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Phenotypic and measurement influences on heritability estimates in childhood ADHD

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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;

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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 T1 1991: 4–12 years old T2 1994/1995: 8–16 years old T3 1999: 12–20 years old	ATBRS DISC (P) SWAN	ODDT, CDT, SADT, GADT, RD, language: ATBRS ODD, CD, SAD: DISC (P)
	[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) 8–16 years old Wave 2: 1996/1997 (plus NW England) 5–16 years old Wave 3: 2000 5–17 years old Wave 4: 2004/2005 12–20 years old	DuPaul ADHD rating scale (P, T) DSM-III-R/DSM-IV Rutter-A scale (P) Conners scale (P,T) SDQ (P,T,C)	DEP: MFQ (P,C), HADS (P) ANX: RCMAS (P,C) DRUG: AHQ, ASAQ CDT: Rutter-A/B scale (P, T, C) ODDT/CDT: SDQ (P,C)
Colorado, USA (CLDRS)	[34, 41, 88, 117–119, 121, 122]	Wave 1: 1996, ongoing; 8–18 years old Wave 2: 2000, ongoing; mean age 11.4 (± 2.4) years old Wave 3: CLTS, 5–6 years follow-up; mean age 7.7–20.5 years old	DICA (P) SNAP-IV (P,T) DBRS DICA (P,C) DBRS (P,T)	RD: PIAT ODD/CD/GAD/MDD: DICA (P) ODDT: SNAP-IV (T) DEP: CDI (C) Broadband: CBCL IQ: WISC-R RD (C): PIAT IQ: WISC-R, WAIS-R 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) DSM-III-R	ODDT, CDT: C-SSAGA-A (C)
Georgia, USA	[86]	5–16 years old	ECRS (P) DSM-IV	
Minnesota, USA	[16, 17, 96, 97]	Sample 1: 11 years old, boys only Sample 2: 10–12 years old, males and females	Conners Items (T) Rutter-B scale Items (T) DICA-R (M) DSM-III-R DICA-R (P) DSM-III-R	ODD; CD: DICA-R
Missouri, USA	[47, 69, 81, 83, 109, 114]	Sample 1: 12–23 years old, females only	DICA-R (P) C-SSAGA (C) SSAGA (P) DSM-IV/latent class subtypes	ODDT, SADT: SSAGA (P) DEP: C-SSAGA (C)

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.

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