Family and Twin Studies in Attention-Deficit Hyperactivity Disorder

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Abstract

Twin and family studies in attention-deficit hyperactivity disorder (ADHD) did result in the findings of a strong heritable component (60–80\%) of this disorder in children and adolescents. Twin studies have not yet been performed in adults. In addition to increased rates of ADHD in parents and siblings of children with ADHD, family studies resulted in a high risk for ADHD in the offspring of parents with ADHD implying strong familial, i.e. genetic or environmental risk factors in the adult form. This corroborates findings from twin studies, which suggested that persistent ADHD might be an interesting phenotype for molecular genetic studies. The present review thoroughly presents findings from twin and family studies with regard to ADHD subtypes, sex differences, comorbidity rates, diagnostic aspects and environmental influences on ADHD. Besides persistent ADHD, ADHD with symptoms of conduct disorder 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.

All psychiatric disorders are environmentally as well as genetically determined. To quantify the impact of these different factors on disease status or disease severity, family and twin studies are performed. These studies either estimate concordance rates of disease status in families or in monozygotic (MZ) and dizygotic twins (DZ) or the heritability of a disorder, i.e. the phenotypic variation due to additive genetic effects. Family studies allow to estimate a recurrence risk for the disorder, which can be translated into a heritability estimate, and additionally may allow to elicit a certain pattern of inheritance, if the disorder of interest seems to be a mendelian disorder. Heritability estimates as well as the quantification of shared and non-shared environmental effects in twin studies are obtained by a comparison of the phenotypic variance within and between MZ and DZ twin pairs. Studies on twins reared apart or adoption studies are other designs to assess the influence of genetic and environmental risk factors. Estimation of genetic and environmental effects on the disorder
in these studies is based on the assumption of random mating, absence of gene-gene and gene-environment interaction and unlinked loci.

In attention-deficit hyperactivity disorder (ADHD) most family and twin studies have been performed in children and adolescents, and not in adults. This mainly has been due to the diagnostic difficulties encountered in adult ADHD (see chapter 3) and in the past also due to a limited recognition of the disorder in adults. This chapter, therefore, differentially reports results of family and twin studies in children and adolescents as well as of family studies in adults. It further discusses the stability of environmental and genetic influences over the lifespan on disease status or disease severity as well as on rates of comorbidity (also see chapter 4).

**Twin Studies**

The earliest twin study on the heritability of hyperactivity was performed by Willerman [1] in 1973. This study, however, used a volunteer sample and questionnaires of uncertain validity. Due to the nature of the variance components method used to assess heritability, a volunteer sample might falsify results, because the more equal the environment the stronger the calculated genetic effects and vice versa. The first representative twin study, which assessed ADHD symptoms by the Rutter teacher and parent questionnaires, found that genetic effects accounted for around 75% of the explainable variance of hyperactivity and attention difficulties [2, 3]. Since then, numerous twin studies in children and adolescents have been performed, and the finding of a heritable component of about 60–80% [4] was replicated in different populations, however mainly of Caucasian origin. These heritability estimates were independent of age and sex distribution of the twin samples. Several issues as the definition of ADHD as category or continuum, subtypes within ADHD, assessment instruments, differential effects of informants or rater contrast, sex differences, comorbidity rates, environmental risk factors, and the impact of genetic and environmental risk factors on the course of the disorder were additionally addressed. Only one twin study in adults has been performed to date, which assessed the efficacy of retrospective recall of ADHD symptoms in adults around age 50 years [5].

*Categorical Diagnosis or Continuously Distributed Trait*

Differing from family studies, which often obtained categorical diagnoses and compared rates of disorders in relatives, most twin studies were based on rating scales, resulting in a continuously distributed measure of ADHD symptoms in the study population. The study by Levy et al. [6] compared heritability estimates obtained either by continuous or categorical data, and also estimated heritability by sibling data. A rating scale based on DSM-III-R diagnostic criteria as well as a structured diagnostic interview was used. Definition of ADHD by continuous or categorical data as well as familial relationship did not change the resulting estimates of an additive genetic
effect in the range of 75–90%. This finding is supportive of a continuously underlying trait, which most likely is mediated by several genes. Therefore, ADHD might be conceptualized as an oligogenic or polygenic disorder. The concordance rate <100% in MZ twins, however, also implies environmental effects in ADHD.

Another study [7] found a heritability of 89% by comparing concordance rates (categorical diagnoses) obtained through a structured interview with the mother, and a heritability of 73% by categorical diagnoses obtained through teacher questionnaires. Combined mother and teacher data resulted in a heritability estimate of 79%. This points to differential reporter or rater effects (see below). It can be concluded that categorical or continuous measurements did result in comparable heritability estimates for childhood ADHD from twin studies.

The above-mentioned and other twin studies [8–10] assessed attention and hyperactivity/impulsivity symptoms together. In DSM-IV [11], however, the inattentive subtype has become a separate diagnosis from the hyperactive/impulsive subtype and the combined disorder. This has posed, first, the question of heritability of the respective subtypes and, second, of shared genetic factors underlying these subtypes.

**Heritability of ADHD Subtypes**

The heritability of attention difficulties as measured by the Child Behavior Checklist (CBCL), a parent questionnaire [12], was assessed by several twin studies [13–16]. Estimates of heritability of attention problems lay around 70–80%, with non-shared environmental influences accounting for the remaining variance. The CBCL, however, does not contain the same attention items as DSM-IV or DSM-III-R. Therefore, it was necessary to replicate these findings for attention difficulties as assessed by DSM-III-R or DSM-IV criteria.

In boys, one study [17] did show far lower heritability estimates for attention difficulties due to DSM-III-R criteria as rated by teachers (39%) compared to mothers (69%). The hyperactivity/impulsivity subtype, which was also assessed in this study, was found to show a higher heritability, both in teacher (69%) and mother ratings (91%). The same study found that common genetic factors might influence both subtypes, however, again teacher ratings (33%) and mother ratings (86%) did differ considerably. These findings again are indicative of rater effects, which can confound heritability estimates (see below).

Still, the study shows stronger genetic influences on hyperactivity/impulsivity symptoms than on attention problems. Strong genetic influences on hyperactivity symptoms as assessed by the Rutter A scale as well as indication of a rater-contrast effect were also observed in two other twin studies [18, 19].

A further study in 8- to 16-year-old twins [9] assessed the three dimensions inattention, hyperactivity and impulsivity separately at two different time points. In contrast to the above-mentioned study, data were indicative of a differential genetic determination of inattention as compared to hyperactivity and impulsivity, the latter, however, sharing the same genetic risk factors. Similar results had been obtained in
the analysis of a bigger set of twin data from the same study at only one time point [20]. In the latter study, additionally multiple measures of ADHD symptomatology were compared, i.e. an investigator-based interview, the Rutter parent and teacher questionnaires and the CBCL. Maternal measures indicated that on the phenotypic level the different measurement instruments assessed the same underlying behavioral construct for inattention, hyperactivity and impulsivity problems respectively. Again, rater-specific variance was found for both parent and teacher data.

Another approach assessing subtypes has been data-driven. These studies first established the latent class structure of DSM-IV 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 risk in MZ and DZ twins were compared to differentially assess the genetic background of each subtype. DSM-IV symptoms were obtained by mother/parent ratings only. Studies across cultures (USA and Australia) elicited 8 subtypes, of which 3 were severe classes (severe inattentive, severe combined, severe hyperactive/impulsive) which roughly correspond to the DSM-IV-based subtypes. The other 5 classes consisted of individuals with mild inattentive, mild hyperactive/impulsive or mild combined symptoms, which did not reach diagnostic criteria according to DSM-IV. The few symptom class was comprised of unaffected individuals. One symptom pattern emerged which is not covered by DSM-IV, a talkative-impulsive subtype [21–24]. Differences between MZ and DZ in either concordance rates or recurrence risks were found for the 3 severe and the 3 mild classes as well as for the talkative-impulsive subtype, with strongest genetic influences on the severe inattentive and the severe hyperactive-impulsive subtypes [24, 25]. Cross-subtype recurrence risks were far lower. These studies, therefore, are supportive of the DSM-IV distinction of attention-deficit, hyperactivity-impulsivity and the combined ADHD and its relevance for genetic studies. Further, they also support the continuous trait model of ADHD. As the mild and severe combined type did show a smaller recurrence risk ratio than the severe inattentive and severe hyperactive-impulsive subtypes, they also indicate a differential genetic determination of attention difficulties and other symptoms in ADHD.

In conclusion, there is some inconsistency between studies regarding the amount of genetic influences on attention problems. The studies agree with regard to a prevailing differential genetic determination of attention problems and hyperactive-impulsive symptoms, however with some genetic overlap between symptoms.

**Rater Effects**

The above-mentioned studies assessed ADHD symptoms by parental and/or teacher questionnaires. Informant-specific ratings were obtained in almost all studies, with considerable varying heritability estimates, when only parental (typically, maternal), teacher or combined ratings were taken into account [7, 8, 17, 26–28]. In most studies, mothers did show a rater-contrast effect by rating the child with high ADHD symptoms higher, and the child with low ADHD symptoms less severely than the
teacher, making ‘true’ differences in behavior unlikely [26]. These rater-contrast effects, however, might also be measurement-specific, as studies assessing ADHD symptoms by the Rutter A scale or the DuPaul ADHD scale did show a stronger difference between DZ twins, indicating rater-contrast effects, than studies using other measurement instruments [6, 14, 20, 27, 29, 30]. Interestingly, a study using the Strengths and Weaknesses of ADHD-Symptoms and Normal-Behavior (SWAN) scale as parent rating scale, which includes above-average performance on attention and activity, resulted in higher DZ twin concordance and lower variability in DZ measurements, implying less rater-contrast effect for this scale [31]. If due to rater-contrast effects variability between DZ twins is estimated higher and concordance lower than between MZ twins, this will result in an overestimation of heritability and underestimation of environmental effects as well as in contradicting results with respect to the impact of shared and non-shared environmental influences on the disorder. On the contrary, the same teacher in one study tended to rate twin pairs in general more similar than different teachers, resulting in a possible underestimation of heritability [26].

In addition to rater-contrast effects, several studies have shown that agreement between mothers/parents and teachers or between teachers on corresponding ADHD scales generally is quite low (e.g. Sherman et al. [17]: r = 0.3 parent-teacher; Simonoff et al. [26]: r = 0.5 teacher-teacher; Thapar et al. [27]: r = 0.4 parent-teacher). This points towards the possibility that mothers/parent and teacher questionnaires might assess somewhat differing pathology. Due to this problem, attempts have been made to utilize pervasive ADHD, i.e. the categorical diagnosis obtained by mother/parent as well as teacher reports simultaneously as phenotype in molecular genetic studies to avoid inclusion of phenocopies of the disorder and to improve power of genetic association studies. It has been shown that the pervasive subtype is as heritable as the mother/parent-rated ADHD, and in some studies has shown a better predictive validity than ADHD as defined by mother/parent or teacher ratings only [20, 28, 32].

Sex Effects
The above-mentioned studies were performed in female and male children and adolescents. As the sex difference in prevalence estimates of ADHD is about 3:1 with slightly higher rates of the combined type in male individuals and slightly lower sex differences for the inattentive subtype [33, 34], twin studies have also been analyzed with regard to differing genetic and environmental effects in female and male twins. No effects of sex on heritability estimates regarding the three subtypes and only small differences in environmental effects regarding shared and non-shared environmental factors were detected. However, the pattern of associated comorbidities (see below) did differ [9, 10, 35, 36]. One study found higher rates of ADHD symptoms in the DZ co-twins or siblings of girls with ADHD compared to boys with ADHD, indicative of a polygenic multiple threshold model [37].
Comorbidity of ADHD

In children with ADHD, high rates of comorbidity are found. In a population-based sample of twins aged 8–18 years, around 70% of the children with the inattentive or the hyperactive/impulsive subtype and around 90% of the children with the combined subtype did show at least one comorbid disorder [38]. 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 [39]. ODD and CD were higher in the combined ADHD subtype only (ODD: 66%; CD: 47%), whereas MDD was associated with the inattentive (24%) and the combined subtypes (22%). Another frequent comorbidity of ADHD is reading disability (RD; around 40%), which in most studies did show a stronger association with attention problems than with hyperactive/impulsive symptoms [39–42].

Regarding the etiology of the comorbid symptoms and disorders, most studies on RD and ADHD agree with respect to common genetic factors influencing RD and inattention [43]. All of these studies used mother/parent reported problems only. In the study by Willcutt et al. [34], about 95% of the phenotypic covariance between RD symptoms of inattention was attributable to common genetic influences, whereas only 21% of the phenotypic overlap between RD and hyperactivity/impulsivity was due to the same genetic factors.

Epidemiological twin studies on maternally/paternally rated comorbidity of ADHD and ODD or CD elicited sex differences with regard to ODD/CD symptom severity with more ODD/CD symptoms in males [18]. A study in 7- to 13-year-old twins, adjusted for rater-contrast effects [36], found ODD/CD symptoms in males to be more strongly genetically determined that in females (heritability males: 66%, females: 50%). Covariation of ADHD and ODD/CD symptoms, however, did not show differences between females and males and implicated a common genetic factor underlying the comorbidity of ADHD and ODD/CD symptoms. About 50% of the additive genetic effects were shared between ADHD and ODD/CD as well as about 40% of the unique environmental effects. Interestingly, with regard to ODD/CD symptoms, no rater-contrast effects were found, contrary to the findings in ADHD. Similar findings were obtained in 5- to 17-year-old twins with or without comorbid CD symptoms. Heritability estimates for CD symptoms lay around 50%, and common genetic influences were postulated for ADHD and CD, indicating a genetically more extreme variant of ADHD [44]. However, additional shared and non-shared environmental influences were found for CD only.

Simultaneous analysis of teacher and parent/mother questionnaires obtained on 8- to 16-year-old twins did result in slightly different findings: no sex differences in heritability for ODD/CD were found, and the genetic correlation between ADHD and CD symptoms was higher (64–82%) [9]. Again, substantial environmental effects were found for ODD/CD only. Further, inattention was influenced by a different...
A genetic factor than hyperactivity/impulsivity, and this factor also did influence the comorbidity of inattention and ODD/CD.

A further study assessed covariation among childhood externalizing disorders by interviews with the 14-year-old twins themselves [45]. Again, covariation among the three disorders ADHD, ODD and CD was attributed to shared genetic influence on the disorders as well as to non-shared environmental influences. For each disorder in this study, however, also some unique environmental influences were found.

Contrary to the above reported findings, a study in 11-year-old twins found a single shared environmental factor most strongly contributing to the covariation of ADHD, ODD and CD symptoms [46]. A bigger sample from the same study was analyzed differently to also assess informant effects, as in the study child and mother interview data were obtained. In males, higher self and mother reported ADHD, ODD and CD symptoms were found than in females. Correlations of mother and child reports were around 25% [47].

Self-reports resulted in less genetic influence on the three disorders as well as in different patterns of correlations between disorders compared to the mother data implying a shared environmental factor underlying the three disorders. Analysis of mother data, on the contrary, resulted in a strong genetic factor underlying the comorbidity of the three disorders.

In conclusion, studies do not agree with regard to genetic and environmental mediation of the high rate of comorbidity of ADHD with ODD or CD. The different findings might be due to the lack of distinction of ODD and CD in some studies (see below, section on family studies), to age differences between samples or to the different measurement instruments used. As child report data do show a limited reliability and validity regarding externalizing disorders compared to parent/mother or teacher reports [48], the findings obtained from studies relying strongly on child report data should be viewed with some caution. Concluding from parent and teacher data, common genetic and non-shared environmental effects seem to influence the comorbidity of ADHD, ODD and CD, however additional genetic and environmental risk factors specific for each disorder cannot be excluded.

The impact of genetic or environmental influences on comorbidity rates of ADHD with MDD and anxiety disorders has rarely been studied in twin samples. In one study, using the latent class approach assessing information on separation anxiety, ODD and depression as well as ADHD symptoms by parent or child report in a sample of female twins aged 13–23 years, 9 latent classes emerged, of which 2 were ‘comorbid’ types, i.e. ADHD inattentive subtype + ODD and ADHD combined subtype + ODD for which heritability estimates of 63 and 81% were obtained. The ADHD combined subtype + ODD latent class comprised additional depression and anxiety items, which might be specific for a female sample [49]. These results support the previously mentioned studies with regard to common genetic as well as environmental effects underlying comorbid ADHD and ODD. No specific additional genetic effects for comorbid MDD or anxiety were detected.
Stability of Genetic and Environmental Influences on Lifespan

Longitudinal twin studies have been performed to assess the stability of ADHD diagnosis, subtype and comorbid ODD/CD to elicit genetic and environmental influences on stability and change. Three studies assessed the stability of ADHD symptoms. In the first study, twins were assessed for DSM-III-R-based ADHD symptoms at age 8–9 years old and reassessed 5 years later [50]. 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 important 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 sample of younger twins aged 2, 3, and 4 years, assessing only 4 ADHD symptoms rated by mothers/parents, a phenotypic correlation of around 50% over the years was elicited [51]. Heritability at age 2, 3, and 4 was estimated around 80% with non-shared environmental influences accounting for the remaining variance. Continuity of ADHD symptoms in this study was mediated 91% by additive genetic influences. The same sample was assessed at age 7 and 8 years by the Strengths and Difficulties Questionnaire and the Conners’ Rating Scales obtained from mothers/parents [29]. In the univariate analysis at age 8 years, in addition to additive genetic (72%) and non-shared environmental factors (14%), also shared environmental risk factors (14%) were found. Phenotypic correlation across time points 2, 3, 4, 7, and 8 years old were mediated by shared genetic influences (59–96%) and child-specific environmental influences the latter of which also accounted for change in behavior.

A third study assessed stability and change of CBCL derived Overactivity (OA) and Attention Problems (AP) in 3-, 7-, 10-, and 12-year-old twins [52]. The older the children, the more stable AP became in the individual. Across ages, additive and dominant genetic effects did influence the stability of AP (around 70%). 30% of the residual variance was explained by non-shared environmental effects. In this study, rater-contrast effects were not controlled for which might have resulted in an overestimation of genetic effects on the stability of symptoms.

One study has been performed which assessed the ADHD hyperactivity/impulsivity and inattention subtypes according to DSM-III and/or DSM-IV symptoms separately at three time points (age 8–9, 13–14, and 16–17 years old; sample of Larsson et al. [50]). Cross-type correlations were as high as subtype-specific correlations. 45–90% of the total genetic variance in each measure was explained by persistent genetic influences. However, in most cases, persistent cross-subtype influences explained more genetic variance than persistent subtype-specific influences. Additionally, age-specific genetic effects were present. Results were interpreted with regard to strongest persistent genetic influences on the ADHD combined type with some support of differential genetic influences on the hyperactive/impulsive and inattentive subtypes. Furthermore, age-limited genetic effects suggested genetic contributions to changes in symptoms of ADHD. The remaining variance again was explained by non-shared environmental effects.
Taken together, from childhood to adolescence, persisting combined ADHD as well as inattention seem to be influenced strongly by genetic effects and to a lesser extent by non-shared environmental effects. Therefore, persistent ADHD might be an interesting phenotype for molecular genetic studies. This also can be expected from ADHD persisting into adulthood. However, the problem of recall bias [5] as well as missing parental information on pregnancy and early development might lead to an increased rate of false-positive or false-negative diagnoses in adults with suspected ADHD reducing the power of molecular genetic studies.

Only one study has assessed the genetic structure underlying the persistence of ADHD and ODD/CD after 19 months in 8- to 16-year-old twins by mother and teacher rating scales [9]. Covariation among phenotypes across informants and over time were governed by a common set of genes, but not a single genetic factor. Substantial environmental effects were found for ODD/CD, but not for the covariation of ADHD and ODD/CD. The findings of this study are limited, as the sample comprised twins of a broad age range who were followed for a relatively short period. However, findings resemble the results of the cross-sectional studies, implying mainly genetic and to a lesser extent environmental risk factors for comorbid ADHD and ODD/CD as well as for their persistence. The genetic risk factors for comorbidity or persistence, however, might be distinct. Similar to persistent ADHD, ADHD with comorbid ODD/CD might be an interesting phenotype for molecular genetic studies in ADHD.

Family Studies

Resembling twin studies, family studies in ADHD have been performed since the 1980s [53, 54]. Compared to twin studies, family studies provide some advantages. They are performed on individuals with ADHD and their families, therefore excluding risk factors associated with twinning itself, e.g. low birth weight, prematurity etc. Low birth weight in one twin study has been found to strongly influence discordant hyperactivity symptoms in MZ twins [55], implying factors associated with low birth weight as either shared or non-shared environmental risk factors for ADHD. On the other hand, genetic and environmental influences cannot easily be singled out in family studies. An increase in familial recurrence risk might be due to genetic as well as environmental risk factors associated with the disorder. One environmental risk factor strongly associated with ADHD, replicated by epidemiological and twin studies, is maternal smoking during pregnancy [56–58]. Most family studies did not control for this risk factor, as it has been replicated only recently.

Adoption Studies

Adoption studies can prove both genetic and environmental influences on the disorder, however they are difficult to perform due to limited numbers of adopted children.
as well as difficulties assessing the biological parents of the adopted children. The adoption studies performed in individuals with ADHD either did not assess the biological parents of the adopted children with ADHD [59] or did not use standardized assessment of ADHD symptoms [60–62]. Also, maternal smoking during pregnancy and other risk factors were not controlled for. Therefore, the findings of these studies are limited, however all studies lent some support to the hypothesis that ADHD has a genetic component.

Segregation Studies
In addition to heritability estimates, family studies also allow to explore the mode of inheritance underlying the genetics of ADHD. Segregation analyzes in families of children with ADHD [63] were indicative of a single major gene with low penetrance in contrast to twin studies, which were indicative of a continuously underlying trait most likely mediated by several genes. To date, both models are still abundant, however, with the exception of some linkage studies [64] molecular genetic research is predominately based on the oligogenic/polygenic model with additional environmental risk factors for ADHD which is supported by most twin studies. In contrast to twin studies, the segregation study by Maher et al. [63] also implicated differential genetic effects in female and male individuals with ADHD. However, the study was based on a distinct clinical population, which limits the generalization of its results.

Family Studies in Children with ADHD
Family studies are performed to elicit the risk that an individual is affected, given that a relative is. Two measures are usually assessed. The recurrence risk is the conditional probability that a relative of a certain degree of relationship to an affected individual is also affected. An alternative measure is the relative risk, i.e. the increase in risk compared to the population prevalence, given that a relative is affected. Heritability estimates can be derived from family studies based on expected phenotypic correlation between relatives. Estimates of genetic and environmental effects on phenotypic measures can be obtained by comparing different relatives with regard to recurrence risk or phenotypic correlation. The latter has rarely been done in family studies on ADHD, as in clinical and epidemiological settings it is difficult to gather data from greater than first-degree relatives.

Rates of ADHD and Other Psychiatric Disorders in Siblings and Parents of Children with ADHD
The first family studies in hyperactive children assessed psychiatric disorders in parents [65–70]. Due to non-blind rating, non-standardized diagnoses, insufficient control for SES or inadequate control groups, the results of these studies have to be viewed with caution. A first study assessing psychopathology in parents and siblings according to DSM-III criteria by direct interview with the parents and controlling for
SES elicited higher rates of attention-deficit disorder (ADD, DSM-III), ODD and MDD in first-degree relatives of 6- to 17-year-old children with ADD (n = 21) compared to the first-degree relatives of healthy control children (n = 20) [53]. Not a single relative with bipolar disorder, mental retardation or pervasive developmental disorder was seen in children with ADD, whereas the rate of enuresis was non-significantly increased. In an enlarged sample (n = 73) with an additional psychiatric control group (n = 26) without ADD, first-degree relatives of children with ADD did show higher rates of ADD, any antisocial disorder (combined ODD, CD, antisocial personality disorder) and drug dependence than both control groups [87]. Anxiety disorders and MDD were increased in first-degree relatives of both, children with ADD and children with another psychiatric disorder. Despite the familial aggregation genetic and environmental effects cannot be fully differentiated from family studies. The latter study, however, did explore psychosocial risk factors (low social class and separation/divorce in the family of origin) which were equally distributed in families with and without ADD, rendering these factors unlikely causes of DSM-III ADD. Comparable results on increased rates of ADDH (equal to ADD in DSM-III) in parents of children with ADDH, ADDH+CD and CD but not in children with emotional disorder or control children were obtained in another family study using DSM-III-R criteria for ADDH [71]. Findings of increased rates of ADHD in parents and siblings of children with ADHD were replicated in several other studies on parents, siblings and one study on second-degree relatives of children with ADHD according to DSM-III-R or DSM-IV criteria [72–75].

Similar to twin studies, the following aspects were differentially addressed in family studies on ADHD: the validity and segregation of the DSM-IV defined subtypes inattention, hyperactivity/impulsivity and combined ADHD, sex differences, rates of comorbid disorders, and environmental risk factors associated with ADHD in children and adolescents.

**ADHD Subtypes**

Only a few family studies have been performed analyzing the familial transmission of the inattentive, combined and hyperactive/impulsive ADHD subtypes separately. A recent study provided an analysis on the pooled data of six studies, exploring the familial transmission of the inattentive and combined ADHD subtypes [76]. New data were analyzed in addition to data from two twin [6, 24] and three family studies [75, 77, 78]. Results were indicative of heterogeneity of the inattentive subtype, sharing some of its etiology with the combined type, however also including cases with non-shared etiology. Further, in boys, the two subtypes were more clearly distinguishable than in girls. With regard to the hyperactive/impulsive subtype, no clear conclusions can be drawn from the family studies, as it is the rarest subtype, and family studies therefore lacked the power to elucidate differences regarding this subtype. Only one study indicated specificity of this subtype [79]. Taken together, results from family and twin studies agree on implying a prevailing differential genetic determination of
attention problems and hyperactive-impulsive symptoms, however, with some genetic overlap between symptoms.

Sex Differences
Contrary to the studies assessing subtypes, most studies assessing ADD according to DSM-III or DSM-III-R did not find any differences between girls and boys regarding ADD and other psychiatric disorders in first-degree relatives of children with ADD [73, 79]. Only one study found a higher rate of ADHD in parents of sibling pairs who both were affected by ADHD and one of whom was female compared to male sibling pairs only [78], which might be indicative of a multifactorial threshold model, also suggested by the findings of one twin study [80]. Another study focusing on families with a parent with antisocial personality disorder or with the index child showing comorbid conduct disorder found a higher risk for ADHD in the siblings of boys with ADHD+CD but not of girls with ADHD+CD according to DSM-III-R diagnoses [81]. In families without antisocial disorders, these sex differences were not found. Findings again corroborate the results of twin studies, indicating no sex differences with respect to combined ADHD, but differential genetic and/or environmental effects in girls and boys regarding ADHD comorbid with CD and possible differences regarding the DSM-IV inattentive subtype [76].

Comorbid Disorders in Siblings and Parents
A recent review of family studies suggested that family studies based on prevalence rates might have a limited ability to lead to correct conclusions regarding the causes of comorbidity [82]. This renders the results of the presented studies preliminary.

Few family studies have been performed to elucidate the familiality of ADHD versus ADHD comorbid with ODD or CD despite the findings of high rates of ODD, CD or antisocial personality disorder in first-degree relatives in the early family studies (see above). In a study based on DSM-III diagnoses, rates of ADD were increased in first-degree relatives of children with ADD, ADD+oppositional disorder (OD according to DSM-III) and ADD+CD [83]. Morbidity risk for ADD, however, was highest in relatives of children with ADD+CD, implying ADD+CD as a more severe phenotype of ADD, which also has been suggested from results of some twin studies. Antisocial personality disorder was highest in relatives of children with ADD+CD and ADD+OD. In several studies implementing DSM-III-R or DSM-IV criteria, first-degree relatives of children with ADHD+CD did show higher rates of depression, substance abuse and antisocial personality disorder than families of children with ADHD without CD, of which maternal depression and paternal antisocial personality disorder seem to be a specific risk factor for comorbid CD in the offspring [78, 84–87].

Despite higher rates of anxiety disorders in parents of children with ADHD [85, 88, 89] two studies implementing DSM-III or DSM-III-R diagnoses found an independent segregation of anxiety disorders and ADD/ADHD, implying differential risk
factors for both types of disorders [90, 91]. Another study assessing anxiety disorders in parents of young children with ADHD with or without comorbid ODD/CD found increased rates of anxiety disorders in mothers of children with ADHD+CD compared to healthy control children diagnosed according to DSM-III-R criteria [85]. However, when results were adjusted for comorbid anxiety disorders in children, the association of child ADHD+CD with anxiety disorder in the mother disappeared, again implying differential risk factors for both types of disorder.

With regard to MDD in parents of children with ADD, one early study implementing DSM-III criteria found an independent segregation of ADD and MDD [92]. More recent studies using DSM-III or DSM-III-R criteria, however, found some support for a familial link of ADHD and depression, which was most pronounced in ADHD families with antisocial disorders [85, 93–95]. Similarly, in several studies rates of ADHD in children of depressed parents were higher than in children of control parents [96–102]. In a review article on the comorbidity of MDD and ADHD [103] it was concluded, however, that the link between depression and ADHD seemed to be only partially accounted for by comorbid CD or antisocial personality disorder in the family, as depression also was increased in relatives of children with ADHD without CD in some studies. Comorbid MDD and ADHD in children and their first-degree relatives seemed to be influenced by psychosocial risk factors, i.e. marital discord, low social class, large family size, paternal criminality, maternal mental disorder and foster placement, rather than genetic risk factors [104, 105]. Depression in mothers has been related to increased ODD and CD symptoms, predominantly in boys with or without ADHD, therefore presenting a major environmental risk factor for ADHD comorbid with other psychiatric disorders [85, 106].

In addition to MDD, an increased rate of bipolar disorder has been suggested in children with ADHD and their first-degree relatives [107, 108]. A recent study in children with bipolar disorder and ADHD, however, did show that bipolar disorder-I in children and adults share the same diathesis, and ADHD is another, unrelated disorder [109].

A few family studies have explored familiality of ADHD with specific learning disability [110–112]. Specific learning disability and low IQ did not cosegregate with ADHD in most studies despite high rates of reading and writing disability in children with ADHD [113]. These findings differ from the results of twin studies on reading disability and ADHD (see above), which might be due lack of a separate assessment of the inattentive subtype in the family studies.

Other comorbid disorders, which are frequently found to be associated with ADHD in clinical or epidemiological samples, like primary nocturnal enuresis [114] or tic disorders [115, 116], were rarely explored in family studies on ADHD. Two family studies have been performed with regard to ADHD comorbid with Tourette's disorder (TD) [111, 117]. Both studies suggested some relationship of TD with ADHD, however the hypothesis that cases of ADHD might represent a variant expression of TD was refuted. Likewise, TD seemed not to be simply a variant expression of
ADHD. ADHD+TD as well as ADHD and TD seemed to co-occur more frequently in some families, implying heterogeneity in ADHD with regard to comorbid TD. In ADHD+TD families, additionally increased rates of obsessive compulsive disorders (OCD) were found, which also have been described in other studies, implying a unique familial subtype [118, 119].

**Longitudinal Family Studies**
Three longitudinal family studies have been published which focused on the differences between families of children with ADHD without and with comorbid CD. The first study did follow a sample of 140 children with ADHD and 120 normal control children and their siblings for 4 years into adolescence, who were compared with regard to DSM-III-R diagnoses derived from diagnostic interviews with mother and child. Cross-sectional data did show a higher risk for CD in siblings of children and adolescents with ADHD+CD, but not for children with ADHD+ODD or ADHD alone. This pattern was maintained over the 4-year follow-up period, pointing towards ADHD+CD as a distinct subtype of ADHD [103]. In the second study, a somewhat different approach was taken assessing antisocial families, defined by the presence of antisocial personality disorder in a parent according to DSM-III-R [120]. Antisocial personality disorder in a parent at baseline predicted the presence of CD and ODD in the child 4 years later. Siblings of ADHD children with antisocial personality disorder in a parent compared to families of children without had higher rates of alcohol or drug abuse or dependence. ADHD children from antisocial families did differ from ADHD children from non-antisocial families with regard to comorbid CD and alcohol or drug abuse or dependence, after correcting for IQ differences. Elevated rates of ODD, anxiety disorders and MDD were found in both types of ADHD families. Together with the results of cross-sectional studies [81], the longitudinal studies therefore point towards ADHD+CD as a distinct subtype of ADHD, not including ODD.

**Family Studies in Adult Individuals with ADHD**
Despite increasing knowledge about ADHD persisting from childhood into adulthood [121] and recognition of adult ADHD [122], family studies on individuals with adult ADHD and their children or other relatives are scarce. Patterns of comorbidities in adults with ADHD are similar to psychiatric disorder patterns found in parents of children with ADHD, i.e. increased rates of comorbid MDD, dysthymia, anxiety disorders, conduct or antisocial personality disorder and substance abuse/dependence with highest rates in the DSM-IV combined ADHD subtype [122–125]. However, from these patterns, no conclusions with regard to specific genetically or environmentally influenced subtypes can be drawn. Studies on the impact of exposure to parental ADHD on their offspring did show an increased risk for ADHD in children of parents with ADHD, also associated with greater environmental risk factors, especially family conflict [126, 127]. Parental ADHD in one study was independent of
family conflict, in the other study, family conflict was directly influenced by parental ADHD.

Conclusions

Family and twin studies on ADHD in children and adolescents resulted in a strong heritable component of 60–80% for ADHD. Rates of comorbidity as well as persistence or remittance of the disorder during the lifespan indicate heterogeneity of ADHD, which also might be found regarding the inattentive and the combined ADHD subtype. 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 a single major gene with low penetrance. Twin and family studies agree with regard to missing sex differences in the genetic risk for ADHD. Similarly, both types of studies pointed towards ADHD+CD as a strongly genetically influenced subtype of ADHD, however also showing some specific environmental risk factors. Another interesting subtype with strong associated genetic risk factors might be persistent ADHD into adulthood. The presented studies did differ considerably with regard to diagnostic criteria, rating scales or interview methods as well as environmental risk factors addressed. Major problems in studies of children and adolescents/adults with ADHD are informant effects with regard to mother/parent and self-rating. Therefore, pervasive ADHD as defined by meeting criteria in two different settings should be used as the target phenotype in molecular genetic studies.

References


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