heterogeneous subtypes which have been the focus of more recent research (Larsson et al., 2006; Levy et al., 2001; Lowe et al., 2004; Rasmussen et al., 2004; Smoller et al., 2006).

The present study confirms the previous findings of a large genetic overlap between the two symptom dimensions of ADHD but with significant unique genetic effects also. For example, the study by Sherman et al. (1997), which indicated that the two domains of ADHD have approximately 60% of their genes in common. Our much larger sample, however, provides more power to detect the underlying genetic architecture. Additionally, our large sample makes it possible to study sex differences in these bivariate genetic analyses. No quantitative or qualitative sex differences in ACE parameters were found. This is not entirely in agreement with the findings by Eaves et al. (2000) but it's possible that the sex differences that in their study are a result of measurement differences associated with rater contrast effects.

In our findings, variances are greater for boys than girls but this might merely reflect the higher mean scores of boys. The absence of quantitative or qualitative ACE differences between boys and girls implies that the mean difference in the manifestation of these behaviours between boys and girls reflects something that differs much more between than within the sexes, such as hormonal factors. The same genes would be expected to be associated with ADHD symptoms in boys and girls.

In light of these findings, we suggest that molecular genetic studies would benefit from examination of more refined phenotypes of ADHD. Studying the two traits separately would make it possible to identify three sets of genes: genes specific to hyperactive–impulsive behaviours, genes specific to impulsive behaviours, and genes in common to the two traits. These three sets of genes can be used to ask novel questions such as whether differential treatment is warranted, whether they predict differential developmental courses, and whether the pathways from genes to brain to behaviour differ. It appears theoretically important to clarify the genetic architecture of ADHD at the cognitive level: it may be that some of the proposed cognitive deficits or patterns of impairment are more strongly related to the inattentive domain of problems rather than to hyperactivity-impulsivity and vice versa. Cognitive, electrophysiological and brain imaging studies converge in suggesting that there is not a single "core" deficit in ADHD (Kuntsi et al., 2006) and this research might also profit by considering the two dimensions separately as well as together. In clinical samples

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

of ADHD, some cognitive processes have correlated more with one or other behavioural subtype (Nigg et al., 2005). Overall, this highlights the need for homogeneity in the samples used in aetiological investigations of ADHD.

Evidence is emerging for symptoms that are specific to the inattentive subtype, associated only with the absence of prominent hyperactive-impulsive symptoms, in particular sluggish cognitive tempo (Todd et al., 2004). Sluggish cognitive tempo is a collective term for greater deficits in memory retrieval and processing, lower levels of alertness, and more problems with memory/orientation (Lahey et al., 1987). McBurnett et al. (2001) challenged the two-factor solution of DSM-IV and suggested that symptoms of inattention are different dependent on whether or not they occur with hyperactivity-impulsivity. DSM-IV (and consequently the Conners' rating scale) does not include these kinds of inattention symptoms, and, therefore, it may be possible that sluggish cognitive tempo symptomology has a different genetic aetiology to that presented here. Further investigation of the genetic architecture of these symptoms that are specific to the inattentive subtype is required.

This study should be interpreted in the context of its limitations. One limitation is the reliance on parent report as findings may differ according to rater. Our findings, however, are similar to those reported in a previous twin study investigating the genetic architecture of hyperactivity-impulsivity and in attentiveness using teacher data (r_A=0.52) (Sherman et al., 1997). Also, it is not clear from these analyses how the genetic overlap between hyperactivity-impulsivity and inattentiveness will change with development. The analyses reported here refer to cross-sectional data, and further investigation will be undertaken using the next wave of data collection in TEDS from multiple raters so that developmental perspectives and effects of multiple raters may be considered more fully. This study is also subject to the usual limitations of the twin method, including the equal environment assumption. It is optimal to triangulate on these issues with family and adoption designs (Plomin et al., 2001).

In summary, the results of the present study indicate that there is justification in investigating ADHD as a unidimensional construct as the majority of the genes are shared by the two symptom domains. The current findings also suggest that there is sense in examination of refined phenotypes that might reduce heterogeneity in molecular genetic research in ADHD as there is also a minority of specific genetic effects on hyperactivity-impulsivity and inattentiveness. This indicates that additionally considering these behaviours separately may be the best strategy to identify trait-specific as well as trait-general genes and to use these genes in clinical and cognitive research on ADHD.

Acknowledgments

We are indebted to participants of the Twins Early Development Study (TEDS) for making the study possible. The authors have no financial relationships to disclose. TEDS is funded by MRC grant G0500079. Angelica Ronald is funded by a fellowship from Autism Speaks.

Reference List

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. American Psychiatric Association; Washington D.C.: 1994.

Akaike H. Factor analysis and AIC. Psychometrika. 1987; 52:317–32.

Conners CK, Sitarenios G, Parker JD, Epstein JN. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. J Abnorm Child Psychol. 1998; 26:257–268. [PubMed: 9700518]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Eaves L, Rutter M, Silberg JL, Shillady L, Maes H, Pickles A. Genetic and environmental causes of covariation in interview assessments of disruptive behavior in child and adolescent twins. Behav.Genet. 2000; 30:321–334. [PubMed: 11206087]

Faraone SV, Biederman J, Friedman D. Validity of DSM-IV subtypes of attention-deficit/hyperactivity disorder: a family study perspective. J.Am.Acad.Child Adolesc.Psychiatry. 2000; 39:300–307. [PubMed: 10714049]

Freeman B, Smith N, Curtis C, Huckett L, Mill J, Craig IW. DNA from buccal swabs recruited by mail: evaluation of storage effects on longterm stability and suitability for multiplex polymerase chain reaction genotyping. Behav Genet. 2003; 33:67–72. [PubMed: 12645823]

Hudziak JJ, Heath AC, Madden PF, Reich W, Bucholz KK, Slutske W, et al. Latent class and factor analysis of DSM-IV ADHD: a twin study of female adolescents. J.Am.Acad.Child Adolesc.Psychiatry. 1998; 37:848–857. [PubMed: 9695447]

Kuntsi J, Rijsdijk F, Ronald A, Asherson P, Plomin R. Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. Biol.Psychiatry. 2005; 57:647–654. [PubMed: 15780852]

Kuntsi J, McLoughlin G, Asherson P. Attention deficit hyperactivity disorder. Neuromolecular Medicine. 2006

Lahey BB, Schaughency EA, Hynd GW, Carlson CL, Nieves N. Attention deficit disorder with and without hyperactivity: comparison of behavioral characteristics of clinic-referred children. J.Am.Acad.Child Adolesc.Psychiatry. 1987; 26:718–723. [PubMed: 3667501]

Lahey BB, Applegate B, McBurnett K, Biederman J, Greenhill L, Hynd GW, et al. DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. Am.J.Psychiatry. 1994; 151:1673–1685. [PubMed: 7943460]

Larsson H, Lichtenstein P, Larsson JO. Genetic contributions to the development of ADHD subtypes from childhood to adolescence. J.Am.Acad.Child Adolesc.Psychiatry. 2006; 45:973–981. [PubMed: 16865040]

Levy, F.; McStephen, M.; Hay, DA. Attention, Genes and ADHD. Levy, F.; Hay, D., editors. Taylor & Francis; Philadelphia: 2001. p. 35-37.

Lowe N, Kirley A, Hawi Z, Sham P, Wickham H, Kratochvil CJ, Smith SD, Lee SY, Levy F, Kent L, Middle F, Rohde LA, Roman T, Tahir E, Yazgan Y, Asherson P, Mill J, Thapar A, Payton A, Todd RD, Stephens T, Ebstein RP, Manor I, Barr CL, Wigg G, Sinke RJ, Buitelaar JK, Smalley SL, Nelson SF, Biederman J, Faraone SV, Gill M. Joint analysis of the DRD5 marker concludes association with attention-deficit/hyperactivity disorder confined to the predominantly inattentive and combined subtypes. Am J Hum Genet. 2004; 74:348–56. [PubMed: 14732906]

McBurnett K, Pfiffner LJ, Frick PJ. Symptom properties as a function of ADHD type: an argument for continued study of sluggish cognitive tempo. J.Abnorm.Child Psychol. 2001; 29:207–213. [PubMed: 11411783]

Neale, MC.; Cardon, LR. Methodology for Genetic Studies of Twins and Families. Kluwer; Dordrecht: 1992.

Neale, MC. Mx: Statistical Modelling. Department of Psychiatry, Medical College of Virginia; Richmond, VA: 1997.

Neale MC, Miller MB. The use of likelihood-based confidence intervals in genetic models. Behavior Genetics. 1997; 27(2):113–120. [PubMed: 9145549]

Neale MC, Roysamb E, Jacobsen K. Multivariate genetic analysis of sex-limitation in human populations. In press.

Nigg JT, Stavro G, Ettenhofer M, Hambrick DZ, Miller T, Henderson JM. Executive functions and ADHD in adults: evidence for selective effects on ADHD symptom domains. J.Abnorm.Psychol. 2005; 114:706–717. [PubMed: 16351391]

Office for National Statistics. Living in Britain: Results from the 2000/01 General Household Survey. 2002

Pelham WE Jr. Gnagy EM, Greenslade KE, Milich R. Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. J.Am.Acad.Child Adolesc.Psychiatry. 1992; 31:210–218. [PubMed: 1564021]

Europe PMC Funders Author Manuscripts

Plomin, R.; DeFries, JC.; McClearn, GE.; McGuffin, P. Behavioural Genetics. Worth Publishers; New York: 2001.

Price TS, Freeman B, Craig I, Petrill SA, Ebersole L, Plomin R. Infant zygosity can be assigned by parental report questionnaire data. Twin Res. 2000; 3:129–133. [PubMed: 11035484]

Rasmussen ER, Neuman RJ, Heath AC, Levy F, Hay DA, Todd RD. Familial clustering of latent class and DSM-IV defined attention-deficit/hyperactivity disorder (ADHD) subtypes. J.Child Psychol.Psychiatry. 2004; 45:589–598. [PubMed: 15055377]

Rhee SH, Waldman ID, Hay DA, Levy F. Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. Journal of Abnormal Psychology. 1999; 108:24–41. [PubMed: 10066990]

Sherman DK, Iacono WG, McGue MK. Attention-deficit hyperactivity disorder dimensions: a twin study of inattention and impulsivity-hyperactivity. J.Am.Acad.Child Adolesc.Psychiatry. 1997; 36:745–753. [PubMed: 9183128]

Smalley SL, McGough JJ, Del'Homme M, NewDelman J, Gordon E, Kim T, Liu A, McCracken JT. Familial clustering of symptoms and disruptive behaviors in multiplex families with attention-deficit/hyperactivity disorder. J.Am.Acad.Child Adolesc.Psychiatry. 2000; 39(9):1135–1143. [PubMed: 10986810]

Smoller JW, Biederman J, Arbeitman L, Doyle AE, Fagerness J, Perlis RH, et al. Association between the 5HT1B receptor gene (HTR1B) and the inattentive subtype of ADHD. Biol.Psychiatry. 2006; 59:460–467. [PubMed: 16197923]

Spinath FM, Ronald A, Harlaar N, Price TS, Plomin R. Phenotypic 'g' early in life: On the etiology of general cognitive ability in a large population sample of twin children aged 2 to 4 years. Intelligence. 2004; 31:195–210.

Stata Corporation. Stata statistical software. Stata Corp; College Station, TX: 1997. (Release 9.0)

Stawicki JA, Nigg JT, von Eye A. Family psychiatric history evidence on the nosological relations of DSM-IV ADHD combined and inattentive subtypes: new data and meta-analysis. J.Child Psychol.Psychiatry. 2006; 47:935–945. [PubMed: 16930388]

Todd RD, Rasmussen ER, Neuman RJ, Reich W, Hudziak JJ, Bucholz KK, et al. Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. Am.J.Psychiatry. 2001; 158:1891–1898. [PubMed: 11691697]

Todd RD, Rasmussen ER, Wood C, Levy F, Hay DA. Should sluggish cognitive tempo symptoms be included in the diagnosis of attention-deficit/hyperactivity disorder? J.Am.Acad.Child Adolesc.Psychiatry. 2004; 43:588–597. [PubMed: 15100565]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 1

Means and standard deviations for the Conners' subscales by sex and zygosity

			Twin 1 Mean (SD)	Twin 2 Mean (SD)
MZ	Hyperactivity-Impulsivity	Male	0.77 (0.61)	0.76 (0.59)
		Female	0.57 (0.53)	0.56 (0.50)
	Inattentiveness	Male	0.68 (0.60)	0.66 (0.57)
		Female	0.50 (0.51)	0.50 (0.50)
DZSS	Hyperactivity-Impulsivity	Male	0.74 (0.61)	0.74 (0.60)
		Female	0.54 (0.50)	0.54 (0.50)
	Inattentiveness	Male	0.70 (0.61)	0.70 (0.62)
		Female	0.50 (0.50)	0.52 (0.51)
DZOS	Hyperactivity-Impulsivity	Male	0.72 (0.60)	
		Female		0.51 (0.48)
	Inattentiveness	Male	0.74 (0.65)	0.45 (0.48)
		Female		

Means and standard deviations prior to transformation. MZ, monozygotic; DZ, dizygotic same sex twin pairs, DZOS, dizygotic opposite sex twin pairs.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 2
Principal components factor analysis of the 18 Conners' items

	Boys		Girls	
Conners item	**Hyperactivity-impulsivity**	**Inattentiveness**	**Hyperactivity-impulsivity**	**Inattentiveness**
Always on the go	0.67	0.04	0.65	0.04
Avoids sustained mental effort	0.14	0.74	0.08	0.75
Difficulty sustaining attention	0.26	0.71	0.19	0.70
Does not seem to listen	0.35	0.61	0.32	0.61
Runs/climbs excessively	0.61	0.35	0.59	0.28
Fails to follow through or finish	0.23	0.75	0.21	0.72
Difficulty organising	0.11	0.77	0.13	0.72
Talks excessively	0.68	0.08	0.70	0.11
Makes careless mistakes	0.26	0.65	0.21	0.66
Difficulty waiting turn	0.60	0.40	0.56	0.35
Interrupts or intrudes	0.70	0.28	0.65	029
Forgetful	0.14	0.72	0.18	0.67
Fidgets or squirms	0.55	0.40	0.54	0.35
Difficulty playing quietly	0.59	0.35	0.62	0.30
Loses things	0.15	0.65	0.25	0.57
Leaves seat	0.50	0.45	0.47	0.41
Easily distracted	0.46	0.61	0.44	0.61
Blurts out answers	0.66	0.14	0.65	0.12

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 3

Univariate, phenotypic and cross-trait cross twin correlations for boys and girls

		Hyperactivity-Impulsivity	Inattention
MZ twins	Male	0.88 (0.87-0.89)	0.78 (0.76-0.80)
	Female	0.88 (0.86-0.89)	0.80 (0.78-0.82)
DZ twins	Male	0.50 (0.46-0.55)	0.39 (0.34-0.44)
	Female	0.53 (0.48-0.57)	0.37 (0.32-0.42)
DZ Opposite-Sex		0.52 (0.49-0.56)	0.39 (0.35-0.42)
		Cross-Trait Phenotypic Correlations	**Cross-Trait Cross-Twin Correlations**
MZ twins	Male	0.64 (0.60-0.69)	0.57 (0.53-0.61)
	Female	0.60 (0.60-0.62)	0.54 (0.52-0.56)
DZ twins	Male	0.62 (0.60-0.64)	0.35 (0.35-0.38)
	Female	0.62 (0.60-0.64)	0.37 (0.34-0.40)
DZ Opposite-Sex		0.62 (0.60-0.64)	0.36 (0.34-0.39)

Phenotypic correlation, within-twin correlations of hyperactivity-impulsivity and inattentiveness; Cross-trait cross-twin correlation, hyperactivity-impulsivity in Twin 1 correlated with inattentiveness in Twin 2.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 4
Univariate model-fitting results of the Conners' subscales

Behavioural dimension	Model type and details	−2LL	df	Par	χ^2 (df)	AIC
Hyperactivity-Impulsivity	**Saturated**	**14446.53**	**12381**	**25**		
	Variances equated	14454.15	12387	19	7.62 (6)	4.38
	ACE full (quantitative and qualitative)	14513.83	12397	11	67.3 (16)	35.3
	ACE quantitative	14513.83	12398	10	67.3 (17)	33.3
	ACE scalar	14514.50	12400	7	67.97 (19)	29.97
	ACE null	15110.25	12401	6	663.72 (20)	623.72
	AE full (quantitative and qualitative)	14513.83	12399	9	67.3 (18)	31.3
	AE quantitative	14513.83	12400	8	67.3 (19)	29.3
	AE scalar	14514.50	12401	6	67.97 (20)	27.97*
	AE null	15110.32	12402	5	663.79 (21)	621.79
	ADE full (quantitative and qualitative)	14513.83	12397	11	67.3 (16)	35.3
	ADE quantitative	14513.83	12398	10	67.3 (17)	33.3
	ADE scalar	14514.50	12400	7	67.97 (19)	29.97
	ADE null	15110.25	12401	6	663.72 (20)	623.72
Inattention	**Saturated**	**15564.12**	**12380**	**25**		
	Variances equated	15568.63	12386	19	4.52 (6)	7.48
	ACE full (quantitative and qualitative)	15599.94	12396	11	35.822 (16)	3.822
	ACE quantitative	15600.13	12397	10	36.012 (17)	2.012
	ACE scalar	15600.17	12399	7	36.052 (19)	−1.948
	ACE null	16323.15	12400	6	759.032 (20)	719.032
	AE full (quantitative and qualitative)	15599.94	12398	9	35.822 (18)	−0.178
	AE quantitative	15599.94	12399	8	35.822 (19)	−0.178
	AE scalar	15599.98	12400	6	35.862 (20)	−4.138*
	AE null	16319.18	12401	5	755.062 (21)	713.062
	ADE full (quantitative and qualitative)	15998.95	12396	11	34.83 (16)	2.835
	ADE quantitative	15598.95	12397	10	34.835 (17)	0.835
	ADE scalar	15600.17	12399	7	36.05 (19)	−1.946
	ADE null	16323.15	12400	6	759.03 (20)	719.036

*Note. Best fitting model. Each model compared to the saturated model. −2LL, log likelihood fit statistic; df, degrees of freedom; χ^2 with Δdf comparing model to the saturated model; AIC, Akaike information criterion; AE, model excluding variance explained by common environment; ADE, model including genetic dominance effects.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 5
Bivariate model-fitting results of the Conners' subscales

Model type	Details	−2LL	df	Par	χ^2 (df)	AIC
Saturated		**25019.62**	**24741**	**70**		
Correlated Factors	ACE full (quantitative and qualitative)	25194.92	24776	35	175.31 (35)	105.30
	Quantitative (r_A fixed)	25128.68	24769	42	109.06 (28)	53.06*
	Quantitative (r_C fixed)	25128.68	24769	42	109.06 (28)	53.06*
	Scalar	26134.68	24775	36	1115.06 (34)	754.04
	Null	29672.15	24781	30	4652.53 (40)	4946.76
	AE full (quantitative and qualitative)	25263.02	24780	31	243.40 (39)	165.40
	Quantitative (r_A fixed)	25180.57	24773	38	160.95 (32)	96.95
	Quantitative (r_C fixed)	25180.57	24773	38	160.95 (32)	96.95
	Scalar	26168.09	24782	32	1148.47 (38)	1072.47
	Null	29966.38	24784	27	4946.76 (43)	4860.76

*Note: Best fitting model. −2LL, log likelihood fit statistic; df, degrees of freedom; χ^2 test with Δdf comparing model to the saturated model; AIC, Akaike information criterion

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Table 6

Bivariate genetic analyses of hyperactivity-impulsivity and inattentiveness: bivariate genetic (A), shared environment (C), and non-shared environment (E) heritability estimates, which indicate the genetic, shared and non-shared contributions to the phenotypic correlation; bivariate A, C and E correlations (95% CIs in parentheses), which indicate the genetic and environmental overlap between the two symptom domains

	***Biv a*^{2}**	***Biv c*^{2}**	***Biv e*^{2}**	r_A	r_C	r_E
Boys						
	.71 (.62-.80)	.18 (.10-.27)	.10 (.09-.012)	.62 (.59-.66)	.99 (.93-.99)	.42 (.36-.47)
Girls						
	.65 (.55-74)	.25 (.16-.35)	.12 (.11-.13)	.57 (.52-.61)	.99 (.96-.99)	.42 (.36-.47)
Combined boys and girls	0.72 (0.68-0.76)	0.18 (0.14-0.22)	0.10 (0. 09-0.11)	0.61 (0.60-0.63)	1 (0.99-1)	0.38 (0.35-0.41)