Chapter 25

Genetics of ADHD, Hyperactivity, and Attention Problems

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Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by symptoms of inattention, and/or hyperactivity-impulsivity. Inattention symptoms are present when an individual fails to pay attention and has difficulty in concentrating. Children or adults who are hyperactive fidget, squirm and move about constantly and can not sit still for any length of time. Impulsivity can be described as acting or speaking too quickly without first thinking of the consequences. Children with ADHD face developmental and social difficulties. As adults, they may face problems related to employment, driving a car, or relationships (Barkley, 2002). As is the case for many other psychiatric disorders, the diagnosis of ADHD is not based on a specific pathological agent, such as a microbe, a toxin, or a genetic mutation, but instead on the collection of signs and symptoms that occur together more frequently than expected by chance (Todd, Constantino, & Neuman, 2005). Genetic studies of psychiatric disorders are complicated by this lack of clear diagnostic tests (Hudziak, 2001). Heritability estimates in epidemiological genetic studies and the results of gene-finding studies may vary as a consequence of the instrument that is used to assess ADHD, and of other factors such as the specific population that is investigated. In the current chapter we will focus on behavioral measures of ADHD, and not on endophenotypes (i.e., phenotypes that form a link between the biological pathway and the behavioral outcome, for example, executive functioning). An excellent overview of endophenotypes for ADHD can be found in Castellanos and Tannock (2002). In this overview, we will first present epidemiological studies on the prevalence of ADHD (Section *Prevalence of ADHD*). Next, the results of studies reporting the heritability of ADHD and related phenotypes will be discussed (Section *Genetic Epidemiological Studies on ADHD in Children*). We concentrate on variation in these statistics as a result of the specific characteristics of the samples (e.g., age and sex of the children) and as a result of variation in the assessment methods and informants. Finally, we give an overview of studies reporting on the agreement between questionnaire data and diagnostic interviews (Section *The Relation Between Questionnaire Data and Diagnostic Interviews*).

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Prevalence of ADHD

The current guidelines for the diagnosis of ADHD in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) describe three different subtypes of ADHD: (i) ADHD of the inattentive type, which requires the presence of six out of nine symptoms related to inattention; (ii) ADHD of the hyperactive/impulsive type, which requires the presence of six out of nine hyperactive/impulsive symptoms; and (iii) ADHD of the combined type, which requires the presence of six out of nine inattention symptoms and six out of nine hyperactive/impulsive symptoms (American Psychiatric Association, 1994). Additional criteria are the presence of some hyperactive/impulsive or inattentive symptoms before age 7 years, and impairment from the symptoms in two or more settings.

In research settings, the diagnosis of ADHD is not always based on these formal criteria. In some studies, the diagnosis is based on behavior checklists, whose items are summed into a total score. ADHD is then assumed to be present when a child scores above a certain diagnostic cutoff criterion. Diagnoses based on checklists usually do not incorporate additional requirements such as age of onset before age 7 years, or impairment.

Prevalence estimates of ADHD may vary as a result of instrument variance (e.g., DSM diagnoses versus checklists) and as a function of sex and age of the children. We summarize epidemiological studies that report prevalence estimates

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Table 25.1 Prevalence estimates based on clinical diagnosis in community-based samples

Study	N	Method	Any ADHD Boys/girls (sex ratio)	Inattentive Boys/girls (sex ratio)	Hyperactive Boys/girls (sex ratio)	Combined Boys/girls (sex ratio)	Age
Lavigne et al. (1996)*	1150	DSM-III-R diagnosis by clinician	2.4/1.3 (1.8)	–	–	–	2–5
Breton et al. (1999)**	2400	DSM-III-R clinical interview with child 6-month prevalence Impairment not included	3.3	–	–	–	6–14
	2400	Clinical interview with teacher 6-month prevalence Impairment not included	8.9	–	–	–	6–14
	2400	Clinical interview with parent 6-month prevalence Impairment not included	5.0	–	–	–	6–14
Rohde et al. (1999)	1013	DSM-IV clinical interview with parent and child	5.5/6.1 (.90)	2.0	0.8	3.0	12–14
Cuffe et al. (2001)	490	DSM-III-R clinical interview with adolescent and parent	2.6/0.5 (4.9)	–	–	–	16–22
Graetz, Sawyer, Hazell, Arney, and Baghurst (2001)	3597	DSM-IV clinical interview with parent	11.0/4.0 (2.8)	5.1/2.3 (2.2)	2.4/1.4 (1.7)	3.1/0.7 (4.4)	6–17
Costello et al. (2003)	1420	DSM-IV clinical interview with parent 3-month prevalence	1.5/0.3 (5)	–	–	–	9–13
Ford, Goodman, and Meltzer (2003)	10438	DSM-IV clinical interview with parent, teacher, and self (diagnosis based on judgment by clinician)	3.6/0.9 (4.3)	1.0/0.3 (3.0)	0.3/0.04 (7)	2.3/0.5 (4.6)	5–15
Graetz et al. (2005)	2375	DSM-IV clinical interview with parent Impairment not included	19.0/8.8 (2.2)	8.9/4.4 (2.0)	3.4/1.8 (1.9)	6.7/2.6 (2.6)	6–13
Neuman et al. (2005)	1472	DSM-IV clinical interview with parent	7.4/3.9 (1.9)	4.5/0.6 (7.5)	0.5/1.2 (.4)	2.3/2.1 (1.1)	7–19

*This is the weighted N which is calculated based on the information provided in the paper. The weighted prevalence of ADHD is 2%, the number of subjects is 23, so the weighted total number of subjects is 23/0.02=1150.

**Breton et al. do not give the prevalences by sex, but do report the odds ratio's for male:female. These are 4.0 in self-reports, 5.1 in teacher reports, and 2.9 in parental reports.

for ADHD based on DSM criteria in Table 25.1. These prevalences can be compared with the prevalences based on checklist data which are shown in Table 25.2. In both tables, information on the assessment method and on the age and sex of the children has been included.

The prevalences based on *diagnostic interview studies* varied between 1.5 and 19.0% in boys, and between 0.3 and 8.8% in girls. In both boys and girls, the lowest prevalence was reported in a study that used a 3-month prevalence instead of the usual 1 year prevalence which may explain the discrepancy with other findings (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). The highest prevalence was reported in a study that did not include impairment criteria (Graetz, Sawyer, & Baghurst, 2005). Breton et al. (1999) also excluded impairment criteria. Excluding the results of these three studies, the prevalences are in the range of 2.4–11% in boys and 1.3–4% in girls. The prevalences based on *checklist data* range between 2.9 and 23.1% in boys and between 1.4 and 13.6% in girls. Baumgaertel, Wolraich, and Dietrich (1995), who did not show the prevalences by sex, reported a prevalence of 17.8, which is in the upper range for both sexes.

Clearly, higher prevalences are reported when diagnosis is based on questionnaire data compared to clinical diagnoses. How can this discrepancy be explained? Wolraich, Hannah, Baumgaertel, and Feurer (1998) showed that the rate of overall ADHD (i.e., irrespective of subtype) based on checklist data in a sample of 698 boys and girls drops from 16.1 to 6.8% when impairment is required for diagnosis. Similarly, in the study of Breton et al. (1999), the prevalence based on parental reports dropped from 5.0 to 4.0% when including impairment criteria. Because impairment criteria are usually included in diagnostic interview studies and not in studies using questionnaire data, it is likely that the higher prevalence in questionnaire data is the result of the exclusion of impairment criteria.

In Tables 25.1 and 25.2, higher prevalences for ADHD are reported in boys than in girls. The mean sex ratios were calculated by taking the average of the sex ratios across studies. For overall ADHD, the ratio of boys:girls ranges from 0.9:1 to 5:1 with a mean sex ratio of about 2.5:1. The sex ratio is lowest in young children (3–5 years; mean sex ratio is 1.7:1) and highest in older children (5–13 years; mean sex ratio is about 3:1). In adolescents (13–17 years), the sex ratio is about 2.5:1. The sex ratio's do not vary much by subtype. The sex ratio's are 2.5:1, 2.5:1, and 3.5:1 for the inattentive type, the hyperactive-impulsive type, and the combined type, respectively. The male:female ratio is not very high in epidemiological studies (about 3:1), but is clearly higher (about 9:1) in clinical settings (Gaub & Carlson, 1997).

In two studies, the prevalence of ADHD was estimated separately in three age groups (Cuffe, Moore, & McKeown, 2005; Nolan, Gadow, & Sprafkin, 2001). Both studies show a relatively low prevalence of ADHD in young children, an increased prevalence in older children, and again a relatively low prevalence in adolescents. A recent epidemiological study in adults showed that ADHD may be common in adulthood. Broad screening DSM-IV criteria (symptom occurred sometimes or often) identified 16.4% of a population of 966 adults as having ADHD, while 2.9% of the adults met narrow screening criteria (symptom occurred often) (Faraone & Biederman, 2005).

Genetic Epidemiological Studies on ADHD in Children

Many studies report the heritability of ADHD from a comparison of the covariance structure in monozygotic (MZ) and dizygotic (DZ) twins. In these studies, variation in the vulnerability for ADHD is decomposed into genetic and environmental components. The decomposition of variance takes place by comparing the similarity (covariance or correlation) between MZ twins, who are nearly always genetically identical, and DZ twins, who on average share half of their segregating alleles. MZ twins share all additive genetic and non-additive genetic variance. DZ twins on average share half of the additive genetic and one quarter of the non-additive genetic variance (Plomin, DeFries, McClearn, & McGuffin, 2001). The environmental decomposition of the phenotypic variance is into shared environmental variance and non-shared, or specific, environmental variance. The environmental effects shared in common by two members of a twin-pair (C) are by definition perfectly correlated in both monozygotic and dizygotic twins. The non-shared environmental effects (E) are by definition uncorrelated in twin-pairs. A first estimate of additive genetic heritability based on twin data is obtained from comparing MZ and DZ correlations: $a^2 = 2(r_{MZ}–r_{DZ})$. The importance of non-additive genetic influence is obtained from $d^2 = 4(r_{DZ}–r_{MZ})$ and of shared environmental factors $c^2 = 2r_{DZ}–r_{MZ}$. Finally, the estimate of the non-shared environmental component is obtained from $e^2 = 1–r_{MZ}$. In the classic twin design, one cannot estimate D and C simultaneously and usually the choice for an ADE or ACE model is based on the pattern of MZ and DZ twin correlations. Parameters a^2, c^2, d^2, and e^2 are then obtained with, e.g., maximum likelihood estimation using software packages as Mx (Neale, Boker, Xie, & Maes, 2003) or Mplus (Muthén & Muthén, 2000).

Papers reporting on the heritability of ADHD find large genetic influences, irrespective of the choice of instrument, informant, or sex and age of the child. Another general finding is the non-significant influence of the shared environment. We summarize these results by measurements

Table 25.2 Prevalence estimates based on behavioral checklist data in community based samples

Study	N	Method	Any ADHD Boys/girls (sex ratio)	Inattentive Boys/girls (sex ratio)	Hyperactive Boys/girls (sex ratio)	Combined Boys/girls (sex ratio)	Age
Szatmari, Offord, and Boyle (1989)	1486	DSM-III-R rating scale by parent, teacher, and self. Prevalences based on hierarchical log-linear models	10.1/3.3 (3.1)				4–11
	1236	DSM-III-R rating scale by parent, teacher, and self. Prevalences based on hierarchical log-linear models	7.3/3.4 (2.1)	–	–	–	12–16
Baumgaertel et al. (1995)	1077	DSM-IV rating scale by teacher	17.8	9.0	3.9	4.8	5–12
Wolraich, Hannah, Pinnock, Baumgaertel, and Brown (1996)	8258	DSM-IV rating scale by teacher	16.2/6.1 (2.7)	7.2/3.5 (2.1)	3.8/0.9 (4.2)	5.3/1.6 (3.3)	Kinder garten through 5th grade
Nolan et al. (2001)	413	DSM-IV rating scale by teacher	21.5/13.6 (1.6)	3.8/4.0 (.95)	7.6/5.1 (1.5)	10.1/4.6 (2.2)	3–5
	1520	DSM-IV rating scale by teacher	23.1/8.2 (2.8)	14.4/6.0 (2.4)	3.4/1.1 (3.1)	5.3/1.1 (4.8)	5–12
	1073	DSM-IV rating scale by teacher	20.1/8.8 (2.3)	14.5/8.0 (1.8)	1.6/0.0 (incalculable)	4.0/0.8 (5.0)	12–18
Larsson et al. (2004)	2063	DSM-III-R rating scale by parent	4.7	–	–	–	8–9
	2055	DSM-III-R rating scale by parent	3.1	–	–	–	13–14
Levy, Hay, Bennett, and McStephen (2005)	1550	DSM-IV rating scale by mother	–	1/4.3 (2.3)	3.1/1.7 (1.8)	5.8/2.0 (2.9)	4–12
Cuffe et al. (2005)	6933	Strengths and Difficulties Questionnaire	3.1/1.4 (2.2)	–	–	–	4–8
	7431	Strengths and Difficulties Questionnaire	6.3/2.1 (3.0)	–	–	–	9–13
	5636	Strengths and Difficulties Questionnaire	2.9/1.8 (1.6)	–	–	–	14–17

of: (i) ADHD symptoms (i.e., instrument includes both hyperactivity–impulsivity and attention problem symptoms (Table 25.3); (ii) hyperactivity (Table 25.4); and (iii) attention problems (Table 25.5). In the tables, we included information on the instrument that was used to assess ADHD. It should be noted that the majority of the studies used symptom counts rather than categorical diagnosis. If a research group published more than one paper based on the same sample, we included only the study with the largest sample size. The broad-band heritability of ADHD ranges between 35 and 89%. For hyperactivity, the broad-band heritability ranges between 42 and 100%. Finally, for attention problems, the broad-band heritability ranges between 39 and 81%.

Longitudinal studies show that symptom ratings of attention problems are stable between ages 7 and 12 (Rietveld, Hudziak, Bartels, Beijsterveldt van, & Boomsma, 2004). The same is true for symptom ratings of ADHD between 8 and 13 years of age (Larsson, Larsson, & Lichtenstein, 2004). These two studies report remarkably similar correlations of about 0.5 for 5-year test–retest correlations. Likewise, both studies report that the stability of symptom ratings of attention problems is mainly explained by additive genetic effects, but that the genetic effects are far from perfectly stable. Only a subset of the genes that operate at one age does so at a later age.

Although shared environmental influences on ADHD seem to be absent, a number of recent studies have shown that the genetic effects may be mediated by environmental factors (Brookes et al., 2006; Kahn et al., 2003; Seeger et al., 2004). Interaction between genetic and shared environmental influences inflate the estimate of the genetic effects. The finding of significant gene by environment interaction in these studies highlights the importance of considering the effects of both environmental and genetic factors, and their interactions in future studies on ADHD.

Sex Differences in Genetic Influences on ADHD

When examining the genetic architecture of a trait, two different kinds of sex differences can be distinguished. *Quantitative sex differences* reflect sex differences in the magnitude of the genetic influences: do genes explain the same or different amounts of variation in boys and girls? *Qualitative sex differences* reflect differences in the specific genes that are expressed in boys and girls. Below, we discuss quantitative and qualitative sex differences in ADHD.

Thirteen of the studies reported in Tables 25.3, 25.4, and 25.5 tested for quantitative sex differences in ADHD (see Tables 25.3, 25.4, and 25.5). Seven of these studies reported the absence of significant sex differences. In the remaining six studies, the presence of sex differences varied by informant and age. The effect sizes of the statistically significant sex differences were small, and the pattern of sex differences was inconsistent over studies. In some studies heritability was higher in boys, while in other studies heritability was higher in girls. The small effect sizes and the inconsistent pattern of results support the conclusion that the magnitudes of the etiological factors influencing variation in ADHD do not vary much as a function of the child's sex.

Nine studies investigated if different genes are expressed in boys and girls. Eight studies did not find qualitative sex differences. One study reported on different genes in boys and girls, but only for twins who were rated by the same teacher and not for twins rated by parents or different teachers (Saudino, Ronald, & Plomin, 2005). Future studies should reveal if this finding of qualitative sex differences in teacher ratings can be replicated.

Informant Differences

The heritabilities for ADHD rated by father and mother appear to be similar in most studies (Beijsterveldt van, Verhulst, Molenaar, & Boomsma, 2004; Derks, Hudziak, Beijsterveldt van, Dolan, & Boomsma, 2004; Eaves et al., 1997), but not in others (Goodman & Stevenson, 1989). Heritabilities for teacher ratings range between 39 and 81% and are usually lower than the heritabilities based on parental ratings in the same sample (Eaves et al., 1997; Kuntsi & Stevenson, 2001; Simonoff et al., 1998; Vierikko, Pulkkinen, Kaprio, & Rose, 2004, but see Martin, Scourfield, & McGuffin, 2002).

A complexity encountered when teacher ratings are analyzed is that both members of a twin-pair may be rated by the same teacher or by different teachers. Twin correlations are usually higher in children rated by the same teacher than in children rated by different teachers (Saudino et al., 2005; Simonoff et al., 1998; Towers et al., 2000; Vierikko et al., 2004) but not in Sherman, Iacono, and McGue (1997). Simonoff et al. (1998) developed two different models to explore this finding. One model was based on the assumption that teachers have difficulty distinguishing the two children ("twin confusion model"). The other model was based on the assumption that ratings by the same teacher are correlated because (i) raters have their own subjective views on which behaviors are appropriate and which are not or (ii) raters influence the behavior of the child because of the rater's own personality characteristics ("correlated errors model"). Although Simonoff et al. (1998) were not able to differentiate between these two models, Derks, Hudziak, Beijsterveldt van et al. (2006) reported a better fit of the correlated errors model in a large sample of Dutch twins rated by their teacher.

Table 25.3 Heritability estimates based on epidemiological studies of ADHD

Study	Age	N pairs	Sample and assessment instrument	Rater	Heritability (A+D)	Quantitative sex difference in heritability	Contrast or dominance effect
Eaves et al. (1997)	8–16	1412	Virginia Twin Study of Adolescent Behavioral Development Diagnostic interview	Mother and father	71(boys)/74 (girls) (Mother) 78 (boys)/55 (girls) (Father)	No (mother) Yes (father)	AE_S model fits better than ADE model
	8–16	1412	Virginia Twin Study of Adolescent Behavioral Development Questionnaire	Mother, father, and teacher	62 (boys) /54 (girls) (Teacher) 75 (boys) /63 (girls) (Mother) 82 (boys) /76 (girls) (Father)	No	Mother and father: AE_S model fits better than ADE model. Teacher: AE model
Sherman, Iacono, and McGue (1997)	11–12	288	Minnesota Twin Family Study Mother: Diagnostic interview Teacher: Rating Form	Mother and teacher	89 (Mother) 73 (Teacher)	–	–
Coolidge, Thede, and Young (2000)	Mean=9	112	Coolidge Personality and Neuropsychological Inventory	Parent	82	–	AE model
Thapar et al. (2000)	5–17	1321*	Greater Manchester Twin Register DuPaul rating scale (parent and teacher), and Rutter A scale (parent)	Parent and teacher	78 (DuPaul, parent) 84 (Rutter, parent) 77 (DuPaul, teacher)	No	(Parent, DuPaul): ADE (var MZ=varDZ) Parent, Rutter: AE_S (var DZ > var MZ) Teacher: AE model
Young, Stallings, Corley, Krauter, and Hewitt (2000)	12–18	334	Colorado Drug Research Center Diagnostic interview	Self	49	–	AE model
Burt, Krueger, McGue, and Iacono (2001)	10–12	753	Minnesota Twin Family Study Diagnostic Interview	Symptom present when mother or self report it	57	No	–
Price et al. (2001)	2, 3, and 4	3118 (2) 2796(3) 2452(4)	Twins Early Development Study Conners Rating Scale	Parent	83 (boys)/79(girls) (age 2) 81 (age 3) 79 (age 4)	Yes (age 2) No (ages 3,4)	AE_S model fits better than ADE model (ages 2, 3, and 4)
Larsson et al. (2004)	8–9 and 13–14	1106 (8–9) 1063 (13–14)	Young Twins Study DSM-III-R based questionnaire	Parent	35(boys)/68 (girls) (age 8–9) 74 (boys)/61(girls) (age 13–14)	Yes	–
Dick, Viken, Kaprio, Pulkkinen, and Rose (2005)	14	631	FinnTwin12 Diagnostic interview	Self	70	–	–
Kuntsi, Rijsdijk, Ronald, Asherson, and Plomin (2005)	Mean=8	3541	Twins Early Development Study Conners Rating Scale	Parent	72	No	–
Hudziak, Derks, Althoff, Rettew, and Boomsma (2005)	7	1585	Netherlands Twin Register Conners Rating Scale	Mother	78	No	ADE model (var MZ = var DZ)

*The authors report in the abstract that data from 2082 pairs are included, but 162 pairs with unknown zygosity and 599 opposite sex pairs are excluded from statistical analyses. AE_s model includes additive genetic effects, non-shared environmental effects and contrast effects; ADE model includes additive genetic effects, non-additive genetic effects, and non-shared environmental effects; var, variance.

Table 25.4 Heritability estimates based on epidemiological studies of hyperactivity

Study	Age	N pairs	Sample and assessment instrument	Rater	Heritability (A+D)	Quantitative sex difference in heritability	Contrast or dominance effect
Goodman and Stevenson (1989)*	13	213	Medical Research Counsel and Inner London Education Authority (both London) Rutter Behavior Questionnaire	Mother, father and teacher	>100% (mother) 42% (father) 42% (teacher)	–	–
Thapar, Hervas, and McGuffin (1995)	8–16	376	Cardiff Births Survey Rutter A scale	Mother	88	–	AE_S model (var DZ >var MZ)
Sherman et al. (1997)	11–12	288	Minnesota Twin Family Study Teacher: rating form Mother: diagnostic interview	Teacher and mother	69 (teacher) 91 (mother)	–	–
Simonoff et al. (1998)	8–16	1044	Virginia Twin Study of Adolescent Behavioral Development Questionnaire	Mother and teacher	75 (mother same teacher) 69 (mother different teacher) 52 (teacher)	No	Mother: AE_S model fits better than ADE model Teacher: AE model
Kuntsi and Stevenson (2001)	7–11	268	Twins from primary schools in Southern England Conners Rating Scale	Parent and teacher	71 (parent) 57 (teacher)	–	Parent: AE_S model fits better than ADE model Teacher: AE model
Martin et al. (2002)	5–16	682 (Parent) 443 (Teacher)	Cardiff Birth Survey Conners Rating Scale (CRS), and Strengths and Difficulties Questionnaire (SDQ)	Parent and teacher	74 (parent, CRS) 72 (parent, SDQ) 80 (teacher, CRS) 81 (teacher, SDQ)	–	Parent (CRS and SDQ): ADE model fits better than AE_S model Teacher (CRS and SDQ): AE model
Derks et al. (2004)	3	6250 (Father) 9445 (Mother)	Netherlands Twin Register Child Behavior Checklist 2/3	Father and mother	66 (father) 70 (mother)	No	ADE model (var MZ=var DZ)
Vierikko et al. (2004)	11–12	1636	FinnTwin12 Multidimensional Peer Nomination Inventory	Parent and teacher	78 (boys, parent) 81 (girls, parent) 49 (boys, teacher) 55 (girls, teacher)	No (parent) Yes (teacher)	Parent (girls): AE_S model (but var MZ=var DZ) Parent (boys): AE model Teacher: AE model
Saudino et al. (2005)	7	3714	Twins Early Development Study Strengths and Difficulties Questionnaire	Parent and teacher	77 (parent, boys) 75 (parent, girls) 74 (same teacher, boys) 76 (same teacher, girls) 66 (different teacher, boys) 55 (different teacher, girls)	No	–

*The heritability is more than 100% while the authors calculated A, C, and E based on the MZ and DZ correlations, whereas the DZ correlations were lower than half the MZ correlations. AE_S model includes additive genetic effects, non-shared environmental effects, and contrast effects; ADE model includes additive genetic effects, non-additive genetic effects, and non-shared environmental effects; var=variance.

Table 25.5 Heritability estimates based on epidemiological studies of attention problems

Study	Age	N pairs	Sample and assessment instrument	Rater	Heritability (A+D)	Quantitative sex difference in heritability	Contrast or dominance effect
Edelbrock, Rende, Plomin, and Thompson (1995)	7–15	181	Western Reserve Twin Project Child Behavior Checklist	Parent	66	–	
Gjone, Stevenson, and Sundet (1996)	5–9 12–15	390 (5–9) 526 (12–15)	Norwegian Medical Birth Registry Child Behavior Checklist	Parent	73–76 (age 5–9) 75–79 (age 12–15)	–	–
Sherman et al. (1997)	11–12	288	Minnesota Twin Family Study Teacher: Rating form Mother: Diagnostic interview	Mother and teacher	69 (mother) 39 (teacher)	–	–
Hudziak, Rudiger, Neale, Heath, and Todd (2000)	8–12	492	Missouri Twin Study Child Behavior Checklist	Parent	60–76	–	No contrast effect, D was not tested
Schmitz and Mrazek (2001)	4–11	207	Colorado Department of Health Statistics Child Behavior Checklist	Mother	54	–	–
Rietveld et al. (2003)*	7 10 12	3373 2485 1305	Netherlands Twin Register Child Behavior Checklist	Mother	71 (age 7) 70 (boys, age 10) 71 (girls, age 10) 69 (boys, age 12) 73 (girls, age 12)	No (7) Yes (10) Yes (12)	An ADE and an AEs model both provide a good fit to the data
Beijsterveldt van et al. (2004)	5	7679 (mother) 6999 (father)	Netherlands Twin Register Devereux Child Behavior Rating Scale	Mother and father	79 (mother boys) 81 (mother girls) 76 (father boys and girls)	Yes (mother) No (father)	AE_S model (var DZ>var MZ)

*Both the ADE and the AEs model provided a good fit at some ages. The heritability estimates are based on the ADE model because this model provided a good fit at all ages. AE_s model includes additive genetic effects, non-shared environmental effects and contrast effects; ADE model includes additive genetic effects, non-additive genetic effects, and non-shared environmental effects.

Selected Samples (DeFries–Fulker Regression)

Several twin studies have based heritability estimates for ADHD on data from subjects who were selected on a high vulnerability for ADHD. In some of these studies, the subjects with a high vulnerability were selected based on a clinical diagnosis of ADHD, in others they obtained a high behavior checklist score. DeFries and Fulker (1985) developed a multiple regression model that is especially appropriate for the analysis of data in twin-pairs in which one member of a pair has been selected because of a deviant score. The rationale of this method is based on the fact that when probands are selected based on high scores on a heritable trait, MZ cotwins are expected to obtain higher scores on the trait than DZ cotwins because of a lower degree of regression to the mean. In the regression model, the cotwin's score is predicted from a proband's score (P) and the coefficient of relationship (R). The coefficient of relationship equals 0.5 and 1 in DZ and MZ twins, respectively. The basic regression model is as follows: $C = B_1\ P + B_2\ R + A$, where C is a cotwin's predicted score; B_1 is the partial regression of the cotwin's score on the proband's score; B_2 is the partial regression of the cotwin's score on the coefficient of relationship; and A is the regression constant. B_1 is a measure of twin resemblance that is independent of zygosity. A significant regression coefficient B_2 indicates that being a member of the affected group is heritable. The extreme group heritability (h_g^2) equals: $h_g^2 = B_2$/(mean score proband–mean score cotwin). After establishing the heritability of the condition by testing the significance of B_2, direct estimates of h^2 (the extent to which individual differences in the unselected population are heritable) and c^2 (the extent to which individual differences in the unselected population are explained by shared environmental factors) can be obtained by fitting the following extended regression model: $C = B_3P + B_4R + B_5PR + A$, where PR is the product of the proband's score and the coefficient of relationship R. B_5 is a direct estimate of h^2, while B_3 is a direct estimate of c^2. DeFries and Fulker (1985) note that if affected individuals represent the lower end of a normal distribution of individual differences, the estimate of h^2 (heritability of the trait in the unselected sample) should be similar to the estimate of h_g^2 (heritability of extreme group membership).

The DeFries–Fulker regression model has been used to estimate h_g^2 and h^2 in a number of studies (Gillis, Gilger, Pennington, & DeFries, 1992; Rhee, Waldman, Hay, & Levy, 1999; Stevenson, 1992). Gillis et al. studied the heritability of ADHD in a sample of 74 twin-pairs in which at least one of the twin members was diagnosed with ADHD. They report an estimate of 0.98 ($\pm$0.26) for h_g^2. This is in agreement with an estimate of 0.81 ($\pm$0.51) for h_g^2 based on hyperactivity scores in a sample of 196 13-year-old twin-pairs (Stevenson, 1992), although this latter estimate did not reach significance.

A number of studies showed that h_g^2 does not vary as a function of the diagnostic cutoff score that is used for assessing ADHD (Levy, Hay, McStephen, Wood, & Waldman, 1997; Price, Simonoff, & Waldman, 2001; Willcutt, Pennington, & DeFries, 2000). Gjone, Stevenson, Sundet, and Eilertsen (1996) also report an absence of change in group heritability with increasing severity, but a slight tendency toward decreased heritability in the more severely affected groups. This suggests that the extreme group heritability does not vary as a function of the diagnostic cutoff score, although there may be a somewhat lower heritability of ADHD at the extreme of the distribution.

An interesting application of DeFries–Fulker regression was shown in Willcutt et al. (2000) who studied ADHD in 373 8- to 18-year-old twin-pairs. They investigated if h_g^2 of inattention varies as a function of the level of hyperactivity/impulsivity, and vice versa, if h_g^2 of hyperactivity/impulsivity varies as a function of the level of inattention. The etiology of extreme inattention was similar whether the proband exhibited low or high levels of hyperactivity/impulsivity. In contrast, the heritability of extreme hyperactivity/impulsivity was high in individuals who show high levels of inattention, while it was low and non-significant in individuals with low levels of inattention.

The Relation Between Questionnaire Data and Diagnostic Interviews

Derks et al. (2006) reviewed studies that investigated the relation between behavior checklist scores on attention problems and the clinical diagnosis for ADHD and reported on the positive and negative predictive power, sensitivity, and specificity. Many of these studies used the attention problem scale of the Child Behavior Checklist to predict ADHD. Despite its name, the scale also contains items related to hyperactivity–impulsivity. Positive predictive power (PPP) refers to the proportion of children with a high checklist score who obtain a positive DSM diagnosis (i.e., affected), and negative predictive power (NPP) refers to the proportion of children with a low checklist score who obtain a negative DSM diagnosis (i.e., unaffected). Sensitivity and specificity refer to the proportion of children with a positive DSM diagnosis, who score high on the checklist, and the proportion of children with a negative DSM diagnosis, who score low on the checklist, respectively. Table 25.6 summarizes the results of the studies that used these Diagnostic Efficiency Measures (DES). A negative feature of the DES is their dependence on the baseline prevalence of the disorder. Therefore, the baseline prevalence was also included in Table 25.6. On the basis of the results, we can conclude that the association between behavior checklist scores and clinical diagnoses for ADHD

Table 25.6 Diagnostic efficiency statistics of studies that examined the association between behavior checklist scores and ADHD

Study	Sample boys/girls	N	Cutpoint	Prevalence (%)	PPP	NPP	SE	SP
Gould, Bird, and Staghezza Jaramillo (1993)	NR	157	T > 65	23	0.36	0.96	0.46	0.95
Chen, Faraone, Biederman, and Tsuang (1994)	SR	111/108	T ≥ 65	16/8	1.00 (boys) 0.67 (girls)	0.86 (boys) 0.93 (girls)	0.17 (boys) 0.22 (girls)	1.00 (boys) 0.99 (girls)
Eiraldi, Power, Karustis, and Goldstein (2000)	R	192/50	T ≥ 65	83	0.93	0.37	0.78	0.69
Lengua, Sadowski, Friedrich, and Fisher (2001)	R	203	Based on regression	29	0.50	0.71	0.02	0.99
Sprafkin, Gadow, Salisbury, Schneider, and Loney (2002)	R	247/0	T ≥ 60	71	0.78	0.83	0.97	0.33
Hudziak, Copeland, Stanger, and Wadsworth (2004)	SR	101/82	T ≥ 65	36	0.97	0.76	0.47	0.99
Derks et al. (2006)	NR	192/216	Longitudinal	14/12	0.59/0.36	0.96/0.97	0.74/0.80	0.92/0.81

R=clinically referred sample, NR=non-referred sample, SR=siblings of referred children, PPP=Positive Predictive Power, NPP=Negative Predictive Power, SE=Sensitivity, SP=Specificity.

is strong. However, in population-based studies, a low score on the behavior checklist is highly predictive of the absence of ADHD, while a high score is less predictive of ADHD. Derks et al. (2006) further showed that a boy with a high CBCL score has a higher chance of obtaining a positive diagnosis for ADHD than a girl with a high CBCL score. In other words, questionnaire scores better predict clinical diagnosis in boys than girls.

In the field of behavioral genetics, the focus of interest is not only on the genetic and environmental influences on the variance of a trait but also on the genetic and environmental influences on the covariance of two traits. Future studies should investigate the aetiology of the covariance between behavior checklist scores and DSM-IV diagnoses of ADHD. An important issue that needs to be addressed is the overlap of the genetic factors that explain variation in different measures of ADHD.

Current Topics

In the previous sections we gave an overview of the results of epidemiological studies on ADHD. A few general findings emerged, among which a higher prevalence of ADHD in boys than girls, and a high heritability of ADHD in children irrespective of sex, age, or informant. In Section *Measurement Invariance with Respect to Sex*, *Genetic Dominance or Rater Bias/Sibling Interaction*, *Multiple Informants*, *Are the Subtypes of ADHD Genetically Heterogeneous?*, *Is Liability to ADHD Continuous or Categorical?*, and *Molecular Genetic Studies of ADHD*, we discuss current topics in the research field of ADHD. Section *Measurement Invariance with Respect to Sex* addresses the question if measurement instruments assess ADHD equally well in boys and girls. Section *Genetic Dominance or Rater Bias/Sibling Interaction* discusses the controversy between studies claiming the presence of contrast effects versus non-additive genetic effects on individual differences in ADHD. In Section *Multiple Informants* we report on the results of genetic analyses in which the ratings from multiple informants are analyzed simultaneously. Sections *Are the Subtypes of ADHD Genetically Heterogeneous?* and *Is Liability to ADHD Continuous or Categorical?* show two applications of latent class analyses: examination of genetic heterogeneity of the ADHD subtypes and investigation of the categorical versus continuous distribution of the liability for ADHD. Finally, in Section *Molecular Genetic Studies of ADHD*, we provide a brief overview of the results obtained in gene-finding studies on ADHD.

Measurement Invariance with Respect to Sex

The prevalence of ADHD is about 2.5 times higher in boys than girls, and there are sex differences in the association between checklist scores and clinical diagnoses. Heritability seems not to vary much as a function of the child's sex, and only one out of nine studies suggests that different genes are expressed in boys and girls.

Before any sex differences in ADHD can be interpreted, we should first establish if the measurement instrument is not biased with respect to sex. Stated differently, the instru-

ment should measure the same construct, i.e., latent variable of interest, in boys and girls (Mellenbergh, 1989; Meredith, 1993). If this is the case then we expect the observed score (i.e., the score obtained on the measurement instrument) of a person to depend on that person's score on the latent construct, but not on that person's sex. If this is not the case, a boy and a girl with identical levels of problem behavior may obtain systematically (i.e., regardless of measurement error) different scores on the instrument. This is undesirable because obviously we wish our measurements to reflect accurate and interpretable differences between cases in different groups. If the measurement instrument is not biased with respect to sex, we say that it is measurement invariant (MI) with respect to sex.

The criteria of MI are empirically testable in the common factor model (Meredith, 1993). Factor analysis may be viewed as a regression model in which observed variables (e.g., item scores) are regressed on a latent variable or common factor. In terms of this regression, the MI criteria are (1) equality of regression coefficients (i.e., factor loadings) over groups; (2) equality of item intercepts over groups (i.e., differences in item means can only be the result of differences in factor means), and (3) equality of residual variances (i.e., variance in the observed variables, not explained by the common factor) over groups. When satisfied, these restrictions ensure that any group differences in the mean and variance of the observed variables are due to group differences in the mean and variance of the latent factor.

In a sample of 800 boys and 851 girls rated by their teacher, Derks, Dolan, Hudziak, Neale, and Boomsma (2007) established measurement invariance with respect to sex for the Cognitive problems-inattention scale, the Hyperactive scale, and the ADHD-index of the Conners Teacher Rating Scale-Revised. This implies that teacher ratings on ADHD are not biased as a result of the child's sex. Although future studies should show if measurement invariance is also tenable for parental ratings on ADHD, the results in teacher ratings suggest that sex differences in the prevalence of ADHD, and on the predictive value of questionnaire scores are not the result of measurement bias.

Genetic Dominance or Rater Bias/Sibling Interaction

When reviewing the literature on ADHD, it is remarkable that many studies report very low DZ correlations for parental ratings but not for teacher ratings on ADHD. Low DZ correlations can be explained either by the presence of non-additive genetic effects (Lynch & Walsh, 1998) or by social interaction. The effects of social interaction among siblings were discussed by Eaves (1976) and others (Boomsma, 2005; Carey, 1986). Social interactions between siblings may create an additional source of variance and can either be cooperative (imitation) or competitive (contrast). Cooperation implies that behavior in one sibling leads to similar behavior in the other siblings. In the case of competition, the behavior in one child leads to the opposite behavior in the other child.

In the classical twin design, cooperation, or positive interaction, leads to increased twin correlations for both monozygotic (MZ) and dizygotic (DZ) twins. The relative increase is larger for DZ than for MZ correlations, and the pattern of correlations thus resembles the pattern which is seen if a trait is influenced by the shared environment. Negative sibling interaction, or competition, will result in MZ correlations which are more than twice as high as DZ correlations, a pattern also seen in the presence of non-additive genetic effects.

In data obtained from parental ratings on the behavior of their children, the effects of cooperation and competition may be mimicked (Simonoff et al., 1998). When parents are asked to evaluate and report upon their children's phenotype, they may compare the behavior of siblings. Parents may either stress similarities or differences between children, resulting in an apparent cooperation or competition effect.

The presence of a contrast effect, caused by either social interaction or rater bias, is indicated by differences in MZ and DZ variances. If there is a contrast effect the variances of MZ and DZ twins are both decreased, and this effect is greatest on the MZ variance. Contrast and non-additive genetic effects can theoretically be distinguished by making use of the fact that contrast effects lead to differences in variances in MZ and DZ twins, while non-additive genetic effects do not. However, Rietveld, Posthuma, Dolan, and Boomsma (2003) showed that the statistical power to separate these effects is low in the classical twin design.

In Tables 25.3, 25.4, and 25.5, we included information on the influence of non-additive genetic effects and contrast effects on individual differences in ADHD. In the 14 studies testing for the presence of these effects, a consistent finding was the absence of non-additive genetics and contrast effects in teacher ratings. In parental ratings, nine studies reported significant contrast effects. However, one of these studies did not report larger variances in DZ than MZ twins, and the presence of non-additive genetic effects was not considered (Vierikko et al., 2004). Another study reported significant contrast effects on the Rutter scale, but significant non-additive genetic effects on the DuPaul rating scale (Thapar, Harrington, Ross, & McGuffin, 2000). The authors argue that rater contrast effects may be more pronounced for some scales, as a result of differences in the number of items or in the format of the questionnaires. The influence of non-additive genetic effects was also reported in two other studies on hyperactivity. Furthermore, Rietveld, Hudziak, Bartels, Beijsterveldt van, and Boomsma (2003) reported

that a model with non-additive genetic effects and a model with contrast effects both provided a good fit to the data. Finally, two studies found no significant influences of either contrast or non-additive genetic effects. Teacher ratings do not indicate the presence of either one of these influences, suggesting that rater bias rather than genetic dominance plays a role in parental ratings. However, this is contradicted by the non-significant variance differences in MZ and DZ twins in some studies. So far, the results on the presence of non-additive genetic effects or contrast effects in parental ratings on ADHD are inconclusive. The issue may be resolved by including ratings from other family members which increases the statistical power to detect genetic dominance.

Multiple Informants

When investigating genetic and environmental influences on individual differences in problem behavior, we should acknowledge the fact that ratings of problem behavior may be influenced by the rater's personal values and by the unique settings in which the rater and child co-exist. Agreement between raters shows that some aspects of the behavior can be reliably assessed across settings and by different informants. Disagreement may reflect the fact that different raters assess unique aspects of the behavior, which are apparent in a particular set of circumstances, but not in others. For example, a child's inability to concentrate or sit still may be obvious in the classroom setting, but less evident in other settings, where sustained attention is less important (e.g., at play or at home with family members). For CBCL-AP scores, paternal and maternal ratings correlate 0.73, while parent and teacher correlations show a lower correlation of 0.44 (Achenbach & Rescorla, 2001).

Different models for twins rated by multiple informants have been developed. In this chapter, we will restrict the discussion to the psychometric model (Hewitt, Silberg, Neale, Eaves, & Erickson, 1992; Neale & Cardon, 1992).

In the psychometric model (see Fig. 25.1), the ratings of the child's behavior are allowed to be influenced by aspects of the child's behavior that are perceived both by raters (common factor) and uniquely by each rater (rater-specific factors). Unique perceptions could arise if the child behaves differentially toward his or her parents, or if the parents observe the child in different situations. The common and unique aspects are both allowed to be influenced by genetic and environmental factors.

Maternal and *paternal* ratings on overactive behavior in 3-year-olds correlate between 0.66 and 0.68 in boys, girls, and opposite-sex twins. Bivariate analyses showed that 68% of the variance is explained by a factor that is stable across informant (Derks et al., 2004). The remaining variance is explained by rater-specific factors. The heritability of the common factor is high (72%). In addition, genes explain more than half of the variation of the rater-specific factors (55% for fathers and 67% for mothers). The fact that variation in the rater-specific factors is not completely explained by environmental factors, implies that disagreement between parents is not only the result from rater-specific views (i.e., measurement error). In contrary, paternal and maternal ratings are influenced by aspects of the child's behavior that are uniquely perceived by each parent.

To determine how much of the variation in *parent* and *teacher* ratings is due to rating similar versus situation-specific components of behavior, some investigators employed bivariate model fitting analyses, which revealed that maternal and teacher ratings partly reflect a common latent phenotype (Derks et al., 2006; Martin et al., 2002; Simonoff et al., 1998). In Martin et al., 42% of the variation in the Strengths and Difficulties Questionnaire (SDQ) is explained by a factor that is common to parent and teacher ratings, the heritability of this factor is 90%. The heritability of the rater-specific factors is 22% in parent ratings and 65% in teacher ratings. The authors also obtained parental and teacher Conners Rating Scale (CRS) scores. Variation in parent and teacher's CRS scores was for 38% explained by a common factor. This factor showed a heritability of 82%. The rater-specific factors showed heritabilities of 65 and 79% for parent and teacher ratings, respectively. Simonoff et al. reported a heritability of 89% for the common factor. The genetic component of this common factor was greater than in the univariate models (52 and 69–75% in teacher and maternal ratings, respectively). Derks et al. (2006) also showed a higher heritability of the common factor (78%) than of the rater-specific factors (76 and 39% for maternal and teacher ratings, respectively). In summary, all three studies report a higher heritability of the common factor than of the rater-specific factors. This can be explained by the fact that when multiple indicators for a latent phenotype are used (e.g., over time or across raters), only a proportion of the measurement error of the individual ratings is passed on to the latent phenotype (Simonoff et al., 1998). Therefore, future gene finding studies could increase statistical power by focusing on the highly heritable common factor because it is less subject to measurement error.

Are the Subtypes of ADHD Genetically Heterogeneous?

ADHD is a disorder that may include symptoms of inattention, hyperactivity/impulsivity, or both. Because of this heterogeneity in symptom profiles, concerns have been raised over the validity of the DSM-IV subtypes (Todd, 2000). In

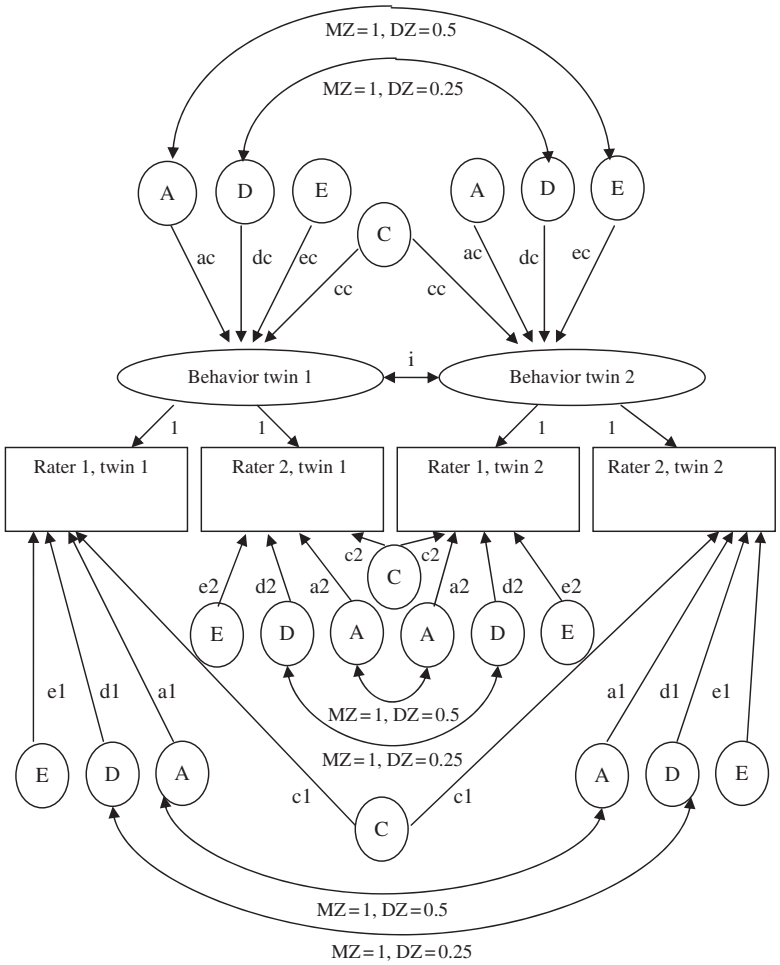

Fig. 25.1 Rater model

Note: The illustrated model is a psychometric model. Both twins are rated by two informants (rater 1 and rater 2). Variation in behavior is explained by common A, C or D, and E (shown in the upper part of the figure), and rater-specific A, C or D, and E (shown in the lower part of the figure). A=additive genetic factor; D=dominant genetic factor; C=shared environmental factor; E=non-shared environmental factor; ac=additive genetic common; dc=dominant genetic common; ec=non-shared environment common; cc=shared environment common; a1=additive genetic rater 1; d1=dominant genetic rater 1; e1=non-shared environment rater 1; c1=shared environment rater 1; a2=additive genetic rater 2; d2=dominant genetic rater 2; e2=non-shared environment rater 2; c2=shared environment rater 2, i=social interaction path

this section, we address the question if the different subtypes of ADHD are genetically heterogeneous. In other words, is the variability in symptoms profiles explained by different genetic influences on the inattentive type, the hyperactive/impulsive type, and the combined type? A number of papers have looked at the familiality and heritability of the DSM-IV subtypes of ADHD. These studies failed to identify significant familial (i.e., genetic or shared environmental) clustering of the subtypes and concluded that symptom variability is largely a function of non-familial causes (Faraone, Biederman, & Friedman, 2000; Faraone, Biederman, Mick, et al., 2000; Smalley, McCracken, & McGough, 2001).

Todd et al. (2001) used latent class analysis (LCA; McCutcheon, 1987) to examine if the clustering of symptoms can be described with more meaningful subtypes. LCA assumes the presence of a number of latent classes with a categorical rather than a continuous distribution. Estimates are provided for (i) the number of latent classes; (ii) the prevalence of each class; and (iii) the item endorsement probabilities conditional on latent class membership. Todd et al. (2001) applied LCA to parent reports on 2018 female adolescent twin pairs from the state of Missouri and investigated if the original DSM-IV subtypes and the derived latent classes represent independent genetic entities. The DSM-IV combined type and inattentive type showed a lack of familial specificity (e.g., a proband with the inattentive type has a higher chance of having a cotwin with either the inattentive or the combined type, but does not have a higher chance of having a cotwin with the hyperactive/impulsive type). The hyperactive/impulsive type did show familial speci-

ficity (e.g., a proband with the hyperactive/impulsive type has a higher chance of having a cotwin with the hyperactive/impulsive type, but does not have a higher chance of having a cotwin with the inattentive or combined type). This suggests that the hyperactive/impulsive type is independent of the other two subtypes. The LCA resulted in an eight-class solution. This eight-class solution was replicated in a sample of Australian twins (Rasmussen et al., 2002) and a similar (7-class) solution was found in an independent sample from Missouri (Volk, Neuman, Joyner, & Todd, 2005). In contrast to the DSM-IV subtypes, the eight latent classes appeared to represent pure genetic categories. The authors conclude that "these results are most compatible with the presence of independent, familial forms of ADHD that are approximated by latent-class analysis and are imperfectly operationalized by DSM-IV criteria".

Is Liability to ADHD Continuous or Categorical?

Another interesting feature of LCA is that it can help clarify whether ADHD shows a categorical or a continuous distribution. If the underlying nature of the phenotype is a continuum of problems with inattention, hyperactivity/impulsivity, or both, then symptoms endorsement profiles of the observed classes will reflect differences in severity or frequency of the reporting of symptoms only (Hudziak et al., 1998). Analyzing data on 1549 female twin-pairs, Hudziak et al. (1998) showed symptom profiles that indicated the presence of three separate continua of severity of problems: inattention, hyperactivity/impulsivity, and combined type. Thus, within the domains, the symptoms are better described as existing on a continuum rather than as discrete disease entities. Future studies should reveal if there are indeed significant cross-class heritabilities among the mild and severe latent classes, as would be expected if the distribution of ADHD is continuous.

Molecular Genetic Studies of ADHD

Molecular genetic studies address the question which genes explain the high heritability of AHDH. It is beyond the scope of this paper to provide an extensive overview of the results of molecular genetic studies. Recently, a number of review studies on the molecular genetics of ADHD have been published (Asherson, 2004; Bobb, Castellanos, Addington, & Rapoport, 2005; Faraone et al., 2005; Thapar, O'Donovan, & Owen, 2005).

Faraone et al. (2005) reviewed candidate gene studies of ADHD and computed pooled odds ratio's (ORs) across studies for gene variants examined in three or more case–control or family-based studies. Seven gene variants showed a pooled OR that is significantly larger than 1: dopamine receptor D4 (DRD4), dopamine receptor D5 (DRD5), dopamine rransporter (DAT), dopamine β-hydroxylase (DBH), synaptosomal-associated protein 25 (SNAP-25), serotonin transporter (5-HTT), and serotonin receptor (HTR1B). These small ORs are consistent with the idea that the genetic vulnerability to ADHD is mediated by many genes of small effect.

Five groups have conducted genome-wide linkage scans in an attempt to find regions of chromosomes that are involved with ADHD. We will discuss the regions for which LOD scores higher than 2 ($p<\sim0.002$) were found. The first genome-wide scan on ADHD was published in 2002 by Fisher et al. (2002) who analyzed data from 126 affected sibling pairs in 104 families. In 2003, the sample was extended and contained 204 families with 207 affected sibling pairs (Ogdie et al., 2003). In the extended sample, LOD $>$ 2 was found at chromosome 16p13 and 17p11. Bakker et al. (2003) performed a genome scan on 238 children from 164 Dutch affected sib pairs with ADHD. They report a LOD score of 3.04 at chromosome 7p and of 3.54 at chromosome 15q. Arcos-Burgos et al. (2004) analyzed data from 16 genetically isolated families in Columbia. They reported linkage peaks (LOD score $>$ 2) at chromosomes 4q, 8q, and 11q in specific families. The fourth genome-wide scan was performed in a sample of 102 families encompassing a total of 229 affected children (Hebebrand et al., 2006). For clinical diagnosis of ADHD, the highest LOD score of 2.74 was reported on chromosome 5p. A LOD score $>$ 2 was also found at chromosome 12q. For quantitative DSM-IV measures, the highest LOD scores were observed on chromosome 5p (total an inattentive scores) and chromosome 12q (inattentive scores). For hyperactivity, no LOD scores $>$ 2 were reported. Finally, Gayan et al. (2005) reported linkage for ADHD at chromosomes 14q32 and 20q11.

The linkage peaks of these four studies do not show much overlap. An interesting resemblance between the studies is that four genome-wide scans report modest evidence (LOD $>$ 1) for linkage at chromosome 5p. An obvious candidate gene at chromosome 5p, is the DAT gene, but in the study of Hebebrand et al., allelic variation at the DAT1 was not responsible for the linkage signal. Furthermore, the gene with the largest pooled OR as reported by Faraone et al., DRD4, is located at chromosome 11p. None of the genome-wide scans reported a linkage peak at this location.

The results of these four studies are inconsistent. This may be due to the different sampling procedures which are applied to select subjects or to differences in the definition of the phenotype. Furthermore, because each gene is expected to show a small effect and because a correction to the type-I error

(α) has to be made because of multiple testing, the statistical power in each study is low.

Some Directions for Future Research

Phenotype Definitions: Application of Item Response Theory (IRT)

In many instances, heritability of a trait is estimated for sum scores (e.g., of items or symptoms) and the distribution of sum scores often displays a large degree of skewness and kurtosis. Especially when analyzing symptom data on psychopathology, the distribution of sum scores is usually L-shaped, due to the fact that the vast majority of subjects displays a few or no symptoms (Oord van den et al., 2003). Derks et al. (2004) showed in simulated data with such an L-shaped distribution that if the true model is an ADE model, and parameters are estimated with normal theory maximum likelihood, the additive genetic component is underestimated, and the non-additive genetic component and the non-shared environmental component are overestimated. They recommend the use of a liability threshold model when analyzing sum scores with an L-shaped distribution (Lynch & Walsh, 1998).

Another concern when analyzing sum scores, that is not resolved by using a threshold model for the sum scores, is that some of the information that is contained in the original item scores is ignored when analyzing sum scores. The fact that the relationship between the latent trait and the observed item score may well be probabilistic (i.e., a person who is below the threshold on the latent trait, has a relatively low probability to score positive on the item), instead of deterministic (i.e., a person who is below the threshold, has a zero probability to score positive on the item) may also cause bias in the heritability estimate. Within the item response theory (IRT) framework, item scores are modeled as a function of one or more latent factors. Two recent papers show the advantages of IRT in the behavior genetic research field (Eaves et al., 2005; Berg van den, Glas, & Boomsma, 2007). According to Berg van den et al., advantages of using an IRT framework include (i) IRT provides a model for the relation between item scores and the latent phenotype; (ii) it supports the use of incomplete item administration and handling of missing data; (iii) it accounts for measurement error both in dependent and in independent variables, and (iv) it handles the problem of L-shaped distributed data. The application of this approach in future studies on ADHD is particularly interesting for gene finding studies while it may increase statistical power to detect the influence of genes with small effects.

Heritability of ADHD in Adults

The heritability of ADHD has been studied extensively in children. In contrast, not much is known on the magnitude of the genetic and environmental influences on individual differences in ADHD in adults. This may partly be explained by the fact that some of the earlier work suggested that ADHD is rare in adulthood. However, Faraone et al. (2005) performed a meta-analysis of follow-up studies on ADHD. They show that syndromatic persistence (i.e., the maintenance of full diagnostic status) is low (∼15%), but that symptomatic persistence (i.e., the maintenance of partial diagnostic status with impairment) is much higher with a persistence rate of 40–60% (the higher estimate excludes two outlying observations). Therefore, future research should focus on the identification of the genetic and environmental influences on individual differences in ADHD in adults.

The only study that investigates the etiological influences on attention problems in adults estimates genetic and environmental influences based on self-report data from The Netherlands Twin Register at three different time waves (Berg van den, Willemsen, Geus de, & Boomsma, 2006). The mean age of the young adults is 19.6, 21.3, and 22.8 years at wave 1, 2, and 3, respectively. Irrespective of measurement wave, the heritability of attention problems is about 40%. The authors further showed that the stability in attention problems is largely explained by genetic factors. In addition, variation in ADHD at different ages in young adulthood is mainly explained by the same genes. It is unclear if the lower heritabilities in adults compared to children can be explained by age effects or by the fact that ratings of ADHD are usually based on parental or teacher reports in children and on self-reports in adults. Future studies of The Netherlands Twin Register will look into genetic and environmental influences on stability of the attention problems from early childhood (parent and teacher reports), through adolescence (parent, teacher, and self-reports) into adulthood (self-reports).

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References

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA preschool forms & profiles*. Burlington, VT: University of Vermont, Department of Psychiatry.

American Psychiatric Association. (1994). *Task force on DSM-IV. Diagnostic and statistical manual of mental disorder: DSM-IV* (4th ed.). Washington, DC: American Psychiatric Association.

Arcos-Burgos, M., Castellanos, F. X., Pineda, D., Lopera, F., Palacio, J. D., Palacio, L. G., et al. (2004). Attention-deficit/hyperactivity disorder in a population isolate: Linkage to loci at 4q13.2, 5q33.3, 11q22, and 17p11. *American Journal of Human Genetics, 75*, 998–1014.

Asherson, P. (2004). Attention-deficit hyperactivity disorder in the post-genomic era. *European Child and Adolescent Psychiatry, 13 Suppl 1*, I50–I70.

Bakker, S. C., Meulen van der, E. M., Buitelaar, J. K., Sandkuijl, L. A., Pauls, D. L., Monsuur, A. J., et al. (2003). A whole-genome scan in 164 Dutch sib-pairs with attention-deficit hyperactivity disorder: Suggestive evidence for linkage on chromosomes 7p and 15q. *American Journal of Human Genetics, 72*, 1251–1260.

Barkley, R. A. (2002). Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry, 63*, 10–15.

Baumgaertel, A., Wolraich, M. L., & Dietrich, M. (1995). Comparison of diagnostic-criteria for attention-deficit disorders in a German elementary-school sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*, 629–638.

Beijsterveldt van, C. E. M., Verhulst, F. C., Molenaar, P. C. M., & Boomsma, D. I. (2004). The genetic basis of problem behavior in 5-year-old Dutch twin pairs. *Behavior Genetics, 34*, 229–242.

Berg van den, S. M., Glas, C. A., & Boomsma, D. I. (2007). Variance decomposition using an IRT measurement model. *Behavior Genetics, 37*, 604–616.

Berg van den, S. M., Willemsen, G., Geus de, E. J., & Boomsma, D. I. (2006) Genetic etiology of stability of attention problems in young adulthood. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 141*, 55–60.

Bobb, A. J., Castellanos, F. X., Addington, A. M., & Rapoport, J. L. (2005). Molecular genetic studies of ADHD: 1991 to 2004. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 132*, 109–125.

Boomsma, D. I. (2005). Sibling interaction effects. In B. Everitt & D. Howell (Eds.), *Encyclopedia of statistics in behavioral science* (pp. 1831–1832). Chisester: John Wiley & Sons.

Breton, J. J., Bergeron, L., Valla, J. P., Berthiaume, C., Gaudet, N., Lambert, J., et al. (1999). Quebec child mental health survey: Prevalence of DSM-III-R mental health disorders. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 40*, 375–384.

Brookes, K. J., Mill, J., Guindalini, C., Curran, S., Xu, X., & Knight, J., et al. (2006). A common haplotype of the dopamine transporter gene associated with attention-deficit/hyperactivity disorder and interacting with maternal use of alcohol during pregnancy. *Archives of General Psychiatry 2006; 63*, 74–81.

Burt, S. A., Krueger, R. F., McGue, M., & Iacono, W. G. (2001). Sources of covariation among attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder: The importance of shared environment. *Journal of Abnormal Psychology, 110*, 516–525.

Carey, G. (1986). Sibling imitation and contrast effects. *Behavior Genetics, 16*, 319–340.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: The search for endophenotypes. *Nature Reviews Neuroscience, 3*, 617–628.

Chen, W. J., Faraone, S. V., Biederman, J., & Tsuang, M. T. (1994). Diagnostic accuracy of the child behavior checklist scales for attention-deficit hyperactivity disorder: A receiver-operating characteristic analysis. *Journal of Consulting and Clinical Psychology, 62*, 1017–1025.

Coolidge, F. L., Thede, L. L., & Young, S. E. (2000). Heritability and the comorbidity of attention deficit hyperactivity disorder with behavioral disorders and executive function deficits: A preliminary investigation. *Developmental Neuropsychology, 17*, 273–287.

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry, 60*, 837–844.

Cuffe, S. P., McKeown, R. E., Jackson, K. L., Addy, C. L., Abramson, R., & Garrison, C. Z. (2001). Prevalence of attention-deficit/hyperactivity disorder in a community sample of older adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*, 1037–1044.

Cuffe, S. P., Moore, C. G., & McKeown, R. E. (2005). Prevalence and correlates of ADHD symptoms in the National Health Interview Survey. *Journal of Attention Disorders, 9*, 392–401.

DeFries, J. C., & Fulker, D. W. (1985). Multiple regression analysis of twin data. *Behavior Genetics, 15*, 467–473.

Derks E. M., Dolan C. V., Hudziak J. J., Neale M. C., and Boomsma D. I. (2007). Teacher reports and the role of sex and genetics in attention deficit hyperactivity disorder (ADHD) and oppositional defiant disorder (ODD). *Behavior Genetics, 37*, 559–566.

Derks, E. M., Hudziak, J. J., Beijsterveldt van, C. E. M., Dolan, C. V., & Boomsma, D. I. (2004). A study of genetic and environmental influences on maternal and paternal CBCL syndrome scores in a large sample of 3-year-old Dutch twins. *Behavior Genetics, 34*, 571–583.

Derks, E. M., Hudziak, J. J., Beijsterveldt van, C. E. M., Dolan, C. V., & Boomsma, D. I. (2006). Genetic Analyses of Maternal and Teacher Ratings on Attention Problems in 7-year-old Dutch Twins. *Behavior Genetics, 36*, 833–844.

Derks, E. M., Hudziak, J. J., Dolan, C. V., Ferdinand, R. F., & Boomsma, D. I. (2006). The relations between DISC-IV DSM diagnoses of ADHD and multi-informant CBCL-AP syndrome scores. *Comprehensive Psychiatry, 47*, 116–122.

Dick, D. M., Viken, R. J., Kaprio, J., Pulkkinen, L., & Rose, R. J. (2005). Understanding the covariation among childhood externalizing symptoms: Genetic and environmental influences on conduct disorder, attention deficit hyperactivity disorder, and oppositional defiant disorder symptoms. *Journal of Abnormal Child Psychology, 33*, 219–229.

Eaves, L. J. (1976). A model for sibling effects in man. *Heredity, 36*, 205–214.

Eaves, L. J., Silberg, J. L., Meyer, J. M., Maes, H. H., Simonoff, E., Pickles, A., et al. (1997). Genetics and developmental psychopathology .2. The main effects of genes and environment on behavioral problems in the Virginia twin study of adolescent behavioral development. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 38*, 965–980.

Eaves, L., Erkanli, A., Silberg, J., Angold, A., Maes, H. H., & Foley, D. (2005). Application of Bayesian inference using Gibbs sampling to item-response theory modeling of multi-symptom genetic data. *Behavior Genetics 35,* 765–780.

Edelbrock, C., Rende, R., Plomin, R., & Thompson, L. A. (1995). A twin study of competence and problem behavior in childhood and early adolescence. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 36*, 775–785.

Eiraldi, R. B., Power, T. J., Karustis, J. L., & Goldstein, S. G. (2000). Assessing ADHD and comorbid disorders in children: The Child Behavior Checklist and the Devereux scales of mental disorders. *Journal of Clinical Child Psychology, 29*, 3–16.

Faraone, S. V., & Biederman, J. (2005). What is the prevalence of adult ADHD? Results of a population screen of 966 adults. *Journal of Attention Disorders, 9*, 384–391.

Faraone, S. V., Biederman, J., & Friedman, D. (2000). Validity of DSM-IV subtypes of attention-deficit/hyperactivity disorder: A family study perspective. *Journal of the American Acadamy of Child and Adolescent Psychiatry, 39*, 300–307.

Faraone, S. V., Biederman, J., Mick, E., Williamson, S., Wilens, T., Spencer, T., et al. (2000). Family study of girls with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 157*, 1077–1083.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., et al. (2005). Molecular genetics of

attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 1313–1323.

Fisher, S. E., Francks, C., McCracken, J., McGough, J. J., Marlow, A. J., MacPhie I. L., et al. (2002). A genomewide scan for loci involved in attenion-deficit/hyperactivity disorder. *American Journal of Human Genetics, 70*, 1183–1196.

Ford, T., Goodman, R., & Meltzer, H. (2003). The British child and adolescent mental health survey 1999: The prevalence of DSM-IV disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*, 1203–1211.

Gaub, M., & Carlson, C. L. (1997). Gender differences in ADHD: A meta-analysis and critical review. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 1036–1045.

Gayan, J., Willcutt, E. G., Fisher, S. E., Francks, C., Cardon, L. R., Olson, R. K., et al. (2005). Bivariate linkage scan for reading disability and attention-deficit/hyperactivity disorder localizes pleiotropic loci. *Journal of Child Psychology and Psychiatry and Allied Discipline, 46*, 1045–1056.

Gillis, J. J., Gilger, J. W., Pennington, B. F., & DeFries, J. C. (1992). Attention deficit disorder in reading-disabled twins: Evidence for a genetic etiology. *Journal of Abnormal Child Psychology, 20*, 303–315.

Gjone, H., Stevenson, J., & Sundet, J. M. (1996). Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 588–596.

Gjone, H., Stevenson, J., Sundet, J. M., & Eilertsen, D. E. (1996). Changes in heritability across increasing levels of behavior problems in young twins. *Behavior Genetics, 26*, 419–426.

Goodman, R., & Stevenson, J. (1989). A twin study of hyperactivity .2. The etiological role of genes, family relationships and perinatal adversity. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 30*, 691–709.

Gould, M. S., Bird, H., & Staghezza Jaramillo, B. (1993). Correspondence between statistically derived behavior problem syndromes and child psychiatric diagnoses in a community sample. *Journal of Abnormal Child Psychology, 21*, 287–313.

Graetz, B. W., Sawyer, M. G., & Baghurst, P. (2005). Gender differences among children with DSM-IV ADHD in Australia. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*, 159–168.

Graetz, B. W., Sawyer, M. G., Hazell, P. L., Arney, F., & Baghurst, P. (2001). Validity of DSM-IV ADHD subtypes in a nationally representative sample of Australian children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*, 1410–1417.

Hebebrand, J., Dempfle, A., Saar, K., Thiele, H., Herpertz-Dahlmann, B., Linder, M., et al. (2006). A genome-wide scan for attention-deficit/hyperactivity disorder in 155 german sib-pairs. *Molecular Psychiatry, 11*, 196–205.

Hewitt, J. K., Silberg, J. L., Neale, M. C., Eaves L. J., & Erickson, M. (1992). The analysis of parental ratings of children's behavior using LISREL. *Behavior Genetics, 22*, 293–317.

Hudziak, J. J. (2001). The role of phenotypes (diagnoses) in genetic studies of attention-deficit/hyperactivity disorder and related child psychopathology. *Child and Adolescent Psychiatric Clinics of North America, 10*, 279–97, viii.

Hudziak, J. J., Copeland, W., Stanger, C., & Wadsworth, M. (2004). Screening for DSM-IV externalizing disorders with the Child Behavior Checklist: A receiver-operating characteristic analysis. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45*, 1299–1307.

Hudziak, J. J., Derks, E. M., Althoff, R. R., Rettew, D. C., & Boomsma, D. I. (2005). The genetic and environmental contributions to attention deficit hyperactivity disorder as measured by the Conners' Rating Scales – Revised. *American Journal of Psychiatry, 162*, 1614–1620.

Hudziak, J. J., Heath, A. C., Madden, P. F., Reich, W., Bucholz, K. K., Slutske, W., et al. (1998). Latent class and factor analysis of DSM-IV ADHD: A twin study of female adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*, 848–857.

Hudziak, J. J., Rudiger, L. P., Neale, M. C., Heath, A. C., & Todd, R. D. (2000). A twin study of inattentive, aggressive and anxious/depressed behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry, 39*, 469–476.

Kahn, R. S., Khoury, J., Nichols, W. C., & Lanphear, B. P. (2003). Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. *Journal of Pediatrics, 143*, 104–110.

Kuntsi, J., Rijsdijk, F., Ronald, A., Asherson, P., & Plomin, R. (2005). Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. *Biological Psychiatry, 57*, 647–654.

Kuntsi, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: II. The role of genetic factors. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 42*, 211–219.

Larsson, J., Larsson, H., & Lichtenstein, P. (2004). Genetic and environmental contributions to stability and change of ADHD symptoms between 8 and 13 years of age: A longitudinal twin study. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*, 1267–1275.

Lavigne, J. V., Gibbons, R. D., Kaufer Christoffel, K., Arend, R., Rosenbaum, D., Binns, H., et al. (1996). Prevalence rates and correlates of psychiatric disorders among preschool children. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 204–214.

Lengua, L. J., Sadowski, C. A., Friedrich, W. N., & Fisher, J. (2001). Rationally and empirically derived dimensions of children's symptomatology: Expert ratings and confirmatory factor analyses of the CBCL. *Journal of Consulting and Clinical Psychology, 69*, 683–698.

Levy, F., Hay, D. A., Bennett, K. S., & McStephen, M. (2005). Gender differences in ADHD subtype comorbidity. *Journal of the American Academy of Child and Adolescent Psychiatry, 44*, 368–376.

Levy, F., Hay, D. A., McStephen, M., Wood, C., & Waldman, I. (1997). Attention-deficit hyperactivity disorder: A category or a continuum? Genetic analysis of a large-scale twin study. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 737–744.

Lynch, M., & Walsh, B. (1998). *Genetics and analysis of quantitative traits*. Sunderland, MA: Sinauer Associates.

Martin, N., Scourfield, J., & McGuffin, P. (2002). Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. *British Journal of Psychiatry, 180*, 260–265.

McCutcheon, A. L. (1987). *Latent class analysis*. Newbury Park: Sage Publications.

Mellenbergh, G. J. (1989). Item bias and item response theory. *International Journal of Educational Research, 13*, 127–143.

Meredith, W. (1993). Measurement invariance, factor-analysis and factorial invariance. *Psychometrika, 58*, 525–543.

Muthén, L. K., & Muthén, B. O. (2000). *Mplus. Statistical analyses with latent variables. User's guide (Version 2)*. Los Angeles: Muthén & Muthén.

Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2003). *Mx: Statistical modeling* (6th ed.). Richmond, VA: Department of Psychiatry.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publisher.

Neuman, R. J., Sitdhiraksa, N., Reich, W., Ji, T. H. C., Joyner, C. A., Sun, L. W., et al. (2005). Estimation of prevalence of DSM-IV and latent class-defined ADHD subtypes in a population-based sample of child and adolescent twins. *Twin Research and Human Genetics, 8*, 392–401.

Nolan, E. E., Gadow, K. D., & Sprafkin, J. (2001). Teacher reports of DSM-IV ADHD, ODD, and CD symptoms in schoolchildren.

Journal of the American Academy of Child and Adolescent Psychiatry, 40, 241–249.

Ogdie, M. N., MacPhie, I. L., Minassian, S. L., Yang, M., Fisher, S. E., Francks, C., et al. (2003). A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: Suggestive linkage on 17p11. *American Journal of Human Genetics, 72*, 1268–1279.

Oord van den, E. J., Pickles, A., & Waldman, I. D. (2003). Normal variation and abnormality: an empirical study of the liability distributions underlying depression and delinquency. *Journal of Child Psychology & Psychiatry, 44,* 180–192.

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2001). *Behavioral genetics*. New York: Worths Publishers.

Price, T. S., Simonoff, E., & Waldman, I. (2001). Hyperactivity in preschool children is highly heritable. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*, 1362–1364.

Rasmussen, E. R., Neuman, R. J., Heath, A. C., Levy, F., Hay, D. A., & Todd, R. D. (2002). Replication of the latent class structure of attention-deficit hyperactivity disorder (ADHD) subtypes in a sample of Australian twins. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 43*, 1018–1028.

Rhee, S. H., Waldman, I. D., Hay, D. A., & Levy, F. (1999). Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. *Journal of Abnormal Psychology, 108*, 24–41.

Rietveld, M. J. H., Hudziak, J. J., Bartels, M., Beijsterveldt van, C. E. M., & Boomsma, D. I. (2003). Heritability of attention problems in children: I. Cross-sectional results from a study of twins, age 3–12 years. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 117B*, 102–113.

Rietveld, M. J. H., Hudziak, J. J., Bartels, M., Beijsterveldt van, C. E. M., & Boomsma, D. I. (2004). Heritability of attention problems in children: Longitudinal results from a study of twins, age 3 to 12. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 45*, 577–588.

Rietveld, M. J., Posthuma, D., Dolan, C. V., & Boomsma, D. L. (2003). ADHD: Sibling interaction or dominance: An evaluation of statistical power. *Behavior Genetics, 33*, 247–255.

Rohde, L. A., Biederman, J., Busnello, E. A., Zimmermann, H., Schmitz, M., Martins, S., et al. (1999). ADHD in a school sample of Brazilian adolescents: A study of prevalence, comorbid conditions, and impairments. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*, 716–722.

Saudino, K. J., Ronald, A., & Plomin, R. (2005). The etiology of Behavior problems in 7-year-old twins: Substantial genetic influence and negligible shared environmental influence for parent ratings and ratings by same and different teachers. *Journal of Abnormal Child Psychology, 33*, 113–130.

Seeger, G., Schloss, P., Schmidt, M. H., Ruter-Jungfleisch, A., & Henn, F. A. (2004). Gene-environment interaction in hyperkinetic conduct disorder (HD + CD) as indicated by season of birth variations in dopamine receptor (DRD4) gene polymorphism. *Neuroscience Letters, 366,* 282–286.

Schmitz, S., & Mrazek, D. A. (2001). Genetic and environmental influences on the associations between attention problems and other problem behaviors. *Twin Research, 4*, 453–458.

Sherman, D. K., Iacono, W. G., & McGue, M. K. (1997). Attention-deficit hyperactivity disorder dimensions: A twin study of inattention and impulsivity-hyperactivity. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 745–753.

Sherman, D. K., McGue, M. K., & Iacono, W. G. (1997). Twin concordance for attention deficit hyperactivity disorder: A comparison of teachers' and mothers' reports. *American Journal of Psychiatry, 154*, 532–535.

Simonoff, E., Pickles, A., Hervas, A., Silberg, J. L., Rutter, M., & Eaves, L. (1998). Genetic influences on childhood hyperactivity: Contrast effects imply parental rating bias, not sibling interaction. *Psychological Medicine, 28*, 825–837.

Smalley, S. L., McCracken, J., & McGough, J. (2001). Refining the ADHD phenotype using affected sibling pair families. *American Journal of Medical Genetics, 105*, 31–33.

Sprafkin, J., Gadow, K. D., Salisbury, H., Schneider, J., & Loney, J. (2002). Further evidence of reliability and validity of the Child Symptom Inventory-4: Parent checklist in clinically referred boys. *Journal of Clinical Child and Adolescent Psychology, 31*, 513–524.

Stevenson, J. (1992). Evidence for a genetic etiology in hyperactivity in children. *Behavior Genetics, 22*, 337–344.

Szatmari, P., Offord, D. R., & Boyle, M. H. (1989). Ontario child health study – Prevalence of attention deficit disorder with hyperactivity. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 30*, 219–230.

Thapar, A., Harrington, R., Ross, K., & McGuffin, P. (2000). Does the definition of ADHD affect heritability? *Journal of the American Academy of Child and Adolescent Psychiatry, 39*, 1528–1536.

Thapar, A., Hervas, A., & McGuffin, P. (1995). Childhood hyperactivity scores are highly heritable and show sibling competition effects – Twin study evidence. *Behavior Genetics, 25*, 537–544.

Thapar, A., O'Donovan, M., & Owen, M. J. (2005). The genetics of attention deficit hyperactivity disorder. *Human Molecular Genetics, 14 Spec No. 2*, R275–R282.

Todd, R. D. (2000). Genetics of attention deficit/hyperactivity disorder: Are we ready for molecular genetic studies? *American Journal of Medical Genetics, 96*, 241–243.

Todd, R. D., Constantino, J. N., & Neuman, R. J. (2005). Redefining early-onset disorders for genetic studies: Attention-deficit/hyperactiviy disorder and autism. In C. F. Zorumski & E. H. Rubin (Eds.), *Psychopathology in the genome and neuroscience era* (1st ed., pp. 33–49). Arlington, VA: American Psychiatric Publishing, Inc.

Todd, R. D., Rasmussen, E. R., Neuman, R. J., Reich, W., Hudziak, J. J., Bucholz, K. K., et al. (2001). Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. *American Journal of Psychiatry, 158*, 1891–1898.

Towers, H., Spotts, E., Neiderhiser, J. M., Hetherington, E. M., Plomin, R., & Reiss, D. (2000). Genetic and environmental influences on teacher ratings of the Child Behavior Checklist. *International Journal of Behavioral Development, 24*, 373–381.

Vierikko, E., Pulkkinen, L., Kaprio, J., & Rose, R. J. (2004). Genetic and environmental influences on the relationship between aggression and hyperactivity-impulsivity as reated by teachers and parents. *Twin Research, 7*, 261–274.

Volk, H. E., Neuman, R. J., Joyner, C., & Todd, R. D. (2005). Replication and validation of population derived ADHD phenotypes. *American Journal of Medical Genetics Part B-Neuropsychiatric Genetics, 138B*, 62–63.

Willcutt, E. G., Pennington, B. F., & DeFries, J. C. (2000). Etiology of inattention and hyperactivity/impulsivity in a community sample of twins with learning difficulties. *Journal of Abnormal Child Psychology, 28*, 149–159.

Wolraich, M. L., Hannah, J. N., Baumgaertel, A., & Feurer, I. D. (1998). Examination of DSM-IV criteria for attention deficit/hyperactivity disorder in a county-wide sample. *Journal of Developmental and Behavioral Pediatrics, 19*, 162–168.

Wolraich, M. L., Hannah, J. N., Pinnock, T. Y., Baumgaertel, A., & Brown, J. (1996). Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*, 319–324.

Young, S. E., Stallings, M. C., Corley, R. P., Krauter, K. S., & Hewitt, J. K. (2000). Genetic and environmental influences on behavioral disinhibition. *American Journal of Medical Genetics, 96*, 684–695.