



Phenotypic and measurement influences on heritability estimates in childhood ADHD

Christine M. Freitag, Luis A. Rohde, Thomas Lempp, Marcel Romanos

► To cite this version:

Christine M. Freitag, Luis A. Rohde, Thomas Lempp, Marcel Romanos. Phenotypic and measurement influences on heritability estimates in childhood ADHD. *European Child and Adolescent Psychiatry*, 2010, 19 (3), pp.311-323. 10.1007/s00787-010-0097-5 . hal-00574013

HAL Id: hal-00574013

<https://hal.science/hal-00574013>

Submitted on 7 Mar 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Phenotypic and measurement influences on heritability estimates in childhood ADHD

Christine M. Freitag · Luis A. Rohde ·
Thomas Lempp · Marcel Romanos

Received: 29 June 2009 / Accepted: 20 January 2010 / Published online: 7 March 2010
© Springer-Verlag 2010

Abstract Twin studies described a strongly heritable component of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents. However, findings varied considerably between studies. In addition, ADHD presents with a high rate of comorbid disorders and associated psychopathology. Therefore, this literature review reports findings from population-based twin studies regarding the influence of subtypes, assessment instruments, rater effects, sex differences, and comorbidity rates on ADHD heritability estimates. In addition, genetic effects on the persistence of ADHD are discussed. By reviewing relevant factors influencing heritability estimates more homogeneous subtypes relevant for molecular genetic studies can be elicited. A systematic search of population-based twin studies in ADHD was performed, using the databases PubMed and PsycInfo. Results of family studies were added in case insufficient or contradictory findings were obtained in twin studies. Heritability estimates were strongly influenced by rater effects and assessment instruments. Inattentive and hyperactive-impulsive symptoms were likely influenced by common as

well as specific genetic risk factors. Besides persistent ADHD, ADHD accompanied by symptoms of conduct or antisocial personality disorder might be another strongly genetically determined subtype, however, family environmental risk factors have also been established for this pattern of comorbidity.

Keywords ADHD · Heritability · Phenotype · Comorbidity · Rater effects

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by age-inappropriate hyperactivity, impulsivity, and attention problems [2] and is caused by the interplay of genetic and environmental risk factors. In this literature review, we aim to give a thorough overview on factors differentially influencing heritability estimates in children and adolescents with ADHD. As ADHD is a phenotypically heterogeneous disorder showing a high rate of comorbid symptoms and disorders, it is of crucial relevance for molecular genetic studies to assess the most strongly genetically determined subtypes and to adjust for possible factors influencing or mediating genetic effects. In this review, we focussed on twin studies and only added information from family studies, when they contradicted or completed findings from twin studies. For an overview on the population-based twin studies included in this review, see Table 1.

In general, family, adoption, and twin studies are study designs by which the impact of genetic and environmental risk factors on disease status or a quantitative trait can be estimated. For categorical data as disease status, concordance rates or specific correlation measures are compared;

C. M. Freitag (✉) · T. Lempp
Department of Child and Adolescent Psychiatry,
Psychosomatics and Psychotherapy, JW Goethe University,
Deuschordenstraße 50, 60528 Frankfurt am Main, Germany
e-mail: C.Freitag@em.uni-frankfurt.de

L. A. Rohde
Division of Child Psychiatry, Hospital de Clinicas de Porto
Alegre, Federal University of Rio Grande do Sul,
Porto Alegre, Brazil

M. Romanos
Department of Child and Adolescent Psychiatry,
Psychosomatics and Psychotherapy,
University Hospital of Würzburg, Würzburg, Germany

Table 1 Population-based twin studies which included ADHD measures

Study location	Publications	Year and age at assessments	ADHD measurement instruments	Comorbid disorders/symptom scales
Australia	[42, 54, 55, 80, 81]	Longitudinal study	ATBRS	ODDT, CDT, SADT, GADT, RD, language: ATBRS
		T1 1991: 4–12 years old	DISC (P)	ODD, CD, SAD: DISC (P)
		T2 1994/1995: 8–16 years old	SWAN	
		T3 1999: 12–20 years old		
	[42]	2001: 6–9 years old	SWAN, ATBRS	
	[61]	2004/2005: 6–18 years old	SWAN, ATBRS	DCD: DCDQ
	[82]	18–33 years	ADHD symptom checklist (DSM-IV)	AT: SRS (selection 11/65 items)
CaStANET, UK	[18, 60, 105–107, 112]	Wave 1: 1991–1993 (South Wales)	DuPaul ADHD rating scale (P, T)	DEP: MFQ (P,C), HADS (P)
		8–16 years old	DSM-III-R/DSM-IV	ANX: RCMAS (P,C)
		Wave 2: 1996/1997 (plus NW England)	Rutter-A scale (P)	DRUG: AHQ, ASAQ
		5–16 years old	Conners scale (P,T)	CDT: Rutter-A/B scale (P, T, C)
		Wave 3: 2000	SDQ (P,T,C)	ODDT/CDT: SDQ (P,C)
		5–17 years old		
		Wave 4: 2004/2005		
		12–20 years old		
Colorado, USA (CLDRS)	[34, 41, 88, 117–119, 121, 122]	Wave 1: 1996, ongoing; 8–18 years old	DICA (P)	RD: PIAT
			SNAP-IV (P,T)	ODD/CD/GAD/MDD: DICA (P)
				ODDT: SNAP-IV (T)
				DEP: CDI (C)
				Broadband: CBCL
				IQ: WISC-R
				RD (C): PIAT
		Wave 2: 2000, ongoing; mean age 11.4 (± 2.4) years old	DBRS	
		Wave 3: CLTS, 5–6 years follow-up; mean age 7.7–20.5 years old	DICA (P,C)	IQ: WISC-R, WAIS-R
			DBRS (P,T)	ODD/CD: DICA (P,C)
				Broadband: CBCL, TRF, YSR (P,T,C)
				DEP: CDI (C)
				ANX: RCMAS (P,C)
				RD: PIAT (C)
Finland	[25]	14 years old	C-SSAGA-A (C)	ODDT, CDT: C-SSAGA-A (C)
			DSM-III-R	
Georgia, USA	[86]	5–16 years old	ECRS (P)	
			DSM-IV	
Minnesota, USA	[16, 17, 96, 97]	Sample 1: 11 years old, boys only	Conners Items (T)	
			Rutter-B scale Items (T)	
			DICA-R (M)	
			DSM-III-R	
		Sample 2: 10–12 years old, males and females	DICA-R (P)	ODD; CD: DICA-R
			DSM-III-R	
Missouri, USA	[47, 69, 81, 83, 109, 114]	Sample 1: 12–23 years old, females only	DICA-R (P)	ODDT, SADT: SSAGA (P)
			C-SSAGA (C)	DEP: C-SSAGA (C)
			SSAGA (P)	
			DSM-IV/latent class subtypes	

Table 1 continued

Study location	Publications	Year and age at assessments	ADHD measurement instruments	Comorbid disorders/symptom scales
		Sample 2: 7–19 years old, males and female	MAGIC	CD, ODD, DEP: MAGIC CBCL AT: SRS
Netherlands	[22–24, 45, 77, 89, 90]	Longitudinal study T1: 1 year old T2: 2 years old T3: 3 years old T4: 7 years old T5: 10 years old T6: 12 years old	Age 3 and older CBCL (M): attention problems scale Age 7: plus TRF (T): attention problems scale Age 7: plus Conners (M, T) Age 10: plus SWAN, YSR (C) DISC (M): DSM-IV	ODDT (T): Conners
Norway	[38]	5–9 years old 12–15 years old	CBCL	
Sweden	[48, 52, 53]	Longitudinal study T1: 8–9 years old T2: 13–14 years old T3: 16–17 years old	DSM-III-R symptom checklist (P) DSM-IV symptom checklist (P)	
TEDS: England/Wales, UK	[3, 51, 63, 74, 93, 94, 110]	Longitudinal study T1: 12–18 months T2: 2 years old T3: 3 years old T4: 4 years old T5: 7 years old T6: 9 years old T7: 10 years old T8: 12 years old T9: 14 years old	SDQ (P) RRSPC (P) Conners (P)	DEV: MCDI (P), PARCA (P) RD: TWRE, PIAT-R, GOAL DEV: WISC-III-PI, MSCA, CAT3 DYSC: NELSON ODDT/CDT: SDQ AT: CAST
	[50, 111]	High risk sub-sample: E-risk study	Rutter Scales (P, T); DSM-IV symptoms (M)	IQ: WPPSI-R RD: TWRE CDT: CBCL
Virginia, USA	[26, 44, 65, 67, 98, 99]	Longitudinal study T1: 1990–1992, 8–16 years old T2: 19 months later, 1991–1993, 8–16 years old	CAPA (P) Rutter A (P)/Rutter B (T) scales Conners (T) CBCL	ODD, CD, ANX, DEP: CAPA (P) broadband: CBCL
	[66]	1992–1993: 7–13 years old	CAPA (P, telephone interview) CBCL	ODDT, CDT: CAPA (P) broadband: CBCL

Comorbid disorders: *ANX* anxiety disorder, *AT* autistic traits, *CD* conduct disorder, *CDT* conduct disorder traits, *DCD* developmental coordination disorder, *DEP* depressive disorder, *DEV* developmental assessment, *DRUG* drug use, *DYSC* dyscalculia, *GADT* generalized anxiety disorder traits, *IQ* intelligence quotient, *ODD* oppositional-defiant disorder, *ODDT* oppositional-defiant disorder traits, *RD* reading disability, *SAD* separation anxiety disorder, *SADT* separation anxiety disorder traits

Scales: *AHQ* AddHealth Questionnaire, *ASAQ* Adolescent Substance Abuse Questionnaire, *ATBRS* Australian Twin Behavior Rating Scale, *CAST* Childhood Asperger Syndrome test, *CAT3* Cognitive Abilities Test: Third edition, *CBCL* Child Behavior Checklist, *CDI* Children's depression inventory, *Conners* Conners Rating Scales-revised, *C-SSAGA* (-A) Child Semi-Structured Assessment for the Genetics of Alcoholism (Adolescent Version), *DBRS* Disruptive Behavior Rating Scale, *DICA* (-R) Diagnostic Interview for Children and Adolescents (-revised), *DCDQ* Developmental Coordination Disorder Questionnaire, *DISC* Diagnostic Interview Schedule for Children, *ECRS* Emory Combined Rating Scale, *GOAL* Goal formative assessment in literacy, *MAGIC* Missouri Assessment for Genetic Studies of Children, *MCDI* MacArthur Communicative Development Inventories, *MSCA* McCarthy Scales of Children's Abilities, *NELSON* maths 5–14 Series, *PARCA* Parent Report of Children's Abilities, *PIAT* (-R) Peabody Individual Achievement Test (-revised), *RCMAS* Revised Children's Manifest Anxiety Scale, *SDQ* Strength and Difficulties Questionnaire, *SRS* Social Responsiveness Scale, *SSAGA* Semi-Structured Assessment for the Genetics of Alcoholism, *SWAN* Strength and Weakness of ADHD Symptoms and Normal Behavior Scale, *SNAP-IV* Swanson, Nolan, and Pelham-IV Questionnaire, *TRF* Teacher Report Form, *TOWRE* test of word reading efficiency, *WISC-R* Wechsler Intelligence Scale for Children revised version, *WISC-III-PI* Wechsler intelligence Scale for Children-III, *WPPSI-R* Wechsler Primary and Preschool Rating Scales-revised, *YSR* youth self report

Raters: *P* parent, *M* mother, *T* teacher, *C* child

quantitative traits are analyzed by comparing phenotypic variance within and between relatives or monozygotic (MZ) and dizygotic (DZ) twins. Variance component models are based on the assumption of a multivariate normal distribution of the phenotypic measures.

The advantage of twin data is that they allow disentangling genetic from environmental effects. Adoption studies also account for this; however, it is difficult to obtain large samples of adopted children with data on the biological as well as adoptive parents. In addition, adoption studies show some limitations, as e.g. the influence of selective placement. In ADHD, only two adoption studies were performed [1, 64], resulting in higher rates of ADHD in biological than adoptive parents of children with ADHD indicating a genetic etiology of ADHD.

Twin studies rely on many assumptions; the most important one is the equal environments assumption of MZ and DZ twins, which is the focus of considerable debate. For example, MZ and DZ twins develop in different types of placental environment [57]. Due to the greater sharing of prenatal factors, monozygotic twins may exhibit larger similarity due to shared environmental but not genetic effects. Other important—and debated—assumptions are: twins carry a random subset of the gene pool in the general population, random mating of parents, absence of gene–gene and gene–environment interaction, unlinked loci, and twins being treated and behaving similarly to singletons (this latter aspect will be further discussed in the section on rater effects). Several of these assumptions might not hold true for ADHD, especially for ADHD comorbid with CD, as gene–environment interaction clearly has been shown to explain CD in childhood and violent aggressive behavior in adulthood [19, 84]. In addition, results from twin studies including male individuals only apply to autosomal loci.

To obtain heritability estimates, covariance structures, correlations or concordance rates are compared between MZ and DZ twins. Different models including either additive genetic, shared and/or non-shared environmental effects, or additive, dominant genetic and/or non-shared environmental effects (with or without additional rater effects) are compared statistically and the most parsimonious model is chosen. It is not possible to estimate dominant genetic and shared environmental effects simultaneously in samples of twins reared together. An indication of dominant genetic effects is the difference in correlation of MZ and DZ twins. If—in the absence of significant MZ/DZ variance differences—MZ correlation is more than twice the DZ correlation, this is indicative of dominant genetic effects [106]. If MZ variance is smaller than DZ variance, and DZ correlation is very low compared to MZ correlation, this is indicative of a rater contrast effect. Structural equation models allow differentiating between dominant genetic and rater effects [89, 91]. Heritability in the broad sense refers

to additive and dominant genetic effects together; heritability in the narrow sense refers only to additive genetic effects. In this review, “heritability” means additive genetic effects [57].

A recent meta-analysis on ADHD has reported additive and dominant genetic as well as non-shared environmental effects in ADHD, and did not observe common environmental effects [15], a finding, which was discussed and challenged by a comment, emphasizing the role of appropriate data transformation and analysis as well as the limitations of models obtained on twins reared together, possibly underestimating common environmental effects obtained from twin studies on ADHD [124].

Family and adoption studies have the advantage of excluding risk factors associated with twinning itself, e.g. low birth weight which is related to ADHD [48]. On the other hand, genetic and environmental influences cannot easily be singled out in family studies. Family studies specifically allow estimating a mode of inheritance. A segregation study resulted in a model implicating non-Mendelian major gene effects with low penetrance in ADHD [58]. These findings are partly in contrast to the observation of twin studies, which point to a model implying multiple common genetic variants of small effect in the etiology of the disorder [56]. Results of hypothesis-free molecular genetic studies are currently supportive of both models, too, indicating clear genetic heterogeneity in ADHD. Linkage studies elicited several loci likely containing rare genetic variants of major effect only present in single large families, but also common variants of smaller effect present across several families [92]. In addition, genome-wide association studies indicated a very limited number of common variants of small effect to date [33, 62].

Even though the first twin study on the heritability of hyperactivity was published as early as 1973 [123], the first representative data were obtained in the late 1980s, estimating genetic effects to account for around 75% of the explainable variance of hyperactivity and attention difficulties [103]. Since then, numerous twin studies in children and adolescents were performed, trying to elicit factors influencing heritability estimates. Here, we review population-based twin studies in ADHD with regard to measurement and phenotypic aspects which were shown to influence heritability estimates.

Methods

A systematic search of twin and family studies in ADHD was performed, using the databases PubMed and PsycInfo, using the following key words: “ADD”, “ADHD”, “attention”, “hyperactivity”, “impulsivity”, alone and in combination with “twin”, “family”, “conduct

disorder”, “oppositional defiant disorder”, “anxiety disorder”, “depressive disorder”, “reading disability”, “dyslexia”, “tic disorder”, “enuresis”, “rater effect”. Titles and abstracts were screened with regard to the criteria: population-based study, heritability or recurrence risk estimate, and factors influencing heritability and recurrences risk estimate. All articles on results of population-based twin studies assessing ADHD symptoms or diagnoses by parent or teacher ratings/interviews were included in this review. Results of family studies were only mentioned if they added substantial information to the results of the twin studies. As no data analysis was performed in this literature review, data were not extracted according to a specific protocol.

Results

In this section, an overview on measurement as well as phenotypic aspects influencing heritability estimates in childhood ADHD is provided. The impact of these results on the design of molecular genetic studies will be discussed in the following section.

Diagnostic criteria and assessment instruments

According to international psychiatric classification schemes, ADHD is a categorical diagnosis. To prove that the continuous measures obtained from ADHD rating scales are targeting the same phenotype as the categorical diagnosis, heritability estimates obtained by continuous (ATBRS, Table 1) or categorical data (DSM-III-R diagnoses) were compared and did not differ significantly [56].

The influence of different ADHD rating scales on heritability estimates was assessed by two studies [42, 106]. The first study [106] compared the Rutter-A scale, containing 3 hyperactivity items with scores from 0 to 2 (maximum score 6), and the DuPaul-rating scale, containing 18 items covering inattention, hyperactivity, and impulsivity with scores from 0 to 3 (maximum score 54) obtained at the same point in time from mothers. In the DuPaul-rating scale far higher correlations of DZ measures were observed than in the Rutter-A scale, resulting in slightly lower heritability estimates. Also less additive (47%) and more strong dominant genetic effects (31%) were described, which were not observed by the Rutter-A scale (only additive effects: 84%). In addition, data from the Rutter-A scale, but not the DuPaul-Rating Scale were indicative of rater contrast effects as shown by differing variances between MZ and DZ twins.

The second study [42] compared the SWAN and the ATBRS obtained from parents at the same point in time (Table 1). The SWAN scale differs from other ADHD

rating scales by allowing to rate presence of symptoms and positive behavior, i.e. attention to details from “very well” to “not at all” on a 7-point scale ranging from +3 to −3. The ATBRS as other ratings scales only allows to rate problem behavior. The SWAN items yield a more normal, whereas problem behavior rating scales yield a heavily skewed distribution in the general population. Again, DZ correlations were higher on the SWAN than the ATBRS, resulting in far lower additive genetic effects for inattention in the 6–9-years-old group (SWAN 53%, ATBRS 90%) and impulsivity–hyperactivity in the 12–20-years-old group (SWAN 31%, ATBRS 93%). No indication for rater contrast effects was observed by the SWAN.

These different heritability estimates obtained by different scales imply that the currently applied ADHD rating scales might measure different constructs despite a strong overlap with the categorical DSM-III-R or DSM-IV diagnoses. In addition, measurement error might have resulted in contrasting heritability estimates. A recent study showed, that—independent of the implemented scale or interview at age 12 years old (CBCL, Conners, or DSM-IV criteria)—additive (ranging from 0.56 to 0.75) and dominant genetic (ranging from 0.20 to 0.27) effects were roughly comparable as estimated from the different scales, however, instrument-specific additive genetic and environmental effects also were obtained [23].

Interestingly, when hyperactivity was not assessed by rating scales but measured objectively by actigraph, heritability estimates in 7–9-year-old children were lower (36%), and common environmental effects (39%) accounted for the largest part of the remaining variance [125]. Another study in 2-year-old twins also reported heritability of actigraph measures in different situations at home, in the laboratory during a test and during free play (30–52%), however, situation-specific factors were also observed, especially shared environmental effects on the activity level at home (52%) [95].

Rater effects

Most twin studies assessed ADHD symptoms by parental and/or teacher questionnaires with considerable varying heritability estimates, when only parental (typically, maternal), teacher, or combined ratings were taken into account. When results of the Rutter-A and -B scales or from the parent or teacher rated DBRS were compared (Table 1), teacher ratings often resulted in lower heritability estimates (around 50%) than parent ratings and additionally described shared and non-shared environmental effects [41, 67, 97, 99, 106]. Besides possible measurement error, findings imply that parents and teachers might rate different ADHD behavior, which has explicitly been shown for differences in the ratings of

mothers and fathers [43, 113]. It therefore, was suggested to combine information from parents and teacher ratings to diagnose a genetically more clearly determined subtype, as combined ratings showed an additive genetic effect of 79% in two independent studies using items of the Rutter-A and -B scales [97, 106].

Mother ratings, in addition, were also indicative of rater contrast effects, i.e. rating the child with high ADHD symptoms higher, and the child with low ADHD symptoms less severely. If these contrast effects are not accounted for in the analysis, mother ratings will result in lower DZ concordance rates and successively in an overestimation of heritability. Rater contrast effects were described for the Rutter-A scale, the DBRS, parental interview data obtained by the CAPA (Table 1) and for the CBCL at age 3 only but not for children aged 7–12 years old [47, 89, 90].

Subtype effects

The heritability of attention difficulties as measured by the CBCL was estimated at 70–80% [27, 38, 47, 89]. Several studies additionally assessed the bivariate heritability of attention problems and hyperactive–impulsive symptoms to elicit, if attention problems and hyperactive–impulsive problems were mediated by the same or different genetic risk factors. Despite an early finding of high bivariate heritability suggesting that the same genetic influences contribute to attention problems and hyperactivity/impulsivity in DSM-III [96], more recent studies resulted in the findings of common as well specific genetic effects for each subtype [52, 65, 67, 120]. These findings are supported by a meta-analysis of family studies which also reported small subtype-specific transmission effects [102].

Another approach assessing subtypes has been data driven. These studies first assessed the latent class structure of parent-rated DSM-IV ADHD symptoms in population-based samples of twins to parse individuals empirically into subtypes on a purely statistical, i.e. probabilistic level. Second, concordance rates or recurrence risks in MZ and DZ twins were compared to differentially assess the genetic background of each subtype. Eight subtypes were described, of which three were severe classes corresponding to DSM-IV (severe inattentive, severe combined, and severe hyperactive/impulsive). The other classes consisted of individuals with mild inattentive, mild hyperactive/impulsive, or mild combined symptoms. The few symptom classes were comprised of unaffected individuals. One symptom pattern emerged which is not covered by DSM-IV, a talkative-impulsive subtype [46, 70, 80, 109]. Differences between MZ and DZ in either concordance rates or recurrence risks were observed for the three severe and the three mild classes as well as for the talkative-impulsive subtype, with strongest genetic influences on the severe

inattentive and the severe combined subtypes [81, 109]. Cross subtype recurrence risks were far lower. These studies, therefore, are supportive of the DSM-IV distinction of attention-deficit, hyperactivity–impulsivity and combined ADHD and its relevance for genetic studies. Further, they also support the continuous trait model of ADHD.

Sex effects

As the sex difference in prevalence estimates of ADHD is about 2.5–3:1 [76, 119], twin studies have also been analyzed with regard to sex differences. Different scales resulted in slightly different heritability estimates for girls and boys, and in one study, an effect of age was detected with lower heritability estimates in 8–9-year-old boys than girls and higher heritability estimates in 13–14-year-old boys than girls based on a DSM-III-R questionnaire [53, 67]. For combined ADHD as assessed by the CAPA, a similar genetic factor for girls and boys was described, whereas for the inattentive subtype, a second genetic factor was described which was more common in girls [65, 67].

One study described a higher number of DSM-IV derived ADHD symptoms, assessed by the ECRS (Table 1) in dizygotic twins or siblings of girls with ADHD, supporting a polygenic multiple threshold model for ADHD implying that girls are less frequently affected by ADHD because they have a higher threshold for the level of liability needed to manifest ADHD than boys. Here, findings were similar for combined, inattentive, and hyperactive–impulsive symptoms [86, 87].

The relevance of the inattentive subtype for girls was also shown by the finding, that in girls only, a specific genetic correlation of anxiety disorder and inattentive symptoms was observed, which was not present in boys, whereas the genetic correlation of combined ADHD and ODD/CD symptoms did not differ between girls and boys [55, 65, 66].

Comorbid disorders

Comorbidity in ADHD is more common than “pure” ADHD. In a population-based twin study up to 90% of the children with ADHD were affected by at least one comorbid disorder [119]. The most prevalent comorbid disorders were oppositional defiant disorder (ODD; 40–65%), conduct disorder (CD; 27–47%), major depressive disorder (MDD; 0–24%), and generalized anxiety disorder (GAD; 13–21%), similar to rates estimated from epidemiological studies [73]. Theoretically, several different models of comorbidity can be formulated, which are explained in more detail elsewhere [68, 88]. Basically, disorders can co-occur (1) by chance; (2) through multifactority, i.e. the presence of one disorder increases the

liability for the second disorder and vice versa; (3) as three independent disorders (A, B, and A + B); and (4) due to correlated risk factors.

ODD/CD

Early twin studies most often did not differentially assess ODD and CD, but used rating scales combining ODD and CD symptoms on the same scale. These studies reported that comorbid ODD/CD symptoms imply a more severe and more strongly genetically determined ADHD phenotype, present predominantly in males [66, 98]. More recent twin studies resulted in somewhat contradictory findings. Two studies resulted in common genetic and non-shared environmental risk factors, showing, that ADHD + CD likely is not a specific subtype, but a quantitative variant of ADHD showing higher genetic loading [88, 105]. Additionally, shared and non-shared environmental risk factors specific for CD were observed. Another study was indicative of a strong effect of specific environmental risk factors especially for severe CD symptoms in ADHD [20].

Two other studies employing interview data with adolescent twins themselves, reached opposite conclusions. One study described only common and specific genetic risk factors for ADHD, ODD, and CD, and almost no environmental effects [25], the other resulted in common environmental and unique genetic risk factors for ADHD, ODD, and CD [16, 17]. These differing results might be due to the implemented scales, the different raters (interview with adolescents only versus interview with parents and adolescents), presence of rater contrast effects, age effects, and not breaking down the ADHD phenotype into its subtypes.

Longitudinal twin studies also suggested that common genetic factors substantially underlie the comorbidity of ADHD and ODD/CD [65]. Results from family studies similarly support the notion of a strong genetic component especially for comorbid CD, since the risk for ADHD was higher in first degree relatives of children with ADHD + CD compared to ADHD alone or ADHD + ODD [29].

MDD/Anxiety

The impact of genetic or environmental influences on comorbidity rates of ADHD with MDD and anxiety disorders has rarely been studied in twin samples. One study using the latent class approach in a female twin sample suggested that one cluster characterized by the ADHD combined subtype and ODD was accompanied by depression and anxiety symptoms [69]. However, no specific additional genetic effects for comorbid MDD or anxiety were detected. Another twin study described a

higher rate of anxiety disorder symptoms in girls with the inattentive and combined ADHD subtype than in boys, but bivariate heritability was not assessed in this study [55].

Despite higher rates of anxiety disorders in parents of children with ADHD [8, 21, 71] anxiety disorders and ADHD segregated independently in families implying differential risk factors for both types of disorders [9, 14, 21]. With regard to MDD in parents of children with ADHD, one early study found an independent segregation of ADHD and MDD [13], whereas more recent studies provided some support for a familial link of ADHD and depression, which in some studies was most pronounced in ADHD families with antisocial disorders [5, 7, 10, 21]. Correspondingly, ADHD was more often observed in children of depressed parents than of control parents [40, 72, 115, 116]. Psychosocial risk factors, i.e. marital discord, low social class, large family size, paternal criminality, maternal mental disorder, and foster placement, seem to play a predominant causal role in comorbid MDD rather than genetic risk factors [11, 12]. Depression in mothers has been identified as a major environmental risk factor for ODD and CD symptoms independent of the presence of ADHD in the children [21, 59]. The suggested comorbidity of ADHD and bipolar disorder [6, 30] is not supported by a recent family study indicating that bipolar disorder-I in children and adults are the same diathesis, and ADHD is another, unrelated disorder [35].

Reading disability

Another frequent comorbidity of ADHD is reading disability (RD; around 40%), which in most studies showed stronger genetic overlap with attention problems than with hyperactive/impulsive symptoms [34, 37, 54, 111, 121]. DSM-III-R and DSM-IV based studies resulted in the finding that around 90% of the phenotypic correlation between ADHD symptoms—attention problems and reading disability, respectively—was due to shared additive genetic factors [111, 121]. In addition, one study excluded non-random mating as major factor for the comorbidity of RD and ADHD [34].

Autistic traits

Recent twin studies aimed to elicit the genetic correlation of autistic traits and ADHD symptoms in population-based samples [83, 93]. Genetic correlations by teacher and parent-rating scales were approximately 50%, pointing toward possible common genetic mechanisms in ADHD and autistic disorders.

Other comorbid disorders

Other comorbid disorders, which are frequently associated with ADHD in epidemiological samples, like primary nocturnal enuresis [4] or tic disorders [49, 101] were rarely explored by a genetically relevant design. Two family studies were performed on ADHD comorbid with Tourette's disorder (TD) [75, 104] and one on TD comorbid with ADHD [39]. In most families, ADHD and TD occurred independently, indicating a different genetic determination of "pure" ADHD and "pure" TD. The combination of ADHD + TD plus symptoms of obsessive-compulsive disorder (OCD), however, seems to be strongly inherited, as in ADHD + TD families increased rates of obsessive-compulsive disorders (OCD) were observed [36, 100], and latent class analysis in a family study reported a heritability of this subtype of 65% [39].

IQ

Several studies described an association of ADHD and lower IQ values. The possible genetic basis of this correlation was assessed by two studies, which showed a strong genetic correlation of ADHD symptoms (86%) or ADHD diagnoses (100%) with lower IQ scores [50] as well as a negative correlation (mothers: $r = -0.28$; teachers: $r = -0.36$) of attention problems at age 5 with IQ scores at age 12 years old [78].

Longitudinal course

Longitudinal twin studies have been analyzed with regard to the stability of ADHD diagnosis, subtype, and comorbid ODD/CD to elicit genetic and environmental influences on stability and change. In three twin studies, the stability of ADHD symptoms was explored.

In the first study, twins were assessed at age 8–9 years old and re-assessed 5 years later [53]. Heritability at the first assessment was 68% for girls and only 35% for boys, whereas at the second assessment, it was 61% for girls and 74% for boys. Genetic and non-shared environmental effects were relevant for stability as well as for change. Due to the low heritability estimates obtained at wave I for boys in this study, however, these results have to be viewed with caution.

In a further twin sample aged 2,3, and 4 years a phenotypic correlation of around 55–60% between age 2 and 3, and 3 and 4 years old, and around 50% between age 2 and 4 years old for ADHD symptoms was elicited [79]. Cross sectional heritability was estimated at around 80% for each age. Continuity of ADHD symptoms between age 2, 3, and 4 years old in this study was mediated by additive genetic influences (91%). In the same sample at age 7 and 8 years, a slightly lower cross sectional heritability at age 8 was

observed by a different rating scale (72%). Stability of ADHD symptoms was around 50–60% in the one year course (independent of age), after 5 years, it was around 35–45% (ages 2–7 and 3–8 years old). Genetic correlation in the one year course was around 40–50% and in the 5-year course it was around 30–35% [51]. Additive genetic effects (86–96%) accounted for the longitudinal phenotypic correlation with the age 8 years measure (Conner's rating scale); additionally, child-specific environmental influences were observed. Lower longitudinal additive genetic effects around 60% were observed for different ages and measurement instruments (SDQ; revised Rutter scale), indicative of a measurement effect in this study.

A third twin study assessed stability and change of CBCL-derived attention problems (AP) from age 3 to 12 years [90]. Correlation of age 3 measures with age 7, 10, and 12 year old measures was between 35 and 40%; correlation of age 7 measures with age 10 and age 12 year measures was between 67 and 75%. This is indicative of a higher stability of ADHD measures in children aged 7 years and older. Additive and dominant genetic effects accounted for the stability of age 3 symptoms and age 7, 10, and 12 symptoms (additive: 59–79%; dominant: 6–31%), whereas for the older age groups, a stronger effect of dominant genetic effects was obtained (additive: 24–53%; dominant: 28–51%). Additive genetic effects were more relevant for girls than for boys.

Only one study assessed the longitudinal stability of ADHD comorbid with ODD/CD over 19 months [65]. Results were indicative of common (ADHD + ODD/CD) and specific genetic and environmental risk factors (ODD/CD only) for the longitudinal course of ADHD comorbid with ODD/CD. Longitudinal family studies support these findings for CD, as siblings of children and adolescents with ADHD + CD showed a higher risk for CD, while siblings of children with ADHD + ODD or ADHD alone did not. This pattern was maintained over the 4-year follow-up period, pointing toward ADHD + CD as a distinct subtype of ADHD [28]. Antisocial personality disorder in a parent at baseline predicted the presence of CD and ODD in the child 4 years later [31].

Discussion and conclusions

Twin studies on ADHD in children and adolescents resulted in a strong genetic component (additive and dominant genetic effects) of around 75% for ADHD [32]. Despite these rather consistent findings, the present review is indicative of several phenotypic and measurement aspects strongly influencing heritability estimates. These findings are relevant for molecular genetic studies, as they will influence the power of these studies.

The most relevant aspect for molecular genetic studies is measurement influences on heritability estimates. From the presented studies it can be concluded, that short rating scales with a limited amount of answer categories resulted in biased heritability estimates overestimating heritability and showing strong rater effects. Detailed questionnaires, teacher ratings, and more objective measures, as hyperactivity assessed by actigraph, resulted in lower heritability estimates.

For molecular genetic studies, the following conclusions can be drawn: when only parent scales are used, a scale should be chosen which did not show rater contrast effects in any of the twin studies. The measurement error induced by scales showing rater effects cannot be controlled in case-control or family-based studies which are most often the basis for molecular genetic association or linkage studies, thus reducing the power of these studies. When possible, phenotypic measures from parents/mothers and teachers should be combined to assess the “pervasive” subtype of ADHD (compare ICD-10, [126]), as these combined measures resulted in higher and replicated heritability estimates in two studies. Possible ADHD endophenotypes, e.g. hyperactivity measures by actigraph, not necessarily resulted in higher heritability estimates than rating scales, and the relevance of these measures for molecular genetic analyses of ADHD still has to be proven.

Results from twin studies assessing the covariation of inattentive and hyperactive-impulsive symptoms as well as comorbid disorders point towards clear heterogeneity in ADHD. Inattentive symptoms are partly mediated by different genetic risk factors than the hyperactive-impulsive symptoms. In addition, sex differences regarding heritability estimates were mainly obtained for inattentive symptoms/subtype. This finding also is relevant for molecular genetic studies, which often did not assess inattentive symptoms separately.

RD and inattentive symptoms likely share the same genetic risk factors, whereas combined ADHD symptoms were more strongly associated with CD in cross-sectional and longitudinal studies. The combined ADHD + CD subtype has been suggested as a more strongly genetically determined subtype than ADHD alone [108], however, cross-sectional as well as longitudinal twin studies also suggested additional environmental as well as specific genetic risk factors for CD. Therefore, well-known environmental risk factors should be accounted for during analysis. It also might be possible that some assumptions of twin studies will not hold true for ADHD with or without comorbid disorders, like the assumption of no gene-gene or no gene-environment interaction, as molecular genetic studies have shown gene-environment interaction for adult ADHD [85]. Future molecular genetic studies in ADHD

should take into account genetic risk factors described for RD or CD without ADHD, as these risk factors might show some overlap with risk factors for ADHD. In addition, the specific genetic and environmental risk factors for the combined and separate disorders need to be assessed specifically in large samples of individuals with the combined and the separate disorders.

A drawback of most twin and family studies assessing the bivariate heritability of comorbid disorders with ADHD is that these studies did not control for the presence of a second or third comorbid disorder. ADHD and the different comorbid disorders can show a very mixed pattern of genetic or environmental correlation, which has e.g. been shown by a study evaluating the association of conduct disorder symptoms and ADHD [111].

Besides attention problems comorbid with RD and ADHD comorbid with CD, persistent ADHD also might be a more strongly genetically determined subtype of ADHD. However, twin studies clearly have shown that different genetic risk factors account for heritability estimates in cross-sectional analyses compared to longitudinal analyses. Therefore, it is likely, that the molecular genetic findings obtained for persistent ADHD might not all be relevant for cross-sectional ADHD and vice versa.

No clear conclusions can be drawn regarding the pattern of inheritance, as twin and family studies indicate different modes of inheritance, i.e. the oligogenic/polygenic model with additional environmental risk factors for ADHD or major gene effects with low penetrance. Results of linkage and GWA studies also are inconclusive to date with regard to the best genetic model for ADHD. Most likely, in addition to phenotypic heterogeneity genetic heterogeneity does exist for ADHD, which implies that molecular genetic studies should focus (1) on analyzing the most homogeneous phenotype, (2) on sufficient power of genome-wide and hypothesis testing association studies to also be able to elicit effects of rare variants, and—in case of hypotheses driven research—(3) to take results of molecular genetic studies of relevant comorbid disorders, like RD or CD into account.

Acknowledgments Part of this work was supported by grants of the German Research Foundation (ME 1923/5-1, ME 1923/5-3, KFO125). C. Freitag was on the speakers' bureau for Eli-Lilly and Janssen-Cilag. M. Romanos was on the speakers' bureau for Janssen-Cilag and Medice. L. Rohde was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, and Novartis in the last three years. Currently, his only industry related activity is taking part of the advisory board/speakers bureau for Eli Lilly and Novartis (less than US\$ 10,000 per year and reflecting less than 5% of his gross income per year). The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Abbott, Bristol-Myers Squibb, Eli-Lilly, Janssen-Cilag, Novartis, and Shire.

Conflict of interest statement None of the authors reported any conflicts of interest.

References

1. Albers-Corush J, Firestone P, Goodman JT (1986) Attention and impulsivity characteristics of the biological and adoptive parents of hyperactive and normal control children. *Am J Orthopsychiatry* 56:413–423
2. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders. American Psychiatric Association, Washington
3. Asbury K, Dunn JF, Pike A, Plomin R (2003) Nonshared environmental influences on individual differences in early behavioral development: a monozygotic twin differences study. *Child Dev* 74:933–943
4. Baeyens D, Roeyers H, Vande WJ, Hoebeke P (2005) Behavioural problems and attention-deficit hyperactivity disorder in children with enuresis: a literature review. *Eur J Pediatr* 164:665–672
5. Bhatia MS, Nigam VR, Bohra N, Malik SC (1991) Attention deficit disorder with hyperactivity among paediatric outpatients. *J Child Psychol Psychiatry* 32:297–306
6. Biederman J, Faraone S, Mick E, Wozniak J, Chen L, Ouellette C, Marrs A, Moore P, Garcia J, Mennin D, Lelon E (1996) Attention-deficit hyperactivity disorder and juvenile mania: an overlooked comorbidity? *J Am Acad Child Adolesc Psychiatry* 35:997–1008
7. Biederman J, Faraone SV, Keenan K, Benjamin J, Krifcher B, Moore C, Sprich-Buckminster S, Uagaglia K, Jellinek MS, Steingard R (1992) Further evidence for family-genetic risk factors in attention deficit hyperactivity disorder. Patterns of comorbidity in probands and relatives psychiatrically and pediatrically referred samples. *Arch Gen Psychiatry* 49:728–738
8. Biederman J, Faraone SV, Keenan K, Knee D, Tsuang MT (1990) Family-genetic and psychosocial risk factors in DSM-III attention deficit disorder. *J Am Acad Child Adolesc Psychiatry* 29:526–533
9. Biederman J, Faraone SV, Keenan K, Steingard R, Tsuang MT (1991) Familial association between attention deficit disorder and anxiety disorders. *Am J Psychiatry* 148:251–256
10. Biederman J, Faraone SV, Keenan K, Tsuang MT (1991) Evidence of familial association between attention deficit disorder and major affective disorders. *Arch Gen Psychiatry* 48:633–642
11. Biederman J, Faraone SV, Monuteaux MC (2002) Differential effect of environmental adversity by gender: Rutter's index of adversity in a group of boys and girls with and without ADHD. *Am J Psychiatry* 159:1556–1562
12. Biederman J, Milberger S, Faraone SV, Kiely K, Guite J, Mick E, Ablon JS, Warburton R, Reed E, Davis SG (1995) Impact of adversity on functioning and comorbidity in children with attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 34:1495–1503
13. Biederman J, Munir K, Knee D, Armentano M, Autor S, Waternaux C, Tsuang M (1987) High rate of affective disorders in probands with attention deficit disorder and in their relatives: a controlled family study. *Am J Psychiatry* 144:330–333
14. Braaten EB, Biederman J, Monuteaux MC, Mick E, Calhoun E, Cattan G, Faraone SV (2003) Revisiting the association between attention-deficit/hyperactivity disorder and anxiety disorders: a familial risk analysis. *Biol Psychiatry* 53:93–99
15. Burt SA (2009) Rethinking environmental contributions to child and adolescent psychopathology: a meta-analysis of shared environmental influences. *Psychol Bull* 135:608–637
16. Burt SA, Krueger RF, McGue M, Iacono WG (2001) Sources of covariation among attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder: the importance of shared environment. *J Abnorm Psychol* 110:516–525
17. Burt SA, McGue M, Krueger RF, Iacono WG (2005) Sources of covariation among the child-externalizing disorders: informant effects and the shared environment. *Psychol Med* 35:1133–1144
18. Button TM, Thapar A, McGuffin P (2005) Relationship between antisocial behaviour, attention-deficit hyperactivity disorder and maternal prenatal smoking. *Br J Psychiatry* 187:155–160
19. Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R (2002) Role of genotype in the cycle of violence in maltreated children. *Science* 297:851–854
20. Christiansen H, Chen W, Oades RD, Asherson P, Taylor EA, Lasky-Su J, Zhou K, Banaschewski T, Buschgens C, Franke B, Gabriels I, Manor I, Marco R, Muller UC, Mulligan A, Psychogiou L, Rommelse NN, Uebel H, Buitelaar J, Ebstein RP, Eisenberg J, Gill M, Miranda A, Mulas F, Roeyers H, Rothenberger A, Sergeant JA, Sonuga-Barke EJ, Steinhausen HC, Thompson M, Faraone SV (2008) Co-transmission of conduct problems with attention-deficit/hyperactivity disorder: familial evidence for a distinct disorder. *J Neural Transm* 115:163–175
21. Chronis AM, Lahey BB, Pelham WE Jr, Kipp HL, Baumann BL, Lee SS (2003) Psychopathology and substance abuse in parents of young children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 42:1424–1432
22. Derks EM, Dolan CV, Hudziak JJ, Neale MC, Boomsma DI (2007) Assessment and etiology of attention deficit hyperactivity disorder and oppositional defiant disorder in boys and girls. *Behav Genet* 37:559–566
23. Derks EM, Hudziak JJ, Dolan CV, van Beijsterveldt TC, Verhulst FC, Boomsma DI (2008) Genetic and environmental influences on the relation between attention problems and attention deficit hyperactivity disorder. *Behav Genet* 38:11–23
24. Derks EM, Hudziak JJ, van Beijsterveldt CE, Dolan CV, Boomsma DI (2006) Genetic analyses of maternal and teacher ratings on attention problems in 7-year-old Dutch twins. *Behav Genet* 36:833–844
25. Dick DM, Viken RJ, Kaprio J, Pulkkinen L, Rose RJ (2005) Understanding the covariation among childhood externalizing symptoms: genetic and environmental influences on conduct disorder, attention deficit hyperactivity disorder, and oppositional defiant disorder symptoms. *J Abnorm Child Psychol* 33:219–229
26. Eaves L, Rutter M, Silberg JL, Shillady L, Maes H, Pickles A (2000) Genetic and environmental causes of covariation in interview assessments of disruptive behavior in child and adolescent twins. *Behav Genet* 30:321–334
27. Edelbrock C, Rende R, Plomin R, Thompson LA (1995) A twin study of competence and problem behavior in childhood and early adolescence. *J Child Psychol Psychiatry* 36:775–785
28. Faraone SV, Biederman J, Jetton JG, Tsuang MT (1997) Attention deficit disorder and conduct disorder: longitudinal evidence for a familial subtype. *Psychol Med* 27:291–300
29. Faraone SV, Biederman J, Keenan K, Tsuang MT (1991) Separation of DSM-III attention deficit disorder and conduct disorder: evidence from a family-genetic study of American child psychiatric patients. *Psychol Med* 21:109–121
30. Faraone SV, Biederman J, Mennin D, Russell R (1998) Bipolar and antisocial disorders among relatives of ADHD children: parsing familial subtypes of illness. *Am J Med Genet* 81:108–116

31. Faraone SV, Biederman J, Mennin D, Russell R, Tsuang MT (1998) Familial subtypes of attention deficit hyperactivity disorder: a 4-year follow-up study of children from antisocial-ADHD families. *J Child Psychol Psychiatry* 39:1045–1053
32. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P (2005) Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57:1313–1323
33. Franke B, Neale BM, Faraone SV (2009) Genome-wide association studies in ADHD. *Hum Genet* 126:13–50
34. Friedman MC, Chhabildas N, Budhiraja N, Willcutt EG, Pennington BF (2003) Etiology of the comorbidity between RD and ADHD: exploration of the non-random mating hypothesis. *Am J Med Genet B Neuropsychiatr Genet* 120:109–115
35. Geller B, Tillman R, Bolhofner K, Zimmerman B, Strauss NA, Kaufmann P (2006) Controlled, blindly rated, direct-interview family study of a prepubertal and early-adolescent bipolar I disorder phenotype: morbid risk, age at onset, and comorbidity. *Arch Gen Psychiatry* 63:1130–1138
36. Geller D, Petty C, Vivas F, Johnson J, Pauls D, Biederman J (2007) Examining the relationship between obsessive-compulsive disorder and attention-deficit/hyperactivity disorder in children and adolescents: a familial risk analysis. *Biol Psychiatry* 61:316–321
37. Gilger JW, Pennington BF, DeFries JC (1992) A twin study of the etiology of comorbidity: attention-deficit hyperactivity disorder and dyslexia. *J Am Acad Child Adolesc Psychiatry* 31:343–348
38. Gjone H, Stevenson J, Sundet JM (1996) Genetic influence on parent-reported attention-related problems in a Norwegian general population twin sample. *J Am Acad Child Adolesc Psychiatry* 35:588–596
39. Grados MA, Mathews CA (2008) Latent class analysis of Gilles de la Tourette syndrome using comorbidities: clinical and genetic implications. *Biol Psychiatry* 64:219–225
40. Grigoriu-Serbanescu M, Christodorescu D, Magureanu S, Jipescu I, Totoescu A, Marinescu E, Ardelean V, Popa S (1991) Adolescent offspring of endogenous unipolar depressive parents and of normal parents. *J Affect Disord* 21:185–198
41. Hartman CA, Rhee SH, Willcutt EG, Pennington BF (2007) Modeling rater disagreement for ADHD: are parents or teachers biased? *J Abnorm Child Psychol* 35:536–542
42. Hay DA, Bennett KS, Levy F, Sergeant J, Swanson J (2007) A twin study of attention-deficit/hyperactivity disorder dimensions rated by the strengths and weaknesses of ADHD-symptoms and normal-behavior (SWAN) scale. *Biol Psychiatry* 61:700–705
43. Hewitt JK, Silberg JL, Neale MC, Eaves LJ, Erickson M (1992) The analysis of parental ratings of children's behavior using LISREL. *Behav Genet* 22:293–317
44. Hewitt JK, Silberg JL, Rutter M, Simonoff E, Meyer JM, Maes H, Pickles A, Neale MC, Loeber R, Erickson MT, Kendler KS, Heath AC, Truett KR, Reynolds CA, Eaves LJ (1997) Genetics and developmental psychopathology: 1. Phenotypic assessment in the Virginia Twin Study of Adolescent Behavioral Development. *J Child Psychol Psychiatry* 38:943–963
45. Hudziak JJ, Derks EM, Althoff RR, Rettew DC, Boomsma DI (2005) The genetic and environmental contributions to attention deficit hyperactivity disorder as measured by the Conners' rating scales—revised. *Am J Psychiatry* 162:1614–1620
46. Hudziak JJ, Heath AC, Madden PF, Reich W, Bucholz KK, Slutske W, Bierut LJ, Neuman RJ, Todd RD (1998) Latent class and factor analysis of DSM-IV ADHD: a twin study of female adolescents. *J Am Acad Child Adolesc Psychiatry* 37:848–857
47. Hudziak JJ, Rudiger LP, Neale MC, Heath AC, Todd RD (2000) A twin study of inattentive, aggressive, and anxious/depressed behaviors. *J Am Acad Child Adolesc Psychiatry* 39:469–476
48. Hultman CM, Torrang A, Tuvblad C, Cnattingius S, Larsson JO, Lichtenstein P (2007) Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *J Am Acad Child Adolesc Psychiatry* 46:370–377
49. Kadesjo B, Gillberg C (2000) Tourette's disorder: epidemiology and comorbidity in primary school children. *J Am Acad Child Adolesc Psychiatry* 39:548–555
50. Kuntsi J, Eley TC, Taylor A, Hughes C, Asherson P, Caspi A, Moffitt TE (2004) Co-occurrence of ADHD and low IQ has genetic origins. *Am J Med Genet B Neuropsychiatr Genet* 124:41–47
51. Kuntsi J, Rijdsdijk F, Ronald A, Asherson P, Plomin R (2005) Genetic influences on the stability of attention-deficit/hyperactivity disorder symptoms from early to middle childhood. *Biol Psychiatry* 57:647–654
52. Larsson H, Lichtenstein P, Larsson JO (2006) Genetic contributions to the development of ADHD subtypes from childhood to adolescence. *J Am Acad Child Adolesc Psychiatry* 45:973–981
53. Larsson JO, 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. *J Am Acad Child Adolesc Psychiatry* 43:1267–1275
54. Levy F, Hay D, McLaughlin M, Wood C, Waldman I (1996) Twin sibling differences in parental reports of ADHD, speech, reading and behaviour problems. *J Child Psychol Psychiatry* 37:569–578
55. Levy F, Hay DA, Bennett KS, McStephen M (2005) Gender differences in ADHD subtype comorbidity. *J Am Acad Child Adolesc Psychiatry* 44:368–376
56. Levy F, Hay DA, McStephen M, Wood C, Waldman I (1997) Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. *J Am Acad Child Adolesc Psychiatry* 36:737–744
57. Lynch M, Walsh B (1998) Genetics and analysis of quantitative traits. Sinauer Associates, Sunderland
58. Maher BS, Marazita ML, Moss HB, Vanyukov MM (1999) Segregation analysis of attention deficit hyperactivity disorder. *Am J Med Genet* 88:71–78
59. Marmorstein NR, Iacono WG (2004) Major depression and conduct disorder in youth: associations with parental psychopathology and parent-child conflict. *J Child Psychol Psychiatry* 45:377–386
60. Martin N, Scourfield J, McGuffin P (2002) Observer effects and heritability of childhood attention-deficit hyperactivity disorder symptoms. *Br J Psychiatry* 180:260–265
61. Martin NC, Piek JP, Hay D (2006) DCD and ADHD: a genetic study of their shared aetiology. *Hum Mov Sci* 25:110–124
62. McCarthy MI, Abecasis GR, Cardon LR, Goldstein DB, Little J, Ioannidis JP, Hirschhorn JN (2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet* 9:356–369
63. McLoughlin G, Ronald A, Kuntsi J, Asherson P, Plomin R (2007) Genetic support for the dual nature of attention deficit hyperactivity disorder: substantial genetic overlap between the inattentive and hyperactive-impulsive components. *J Abnorm Child Psychol* 35:999–1008
64. Morrison JR, Stewart MA (1973) The psychiatric status of the legal families of adopted hyperactive children. *Arch Gen Psychiatry* 28:888–891
65. Nadder TS, Rutter M, Silberg JL, Maes HH, Eaves LJ (2002) Genetic effects on the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and oppositional-defiant disorder/conduct disorder (Odd/CD) symptomatology across informant and occasion of measurement. *Psychol Med* 32:39–53

66. Nadder TS, Silberg JL, Eaves LJ, Maes HH, Meyer JM (1998) Genetic effects on ADHD symptomatology in 7- to 13-year-old twins: results from a telephone survey. *Behav Genet* 28:83–99
67. Nadder TS, Silberg JL, Rutter M, Maes HH, Eaves LJ (2001) Comparison of multiple measures of ADHD symptomatology: a multivariate genetic analysis. *J Child Psychol Psychiatry* 42:475–486
68. Neale MC, Kendler KS (1995) Models of comorbidity for multifactorial disorders. *Am J Hum Genet* 57:935–953
69. Neuman RJ, Heath A, Reich W, Bucholz KK, Madden PAF, Sun L, Todd RD, Hudziak JJ (2001) Latent class analysis of ADHD and comorbid symptoms in a population sample of adolescent female twins. *J Child Psychol Psychiatry* 42:933–942
70. Neuman RJ, Todd RD, Heath AC, Reich W, Hudziak JJ, Bucholz KK, Madden PA, Begleiter H, Porjesz B, Kuperman S, Hesselbrock V, Reich T (1999) Evaluation of ADHD typology in three contrasting samples: a latent class approach. *J Am Acad Child Adolesc Psychiatry* 38:25–33
71. Nigg JT, Hinshaw SP (1998) Parent personality traits and psychopathology associated with antisocial behaviors in childhood attention-deficit hyperactivity disorder. *J Child Psychol Psychiatry* 39:145–159
72. Nomura Y, Wickramaratne PJ, Warner V, Mufson L, Weissman MM (2002) Family discord, parental depression, and psychopathology in offspring: ten-year follow-up. *J Am Acad Child Adolesc Psychiatry* 41:402–409
73. Offord DR, Boyle MH, Szatmari P, Rae-Grant NI, Links PS, Cadman DT, Byles JA, Crawford JW, Blum HM, Byrne C (1987) Ontario Child Health Study. II. Six-month prevalence of disorder and rates of service utilization. *Arch Gen Psychiatry* 44:832–836
74. Oliver BR, Plomin R (2007) Twins' early development study (TEDS): a multivariate, longitudinal genetic investigation of language, cognition and behavior problems from childhood through adolescence. *Twin Res Hum Genet* 10:96–105
75. Pauls DL, Leckman JF, Cohen DJ (1993) Familial relationship between Gilles de la Tourette's syndrome, attention deficit disorder, learning disabilities, speech disorders, and stuttering. *J Am Acad Child Adolesc Psychiatry* 32:1044–1050
76. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA (2007) The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 164:942–948
77. Polderman TJ, Derks EM, Hudziak JJ, Verhulst FC, Posthuma D, Boomsma DI (2007) Across the continuum of attention skills: a twin study of the SWAN ADHD rating scale. *J Child Psychol Psychiatry* 48:1080–1087
78. Polderman TJ, Gosso MF, Posthuma D, van Beijsterveldt TC, Heutink P, Verhulst FC, Boomsma DI (2006) A longitudinal twin study on IQ, executive functioning, and attention problems during childhood and early adolescence. *Acta Neurol Belg* 106:191–207
79. Price TS, Simonoff E, Asherson P, Curran S, Kuntsi J, Waldman I, Plomin R (2005) Continuity and change in preschool ADHD symptoms: longitudinal genetic analysis with contrast effects. *Behav Genet* 35:121–132
80. Rasmussen ER, Neuman RJ, Heath AC, Levy F, Hay DA, Todd RD (2002) Replication of the latent class structure of attention-deficit/hyperactivity disorder (ADHD) subtypes in a sample of Australian twins. *J Child Psychol Psychiatry* 43:1018–1028
81. Rasmussen ER, Neuman RJ, Heath AC, Levy F, Hay DA, Todd RD (2004) Familial clustering of latent class and DSM-IV defined attention-deficit/hyperactivity disorder (ADHD) subtypes. *J Child Psychol Psychiatry* 45:589–598
82. Reiersen AM, Constantino JN, Grimmer M, Martin NG, Todd RD (2008) Evidence for shared genetic influences on self-reported ADHD and autistic symptoms in young adult Australian twins. *Twin Res Hum Genet* 11:579–585
83. Reiersen AM, Constantino JN, Volk HE, Todd RD (2007) Autistic traits in a population-based ADHD twin sample. *J Child Psychol Psychiatry* 48:464–472
84. Reif A, Rosler M, Freitag CM, Schneider M, Eujen A, Kissling C, Wenzler D, Jacob CP, Retz-Junginger P, Thome J, Lesch KP, Retz W (2007) Nature and nurture predispose to violent behavior: serotonergic genes and adverse childhood environment. *Neuropsychopharmacology* 32:2375–2383
85. Retz W, Freitag CM, Retz-Junginger P, Wenzler D, Schneider M, Kissling C, Thome J, Rosler M (2008) A functional serotonin transporter promoter gene polymorphism increases ADHD symptoms in delinquents: interaction with adverse childhood environment. *Psychiatry Res* 158:123–131
86. Rhee SH, Waldman ID (2004) Etiology of sex differences in the prevalence of ADHD: an examination of inattention and hyperactivity-impulsivity. *Am J Med Genet B Neuropsychiatr Genet* 127:60–64
87. Rhee SH, Waldman ID, Hay DA, Levy F (1999) Sex differences in genetic and environmental influences on DSM-III-R attention-deficit/hyperactivity disorder. *J Abnorm Psychol* 108:24–41
88. Rhee SH, Willcutt EG, Hartman CA, Pennington BF, DeFries JC (2008) Test of alternative hypotheses explaining the comorbidity between attention-deficit/hyperactivity disorder and conduct disorder. *J Abnorm Child Psychol* 36:29–40
89. Rietveld MJ, Hudziak JJ, Bartels M, van Beijsterveldt CE, Boomsma DI (2003) Heritability of attention problems in children: I. cross-sectional results from a study of twins, age 3–12 years. *Am J Med Genet B Neuropsychiatr Genet* 117:102–113
90. Rietveld MJ, Hudziak JJ, Bartels M, van Beijsterveldt CE, Boomsma DI (2004) Heritability of attention problems in children: longitudinal results from a study of twins, age 3 to 12. *J Child Psychol Psychiatry* 45:577–588
91. Rietveld MJ, Posthuma D, Dolan CV, Boomsma DI (2003) ADHD: sibling interaction or dominance: an evaluation of statistical power. *Behav Genet* 33:247–255
92. Romanos J, Freitag C, Jacob C, Craig DW, Dempfle A, Nguyen TT, Halperin R, Walitza S, Renner TJ, Seitz C, Romanos J, Palmason H, Reif A, Heine M, Windemuth-Kieselbach C, Vogler C, Sigmund J, Warnke A, Schafer H, Meyer J, Stephan DA, Lesch KP (2008) Genome-wide linkage analysis of ADHD using high-density SNP arrays: novel loci at 5q13.1 and 14q12. *Mol Psychiatry* 13:522–530
93. Ronald A, Simonoff E, Kuntsi J, Asherson P, Plomin R (2008) Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry* 49:535–542
94. Saudino KJ, 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. *J Abnorm Child Psychol* 33:113–130
95. Saudino KJ, Zapfe JA (2008) Genetic influences on activity level in early childhood: do situations matter? *Child Dev* 79:930–943
96. Sherman DK, Iacono WG, McGue MK (1997) Attention-deficit hyperactivity disorder dimensions: a twin study of inattention and impulsivity-hyperactivity. *J Am Acad Child Adolesc Psychiatry* 36:745–753
97. Sherman DK, McGue MK, Iacono WG (1997) Twin concordance for attention deficit hyperactivity disorder: a comparison of teachers' and mothers' reports. *Am J Psychiatry* 154:532–535
98. Silberg J, Rutter M, Meyer J, Maes H, Hewitt J, Simonoff E, Pickles A, Loeber R, Eaves L (1996) Genetic and environmental

- influences on the covariation between hyperactivity and conduct disturbance in juvenile twins. *J Child Psychol Psychiatry* 37:803–816
99. Simonoff E, Pickles A, Hervas A, Silberg JL, Rutter M, Eaves L (1998) Genetic influences on childhood hyperactivity: contrast effects imply parental rating bias, not sibling interaction. *Psychol Med* 28:825–837
 100. Spencer T, Biederman J, Harding M, O'Donnell D, Wilens T, Faraone S, Coffey B, Geller D (1998) Disentangling the overlap between Tourette's disorder and ADHD. *J Child Psychol Psychiatry* 39:1037–1044
 101. Spencer T, Biederman M, Coffey B, Geller D, Wilens T, Faraone S (1999) The 4-year course of tic disorders in boys with attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 56:842–847
 102. Stawicki JA, Nigg JT, von Eye A (2006) Family psychiatric history evidence on the nosological relations of DSM-IV ADHD combined and inattentive subtypes: new data and meta-analysis. *J Child Psychol Psychiatry* 47:935–945
 103. Stevenson J (1992) Evidence for a genetic etiology in hyperactivity in children. *Behav Genet* 22:337–344
 104. Stewart SE, Illmann C, Geller DA, Leckman JF, King R, Pauls DL (2006) A controlled family study of attention-deficit/hyperactivity disorder and Tourette's disorder. *J Am Acad Child Adolesc Psychiatry* 45:1354–1362
 105. Thapar A, Harrington R, McGuffin P (2001) Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design. *Br J Psychiatry* 179:224–229
 106. Thapar A, Harrington R, Ross K, McGuffin P (2000) Does the definition of ADHD affect heritability? *J Am Acad Child Adolesc Psychiatry* 39:1528–1536
 107. Thapar A, Hervas A, McGuffin P (1995) Childhood hyperactivity scores are highly heritable and show sibling competition effects: twin study evidence. *Behav Genet* 25:537–544
 108. Thapar A, Langley K, O'Donovan M, Owen M (2006) Refining the attention deficit hyperactivity disorder phenotype for molecular genetic studies. *Mol Psychiatry* 11:714–720
 109. Todd RD, Rasmussen ER, Neuman RJ, Reich W, Hudziak JJ, Bucholz KK, Madden PA, Heath A (2001) Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. *Am J Psychiatry* 158:1891–1898
 110. Trouton A, Spinath FM, Plomin R (2002) Twins early development study (TEDS): a multivariate, longitudinal genetic investigation of language, cognition and behavior problems in childhood. *Twin Res* 5:444–448
 111. Trzesniewski KH, Moffitt TE, Caspi A, Taylor A, Maughan B (2006) Revisiting the association between reading achievement and antisocial behavior: new evidence of an environmental explanation from a twin study. *Child Dev* 77:72–88
 112. Van Den Bree MB, Rice F, Fowler TA, Shelton KH, Lifford KJ, Scourfield J, Harold GT, Thapar A (2007) The Cardiff Study of all Wales and North West of England Twins (CaStANET): a longitudinal research program of child and adolescent development. *Twin Res Hum Genet* 10:13–23
 113. van der Valk JC, Van den Oord EJ, Verhulst FC, Boomsma D (2001) Using parental ratings to study the etiology of 3-year-old twins' problem behaviors: different views or rater bias? *J Child Psychol Psychiatry* 42:921–931
 114. Volk HE, Neuman RJ, Todd RD (2005) A systematic evaluation of ADHD and comorbid psychopathology in a population-based twin sample. *J Am Acad Child Adolesc Psychiatry* 44:768–775
 115. Weissman MM, Warner V, Wickramaratne PJ, Kandel DB (1999) Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *J Am Acad Child Adolesc Psychiatry* 38:892–899
 116. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Verdelli H, Pilowsky DJ, Grillon C, Bruder G (2005) Families at high and low risk for depression: a 3-generation study. *Arch Gen Psychiatry* 62:29–36
 117. Willcutt EG, Pennington BF (2000) Comorbidity of reading disability and attention-deficit/hyperactivity disorder: differences by gender and subtype. *J Learn Disabil* 33:179–191
 118. Willcutt EG, Pennington BF, Boada R, Ogline JS, Tunick RA, Chhabildas NA, Olson RK (2001) A comparison of the cognitive deficits in reading disability and attention-deficit/hyperactivity disorder. *J Abnorm Psychol* 110:157–172
 119. Willcutt EG, Pennington BF, Chhabildas NA, Friedman MC, Alexander J (1999) Psychiatric comorbidity associated with DSM-IV ADHD in a nonreferred sample of twins. *J Am Acad Child Adolesc Psychiatry* 38:1355–1362
 120. Willcutt EG, Pennington BF, DeFries JC (2000) Etiology of inattention and hyperactivity/impulsivity in a community sample of twins with learning difficulties. *J Abnorm Child Psychol* 28:149–159
 121. Willcutt EG, Pennington BF, DeFries JC (2000) Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *Am J Med Genet* 96:293–301
 122. Willcutt EG, Pennington BF, Olson RK, DeFries JC (2007) Understanding comorbidity: a twin study of reading disability and attention-deficit/hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* 144B:709–714
 123. Willerman L (1973) Activity level and hyperactivity in twins. *Child Dev* 44:288–293
 124. Wood AC (2010) Rethinking shared environment as a source of variance underlying attention-deficit/hyperactivity disorder symptoms. *Psychol Bull* (in press). Comment on Burt (2009)
 125. Wood AC, Saudino KJ, Rogers H, Asherson P, Kuntsi J (2007) Genetic influences on mechanically-assessed activity level in children. *J Child Psychol Psychiatry* 48:695–702
 126. World Health Organisation (1992) The ICD-10 classification of mental and behavioural disorders. Clinical descriptions and diagnostic guidelines. World Health Organisation, Geneva