Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs

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Background: Although the clinical utility of categorically defined attention-deficit hyperactivity disorder (ADHD) is well established, there is also strong evidence supporting the notion of ADHD as an extreme of a continuous trait. Nevertheless, the question of whether the etiology is the same for different levels of DSM-IV ADHD symptoms remains to be investigated. The aim of this study was to assess genetic links between the extreme and the subthreshold range of ADHD symptoms. Method: Parents of all Swedish 9- and 12-year-old twins born between 1992 and 2000 were interviewed for DSM-IV ADHD symptoms and associated conditions. Two validated cutoff values were used for screening and assigning research diagnoses. Response rate was 80%. Twin methods were applied to investigate the extent to which ADHD is etiologically distinct from subthreshold variations in ADHD symptoms. Results: Extremes analyses indicated a strong genetic link between the extreme and the subthreshold variation, with almost identical group heritability estimates around .60 for the diagnostic (prevalence 1.78%) and screening (prevalence 9.75%) criteria of ADHD. Conclusion: A strong genetic link between the extreme and the subthreshold variation of DSM-IV based assessments of ADHD symptoms was found. The data suggest that ADHD is best viewed as the quantitative extreme of genetic and environmental factors operating dimensionally throughout the distribution of ADHD symptoms, indicating that the same etiologic factors are involved in the full range of symptoms of inattention, hyperactivity and impulsivity. Keywords: ADHD, DSM, etiology, twins.

Introduction

Although attention-deficit/hyperactivity disorder (ADHD) is one of the most thoroughly researched disorders in medicine (Goldman, Genel, Bezman, & Slanetz, 1998), the question of whether ADHD is best viewed as a categorical disorder or as an extreme of a continuous trait has yet to be finally determined, with consequences for the impact on future etiologic research, treatment and the upcoming DSM-V conceptualization of ADHD (Thapar & Lewis, 2009).

The two main psychiatric classification systems (ICD-10, DSM-IV) used for the diagnosis of ADHD are exclusively categorical in nature. In many contexts, clinical decisions have to be categorical, and data have supported ADHD as a valid diagnostic category associated with serious consequences for the affected individuals (Biederman, 2005). Nevertheless, sophisticated statistical modeling techniques (e.g. factor mixture and taxometric procedures) have been used to show that ADHD exists on a severity continuum (Frazier, Youngstrom, & Naugle, 2007; Haslam et al., 2006; Lubke, Hudziak, Derks, van Bijsterveldt, & Boomsma, 2009). Comparisons of neuropsychological (Faraone et al., 2006) and personality (Faraone, Kunwar, Adamson, & Biederman, 2009) measures between individuals with subthreshold ADHD and controls provide further support for an ADHD continuum. Thus, although the clinical utility of categorically defined ADHD is well established (Biederman, 2005), there is also strong evidence supporting the notion of ADHD as an extreme of a continuous trait.

Because of the difficulty in identifying sufficient numbers of affected twin pairs, only a few twin studies (Goodman & Stevenson, 1989; Sherman, McGue, & Iacono, 1997; Thapar, Harrington, Ross, & McGuffin, 2000), including one that has used the same sample as the present study (Lichtenstein, Carlstrom, Rastam, Gillberg, & Anckarsater, 2010), have explored the genetic impact on categorically defined ADHD. The heritability estimates from these studies range from 75% to 90%, which is consistent with a large number of studies of quantitative measures (i.e. defining ADHD as a continuous trait; Faraone et al., 2005; Thapar, Holmes, Poulton, & Harrington, 1999). Thus, twin studies report strong genetic effect in ADHD regardless of whether it is treated as a categorically defined diagnosis or as continuously distributed dimension.

A core issue in the categorical versus dimensional discussion is whether the etiology is the same for
different levels of ADHD symptoms. Epidemiological studies provide evidence of dose–response relationships between environmental risks and ADHD symptoms scores across the range of severity (Sechil et al., 1999). Similar treatment response (including improved attention) of low-dose psychostimulant medication has been reported among children diagnosed with ADHD and children with subthreshold problems, which also supports a dimensional model for the neurobiological mechanisms behind ADHD (Rapoport et al., 1980). Twin studies can also be used to address the question whether the genetic and environmental etiology is the same at the extreme end (i.e. at a diagnostic level) and the subthreshold range of a mental health problem, using the so called DeFries–Fulker (DF) extremes analysis (DeFries & Fulker, 1988). Thus, in addition to answering the question whether ADHD is best viewed as a categorical disorder or as an extreme of a continuous trait, this method can clarify whether the different levels of ADHD symptoms have the same or different etiologies. One study of 583 same-sexed twin pairs using the DF approach found that the heritability of ADHD–III–R symptoms was similar at the extreme end of the distribution (92%, confidence interval ± 12) as for the subthreshold range of scores (75%, confidence interval: ± 24; Levy, Hay, McStephen, Wood, & Waldman, 1997). However, this study did not use the ADHD symptoms described in DSM–IV and was not based on a large enough sample to find a sufficient number of children meeting diagnostic criteria, applying instead a five-symptom cutoff that identified around 30% of the male twins as cases. This means that the genetic link between the very extreme end of the distribution and the subthreshold range of ADHD symptoms has not yet been investigated. There is a need for studies addressing the categorical versus continuous nature of ADHD in larger twin samples and using the DSM–IV definition of ADHD, especially in view of this being one of the many questions that the DSM–V Child work group is considering (Rohde, 2008).

In the present report, we use quantitative assessments of ADHD symptoms from 16,858 Swedish 9- and 12-year-old twins to investigate the etiology of the ADHD phenotype.

The large sample size allows us, for the first time, to assess genetic links between the extreme and the subthreshold range of ADHD symptoms using categorical definitions based on validated (Hansson, Svanstrom Rojvall, Rastam, Gillberg, & Anckarsater, 2005; Larson et al., 2010) cutoff values. DF extremes analyses were applied to investigate the extent to which these definitions of ADHD are etiologically distinct from the subthreshold symptom variation. As this twin cohort also includes sufficient numbers of male, female and opposite-sexed twin pairs, sex differences in genetic or environmental effects could be examined.

Methods

Subjects

Parents of all 21,790 Swedish 9- (born between July 1995 and December 2000) and 12-year-old (born between July 1992 and June 1995) twins were identified through the Swedish Twin Registry and contacted for interviews over the phone as part of the Child and Adolescent Twin Study in Sweden (Lichtenstein et al., 2006). The reason for choosing this age group was that most of the major child psychiatric problem constellations have been established by the age of 12, whereas the complex biopsychosocial problems associated with puberty have not yet emerged.

Interviewers from a professional company carried out the interviews after a brief introduction in child and adolescent psychiatry and twin research. The study started in July 2004 and is ongoing. Over 80% of the parents of the cohorts born before May 2000 have responded. The mother was interviewed in 88% and the father in 12% of these cases; in 30 cases (0.4%) another member of the family was interviewed. No significant mean differences in child ADHD symptoms were observed across reporters.

The total study group consisted of 17,432 consenting and assessed individuals. Of these, 156 had documented brain damage syndromes (most commonly cerebral palsy) and 22 had a known genetic syndrome (most commonly Down’s syndrome but also Fragile X). These twins as well as their cotwins were excluded from the analyses.

The data collection was approved by the Ethics Committee at Karolinska Institutet and all participants consented to the study.

Zygosity determination

Zygosity determination for 571 pairs of twins for whom we had DNA from both twins was based on a panel of 48 SNPs derived for zygosity analyses (Hannellius et al., 2007). For the remaining twins, we used an algorithm based on five items concerning twin similarity and confusion (Lichtenstein et al., 2002) derived from the twins with known zygosity. Only twins with more than 95% probability of being correctly classified were assigned a zygosity. Using this algorithm, 734 of 17,100 twins were excluded as ‘zygosity unknown’; and the analyses were performed using the resulting 16,366 twins, 2,242 of whom were monozygotic (MZ) male twins, 3,166 dizygotic (DZ) male twins, 2,330 MZ female pairs, 2,790 DZ female twins and 5,838 DZ opposite-sexed (DZOS) twins.

Measures

Child ADHD symptoms were assessed using the Autism–Tics, ADHD and other Comorbidities inventory (A-TAC), which is designed for large-scale epidemiological research as an easy-to-administer, dimensional, and comprehensive interview for administration by lay persons over the phone. The instrument includes questions to cover 96 specific child psychiatric symptoms, established based on extensive psychometric analyses of a series of validation studies (Hansson et al., 2005; Larson et al., 2010), and assesses specific
problems corresponding to major clinical diagnostic
criteria in child- and adolescent psychiatry, focusing on
neuropsychiatric problems such as autism spectrum
disorders and ADHD. Questions are worded to assess
DSM-IV criteria and other well-described clinical fea-
tures, and should be answered in a life-time perspective
and in relation to age peers. Three response categories
are used: ‘no’ (0), ‘yes, to some extent’ (0.5) and ‘yes’
(1.0). The two modules used to assess ADHD include 19
questions that were identified in order to achieve the
optimal combined sensitivity, specificity and predictive
value for clinical diagnoses of ADHD in the validation
studies of the instrument with a high internal consist-
tency (alpha reliability for the ADHD scale was .92).

The A-TAC ADHD scale can be used to identify cate-
gories, as cutoff values yielding optimal sensitivity (for
cutting) and specificity (for research diagnostics)
have been identified based on two validation studies
(Hansson et al., 2005; Larson et al., 2010). A score of
≥ 6.0 (screening) on the 19 ADHD items identified
9.75% of the children with a ‘screening’ diagnosis and
yielded a sensitivity > .95, whereas a score ≥ 12.5
identified 1.78% of the children with a ‘research’ diag-
nosis and yielded a specificity > .95. The predictive
effect of the score for clinical diagnoses of ADHD was
‘excellent’ (area under a receiver operating character-
istics curve of 0.94 with a 95% confidence interval
between 0.92 and 0.96; Larson et al., 2010).

**Twin method**

The twin method is a natural experiment that relies on
the different levels of genetic relatedness between MZ
and DZ twin pairs to estimate the relative contribution
of genetic and environmental factors for a phenotype.
MZ twins are genetically identical, whereas DZ twins
share on average 50% of their segregating alleles. Spe-
cifically, we used the twin method to decompose the
variance of a phenotype into additive genetic factors
(A) reflecting additive effects of different alleles, non-
additive genetic factors (dominance, D) reflecting
interaction effects between alleles at the same gene
locus, shared environmental factors (C) reflecting non-
genetic influences that contribute to similarity within
pairs of twins and nonshared environmental factors (E)
reflecting experiences that make sibling pairs dissimilar
(Plomin, DeFries, McClearn, & McGuffin, 2008).

Twin correlations (i.e. within-twin pair maximum-
likelihood correlations) were used for an initial exami-
nation of the relative contribution of A, D, C and E.
Specifically, MZ correlations higher than DZ corre-
lations indicate A, whereas E is indicated by the extent
to which MZ correlations are less than unity. DZ corre-
lations higher than half the MZ correlations indicate C,
whereas DZ correlations lower than half the MZ corre-
slations suggest D or sibling interaction effects
(usually labeled ‘s’).

**Extremes analysis**

Twin pairs where at least one member of the pair was
exhibiting an extreme ADHD score were selected for the
extremes analysis. All analyses were conducted using
the two validated ADHD cutoffs (i.e. screening and
research diagnosis) to evaluate the extent to which
genetic and environmental factors operate differently at
varying levels of ADHD cutoffs.

**DeFries-Fulker extremes analysis** explores genetic
links between the extreme and the subthreshold by
bringing together the dichotomized classification
of ADHD and the quantitative dimension of ADHD symp-
toms. Specifically, rather than assessing twin similarity
in terms of individual differences on a quantitative trait
of ADHD or in terms of concordance for a certain cutoff,
DF extremes analysis assesses twin similarity as the
extent to which the mean standardized quantitative
trait score of the cotwins is as high as the mean stan-
dardized score of the selected proband. This measure of
twin similarity, called extreme group correlation, is
accounted for by dividing the quantitative traits scores
of the cotwins by the proband mean, specific for each sex
and zygosity group. Genetic influences are implied if
extreme group correlations are greater for MZ than for
DZ twin pairs. The extent to which genetic factors
account for the mean differences between probands and
the population is called group heritability.

Although DF extremes group heritability can be
estimated by doubling the differences in MZ and DZ
extreme group correlations, DF extremes analysis is
more properly conducted using a regression model
(DeFries & Fulker, 1988). Briefly, the basic DF model is
represented as the regression, C = B1P + B2R + A, in
which the cotwin’s score (C) is predicted from probands
score (P) and the coefficient of relatedness (R). Finding
significant group heritability implies that both extreme and
subthreshold range of ADHD symptoms are heritable
and that there are genetic links between ADHD and the
threshold variation. That is, group heritability itself,
not the comparison between the separate group heri-
tability estimates obtained from using different defini-
tions for the identification of ADHD probands (i.e.
diagnostic and screening criteria of ADHD), indicates
遗传性 links between extreme and the subthreshold
range of ADHD symptoms (for a more detailed descrip-
tion; Plomin & Kovas, 2005). Thus, applying DF ex-
 tremes analyses on two different definitions of ADHD
should be viewed as an attempt to explore whether our
findings are robust across different proband defini-
tions.

**Analysis of individual differences of the full range
of the distribution**

n the model-fitting analyses of the quantitative mea-
sure of ADHD symptoms for the whole sample, we used
a structural-equation modeling program, called Mx
(Neale, Boker, Xie, & Maes, 2003). We used the method

of raw maximum-likelihood estimation. This method allows the inclusion of singletons, where information from only one twin in a pair is available, which increases power in the analyses. The following combinations of variance components were considered in the univariate model-fitting analyses: ACE, ADE, AE, ADEs and AEs (s, sibling interaction term). When modeling parent report data, a negative sibling interaction term often occurs because there is a contrast effect in the parental ratings of their behavior (i.e. parents inadvertently exaggerate behavioral differences between the children). The effect of C and D in the classical twin design is confounded because the effects of C decreases the difference in MZ and DZ twin similarity, whereas the effect of D increases differences in twin similarity. Thus, C and D cannot be estimated simultaneously.

We also fitted a series of sex-limitation models to test for qualitative sex differences, quantitative sex differences and phenotypic variance differences between the sexes. Specifically, using data from same-sex twin pairs, the quantitative sex-differences model examines whether the magnitudes of genetic and environmental influences on a phenotype are different in males and females. As our sample also consists of DZOS twins, additional sex-specific parameters could be included to examine whether different genetic components influence the phenotype in one sex but not the other (qualitative sex-differences model; Neale et al. 2006). Potential phenotypic variance differences between the sexes can be explored using a scalar model. Such a model allows the phenotypic variances to differ between males and females, whereas the genetic and environmental parameter estimates are equated across sexes. Finally, in the constraint model, all variance components were set to be equal between the sexes.

Goodness of fit for the different twin models was assessed by the Akaike’s information criterion. Specifically, AIC was computed as \( \chi^2 - 2 \times df \) where \( \chi^2 \) is the difference in \(-2 \times \text{log likelihood} \) between the saturated and restricted model and \( df \) denotes the difference in degrees of freedom between the two models. A lower AIC value indicates better fit of the model to the observed data. It should be noted that the likelihood-ratio chi-square test revealed identical results (data not shown).

**Results**

Mean ADHD scores in the total sample were 1.76 (SD = 2.81; Table 1). Applying the two cutoff values, 9.75% and 1.78% of the total sample were identified as screen-positive for ADHD and meeting a research diagnosis of ADHD, respectively. The 1,590 twins who scored above the screening cutoff had an average ADHD score of 8.72 (SD = 3.03). The corresponding mean score for the 290 twins scoring above the diagnostic threshold was 13.99 (SD = 1.87). The sex distribution was balanced in the total sample (51% males). As expected, more males than females had a score above the screening (68%) and diagnostic (72%) cutoffs for ADHD.

**Extremes analysis**

Extreme group correlations suggest genetic influences because MZ similarity exceeds DZ similarity (Table 2). All MZ extreme group correlations were <1, suggesting nonshared environmental influences. Extreme group correlations were similar for males and females, and also similar for same-sexed DZ and DZOS twins, which suggest no quantitative or qualitative genetic and environmental sex differences. Finally, extreme group correlations were similar for the screening and the diagnostic cutoffs.

As expected from extreme group correlations, DF extremes analysis provided no evidence for sex differences. That is, the 95% confidence intervals around the estimates of the group heritability and group nonshared environment overlapped (see Table S1). The results suggest a strong genetic link between the extreme and the subthreshold variation, with almost identical group heritability estimates across the screening (.60) and the diagnostic (.62) criteria of ADHD (Table 2). In a follow-up analysis, we applied the DF model to the two symptom dimensions of DSM-IV ADHD (i.e. inattention and hyperactivity–impulsivity). The result indicate that the group heritability for inattention (twins with ≥ 6 DSM-IV inattention symptoms were selected as probands) and hyperactivity–impulsivity (twins with ≥ 6 DSM-IV hyperactivity–impulsivity symptoms were selected as probands) was similar in magnitude; estimated as .53 (.44–.62) and .62 (.53–.71), respectively.

**Analysis of individual differences in the full range of the ADHD distribution**

In the total sample, the within-twin pair correlations of the ADHD scores were similar to the observed extreme group correlations and suggest high heritability, and modest nonshared environmental for both males and females (Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>No. probands (%)</th>
<th>% Males</th>
<th>ADHD mean score (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>1,590 (9.75)</td>
<td>68</td>
<td>8.72 (3.03)</td>
</tr>
<tr>
<td>A-TAC diagnosis of ADHD</td>
<td>290 (1.78)</td>
<td>72</td>
<td>13.99 (1.87)</td>
</tr>
<tr>
<td>Broad screening criteria (raw ADHD score ≥ 6.0)</td>
<td>1,590 (9.75)</td>
<td>68</td>
<td>8.72 (3.03)</td>
</tr>
<tr>
<td>Strict diagnostic criteria (raw ADHD score ≥ 12.5)</td>
<td>290 (1.78)</td>
<td>72</td>
<td>13.99 (1.87)</td>
</tr>
</tbody>
</table>

A-TAC, Autism – Tics, ADHD and other Comorbidities; ADHD, attention-deficit hyperactivity disorder.

Model-fitting analyses show that the scalar AEs model had the lowest AIC value (Table 3). That is, a model that constrains the genetic and environmental parameter estimates to be equal across sex (but allows for variance differences), excludes variance due to the dominant genetic factor (D), and allows for contrast effects (s, sibling interaction term) provided the most parsimonious fit of the data. This best-fitting model (Table 2) estimated the heritability and nonshared environment contribution as .74 and .26, respectively.

**Discussion**

We found a strong genetic link between the extreme and the subthreshold variation of DSM–IV based assessments of ADHD symptoms, corroborating a previous smaller DSM–III–R-based study (Levy et al., 1997) and extending the previous results to include also very narrow definitions of ADHD with a high probability of correspondence to real-life clinical problem presentations. Our data suggest that ADHD is best viewed as the quantitative extreme of genetic and environmental factors operating dimensionally.

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**Table 2** Results of extremes analyses of ADHD symptoms and of analysis of individual differences of the full range of the distribution

<table>
<thead>
<tr>
<th>Extreme group correlations (No. probands)</th>
<th>DeFries–Fulker group estimates (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MZM</td>
<td>DZM</td>
</tr>
<tr>
<td>Broad screening criteria</td>
<td>.62 (248)</td>
</tr>
<tr>
<td>Strict diagnostic criteria</td>
<td>.65 (57)</td>
</tr>
</tbody>
</table>

| Analysis of individual differences of the full range of the distribution |
|-------------------------------------------|----------------------------------------|
| MZM                                       | DZM                                    | MZF | DZF | DZOS | Heritability | Nonshared environment |
| A-TAC ADHD symptom score                  | .69 (.66–.72)                          | .24 (.19–.29) | .65 (.61–.68) | .28 (.27–.33) | .30 (.26–.33) | .74 (.71–.76)          | .26 (.24–.29)          |

A-TAC, Autism – Tics, ADHD and other Comorbidities; ADHD, attention-deficit hyperactivity disorder; MZM, monozygotic male twins; DZM, dizygotic male twins; MZF, monozygotic female twins; DZF, dizygotic female twins; DZOS, dizygotic opposite-sexed twins.

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**Table 3** Model-fitting results of univariate analysis of ADHD symptoms

<table>
<thead>
<tr>
<th>Models</th>
<th>Fit of model compared to saturated model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>fit of model compared to saturated model</td>
</tr>
<tr>
<td>Saturated model</td>
<td>8,585.57</td>
</tr>
<tr>
<td>ADEs Qualitative sex differences</td>
<td>8,622.64</td>
</tr>
<tr>
<td>Quantitative sex differences</td>
<td>8,622.64</td>
</tr>
<tr>
<td>Scalar model</td>
<td>8,623.96</td>
</tr>
<tr>
<td>Constraint model</td>
<td>8,689.41</td>
</tr>
<tr>
<td>ADEs Qualitative sex differences</td>
<td>8,638.31</td>
</tr>
<tr>
<td>Quantitative sex differences</td>
<td>8,638.31</td>
</tr>
<tr>
<td>Scalar model</td>
<td>8,642.30</td>
</tr>
<tr>
<td>Constraint model</td>
<td>8,807.18</td>
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<tr>
<td>ADEs Qualitative sex differences</td>
<td>8,622.85</td>
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<tr>
<td>Quantitative sex differences</td>
<td>8,622.85</td>
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<tr>
<td>Scalar model</td>
<td>8,623.96</td>
</tr>
<tr>
<td>Constraint model</td>
<td>8,689.41</td>
</tr>
<tr>
<td>ADEs Qualitative sex differences</td>
<td>8,666.58</td>
</tr>
<tr>
<td>Quantitative sex differences</td>
<td>8,666.58</td>
</tr>
<tr>
<td>Scalar model</td>
<td>8,672.23</td>
</tr>
<tr>
<td>Constraint model</td>
<td>8,842.69</td>
</tr>
</tbody>
</table>

Best-fitting model indicated in bold. −2LL, likelihood fit statistic; df, degrees of freedom; \(\chi^2\), the difference in −2LL between the saturated and restricted model; \(\Delta df\), difference in df between the saturated and restricted model; \(\Delta AIC\), Akaike’s Information Criterion; s, sibling interaction term; AE, model excluding variance explained by genetic dominance effects.
throughout the distribution of ADHD symptoms, indicating that the same etiologic factors are involved in the full range of symptoms of inattention, hyperactivity and impulsivity.

The results from our DF extremes analysis are important because it is the first to be based on DSM-IV assessments of ADHD symptoms. The use of a large twin data set also allowed us to explore, in contrast to previous studies (Levy et al., 1997), genetic links between the extreme and the subthreshold range of ADHD using clinically relevant threshold definitions. Finding similar estimates for the group heritability of both the diagnostic and screening criteria of ADHD and also the two DSM-IV symptom dimensions of ADHD highlight the robust nature of our results. Our individual differences results suggest high heritability, no shared environment and modest nonshared environmental effects; a finding that is largely consistent with prior twin study results using both categorical and continuous definitions of ADHD (Burt, 2009; Faraone et al., 2005; Thapar et al., 1999) although it should be noted that a small but significant shared environmental contribution has emerged in other studies (Wood, Buitelaar, Rijjsdijk, Asherson, & Kuntsi, 2010).

In line with previously reported twin study results (Levy et al., 1997), our data support the view that ADHD is the quantitative extreme of the genetic and environmental influences that operate across the distribution of inattention, hyperactivity and impulsivity symptoms. As several different research methods with different weaknesses in validity have reached the same conclusion (Faraone et al., 2006, 2009; Frazier et al., 2007; Haslam et al., 2006; Lubke et al., 2009; Rapoport et al., 1980; Scahill et al., 1999), there is now strong evidence supporting the notion of ADHD as an extreme end of a continuous trait rather than as a disorder category. This continuous, higher order trait may consist of normally distributed variations in cognitive abilities (e.g. ‘executive’ functions; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005) and ‘extroverted’ personality traits (e.g. novelty seeking; Anckarsater et al., 2006), giving rise to deficient adaptive strategies and ensuing mental health problems in extreme ends of the distribution. One implication of these findings is that it may not be fruitful for etiologic models of ADHD to only propose causes that are specific to rare diagnosed cases. Rather, it is probably sufficient to also focus on the factors involved in the transition from milder to more severe levels of ADHD symptoms. In addition, if ADHD is the quantitative extreme of genetic and environmental factors operating dimensionally throughout the distribution, gene identification efforts may benefit from examining the dimensional distribution of symptoms that underlie ADHD within the normal population. The high heritability suggests that quantitative ratings of the ADHD symptoms described in DSM-IV could be used as dimensional measures in genetic association studies. Finding genetic links between the extreme and the subthreshold range of ADHD symptoms is also in line with the quantitative trait locus model of molecular genetics (Plomin, Haworth, & Davis, 2009), which predicts that many genes, each with a small effect size, influence the whole phenotypic variations, that is, the genetic effects affecting ADHD may also give rise to subthreshold ADHD and vice versa. Such effects could include a not only large number functional polymorphisms, but also larger structural changes, including so called copy number variants (Franke, Neale, & Faraone, 2009; Poelmans, Pauls, Buitelaar, & Franke, 2011; Williams et al., 2010).

Sex effects are difficult to study because their reliable detection requires large samples and a narrow participant age range, which might explain why prior studies have produced mixed results, with evidence both for (Rhee, Waldman, Hay, & Levy, 1999) and against (Hudziak, Derks, Althoff, Rettew, & Boomsma, 2005) sex differences underlying the etiology of ADHD. We found no evidence for sex differences in heritability across the continuum; a result that is consistent with prior twin studies exploring the extreme end of the ADHD distribution (Levy et al., 1997; Thapar et al., 2000). Our results are also consistent with findings from a prior clinical-based study reporting strong associations between psychosocial adversity and ADHD independently of gender (Biederman, Faraone, & Monuteaux, 2002). Thus, genetic and environmental risk factors appear to act, independently of gender, on ADHD symptoms scores across the range of severity, which indicate that the dimensional model of ADHD seems appropriate for both males and females.

In this very large twin study of childhood ADHD symptoms, we screened 10,895 twin pairs, that is all twins born in Sweden between 1992 and 2000, with a very high response rate (> 80%). An advantage of our design is that we were able to study the etiology at the very extreme end of the distribution and that age/period effects were controlled for. This is a noteworthy strength as prior twin studies have studied the etiology of less extreme levels of ADHD using samples with wide age-ranges. Nevertheless, the results should be interpreted in light of some limitations. First, as this epidemiological study included over 17,000 children, complete clinical evaluations were beyond the feasible, and, therefore we had to rely on parental report. Although the items used here closely mirrored the DSM-IV criteria, parental interviews are not equivalent to a psychiatrist’s diagnosis. However, we used an instrument that has shown good psychometric properties and thorough validation data are available (Hansson et al., 2005; Larson et al., 2010). Second, twins may not be representative of the general population in terms of mental health problems. Some studies have reported that twins might have an increased risk for ADHD compared to singletons.
The question of whether the etiology is the same for different levels of DSM–IV ADHD symptoms remains to be investigated.

Extremes analyses indicated a strong genetic link between the extreme and the subthreshold variation, with almost identical group heritability estimates around 0.60 for the diagnostic and screening criteria of ADHD.

Our data suggest that ADHD is best viewed as the quantitative extreme of genetic and environmental factors operating dimensionally throughout the full range of variation in inattention, hyperactivity and impulsivity. Thus, the data provide evidence for a need to identify the factors involved in the transition from milder to more severe levels of ADHD symptoms.

References


