Summary

The aims of this thesis were i) to investigate sex differences in attention problems, hyperactivity and attention deficit hyperactivity disorder (ADHD), ii) to further the development of statistical methods necessary for the analysis of phenotypic data on a variety of measures of ADHD, and iii) to examine the aetiology of individual differences of ADHD and related behavior problems.

Aim 1: Investigation of sex differences in attention problems, hyperactivity, and ADHD
Sex differences in ADHD were the main focus of interest in chapters' three to five, with an interest in measurement. Chapter three addressed the question whether the higher prevalence of ADHD and oppositional defiant disorder in boys is the result of different liabilities for these disorders, or, alternatively, is due to measurement bias. To investigate the role of measurement bias, we examined if the four scales of the Conners Teacher Rating Scale (CTRS) (Oppositional behavior, Cognitive problems-Inattention, Hyperactivity, and the ADHD-index) measure the same construct, i.e., the same latent variable of interest, in boys and girls. In addition, we studied the presence of quantitative and categorical sex differences in the genetic and environmental contributions to variation in these behaviors. No sex differences in the factor structure of the CTRS were found, which implies that the CTRS is measurement invariant with respect to sex. The heritability (56-71%) was similar in boys and girls. However, constraining the genetic correlation at .5 in opposite sex twins resulted in a significant decrease in model fit for all four scales which supports the idea that in part different genes contribute to individual differences in problem behavior of boys and girls at school.

In chapter four, we examined the relation between Child Behavior Checklist-attention problem (CBCL-AP) scores and the 4th edition Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of ADHD. Children with a low maternal AP-score obtained a negative ADHD diagnosis in 96% of cases. Children with a high AP-score obtained a positive diagnosis in 36% (girls) and 59% (boys) of cases. The positive predictive power of CBCL-AP was significantly greater in boys than girls. A stronger relationship between CBCL-AP and DSM-IV ADHD in boys than girls was

further supported by larger correlations between CBCL-AP and ADHD symptom scores in boys than in girls. In addition, the results of regression analyses show that in children with elevated AP-scores, the number of predicted ADHD symptoms is greater in boys than girls.

Chapter five focuses on the discrepancy of the male:female ratio for ADHD in general populations (3:1) and in clinical settings (9:1). I investigated if this discrepancy was the result of different referral rates in boys and girls. It was shown that boys with ADHD are more often referred for treatment than girls with ADHD. A number of possible explanations for the sex difference in referral rate were investigated. Boys and girls with ADHD showed similar levels of psychiatric illness and school impairment (such as being held back, special class placement, and learning problems) by maternal report. Mothers also reported similar levels of aggression and attention problems in boys and girls with ADHD. In contrast, teachers consistently rated boys with ADHD as having higher scores on reports of attention problems and ADHD related behavior than girls with ADHD. It was concluded that sex differences vary across settings: boys and girls with ADHD are rated as behaving differently at school, but not at home. The higher level of teacher reported problem behavior at school may explain the high male:female ratio for ADHD in clinical settings.

Aim 2: Methodological issues in twin studies of attention problems

A number of methodological issues are particularly relevant to twin studies of behavior problems. The goal of the simulation study in chapter six was to investigate the optimal selection design for the situation in which a cheap measure (X) is observed in a large, representative twin sample and a more expensive measure (Y) is observed in a selected subsample of the twins. This simulation was important to my own study design in which interview data were collected in twins who were selected based on questionnaire data. Scores obtained on X are used to select the most informative twin-pairs with respect to the detection of genetic and environmental influences on the variance of Y. Missingness was introduced in accordance with six selection designs. The percentage of missing data was 88%. It was shown that the selection of informative pairs is most effective when the correlation between traits X and Y is high. The decrease in statistical power as a result of

missingness is relatively small. Furthermore, it was found that a design that selects on an individual level rather than on a pair-wise level, is the best design for detecting influences of A, C, and D. However, the extreme discordant and concordant (EDAC) design is to be preferred, if an additional purpose of a study is to detect Quantitative Trait Loci.

Chapter 7 focused on one of the characteristics of rating scales, namely the skewness and kurtosis in the distribution of the sum scores of behavior problems. Genetic and environmental influences on variance in phenotypic traits are usually estimated with normal theory Maximum Likelihood (ML). However, when the assumption of multivariate normality is not met, this method may result in biased parameter estimates and incorrect likelihood ratio tests. When fitting an ACE model to censored data, ignoring the non-normality leads to an unbiased estimate of the additive genetic effects, underestimation of the shared environmental effects, and overestimation of the non-shared environmental effects. Square root transformation and the use of normal scores did not remove this bias. When fitting an ADE model, the additive genetic effect was underestimated, while the dominant and non-shared environmental effects were overestimated. In all models, the correct parameter estimates were recovered with categorical data analysis. However, with categorical data analysis, the statistical power to detect genetic and environmental influences was lower.

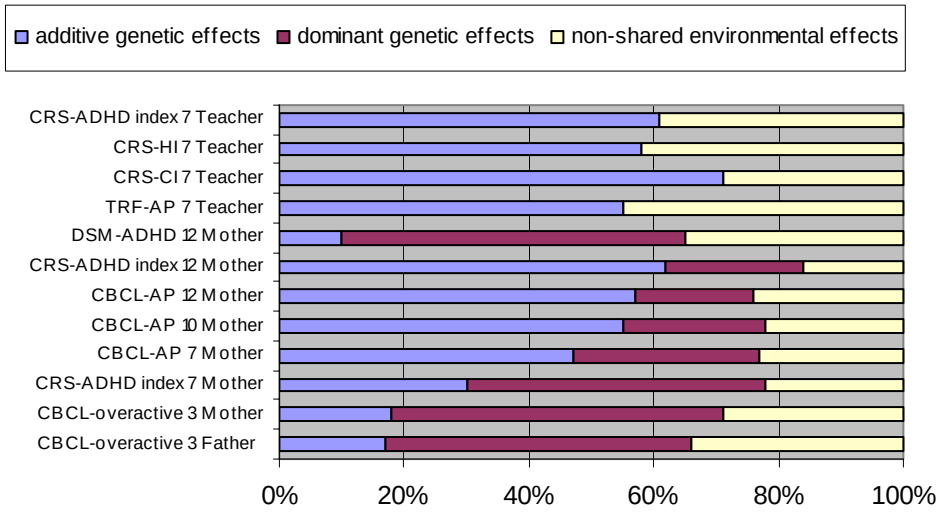
Chapter eight examined a new method to detect violation of the Equal Environment Assumption (EEA) based on multivariate data. In the classic twin design, estimation of genetic and environmental effects is based on the assumption that environmental influences are shared to the same extent by MZ and DZ twins (EEA). We explore the conditions in which the EEA can be tested by estimating the shared environmental correlation in DZ twins using multivariate phenotypic data. Model identification was investigated and the statistical power to detect violation of the EEA was examined in Mx. The amount of bias caused by ignoring violation of the EEA was evaluated. It was shown that bivariate and trivariate models include several instances in which the EEA can be tested. The number of twin-pairs that is needed to detect violation of the EEA with a statistical power of .80 ($\alpha = .05$) varied between 508 and 3576 pairs for the situations considered. The bias in parameter estimates, given misspecification, ranged from 5-34% for additive genetic effects, and from 4-34% for shared environmental

effects. Estimates of the non-shared environmental effects were not biased. The analysis of empirical data on spatial ability and aggression indicated no detectable violation of the EEA.

Aim 3: Studying aetiological influences on individual differences in attention problems, hyperactivity, and ADHD

In chapters 3, 9, 10, and 11, we estimated the influences of additive genetic (A), dominant genetic (D), and non-shared environmental influences (E) on individual differences in attention problems, hyperactivity, and ADHD across informants, instrument, and age. Figure 1 summarizes the results of these studies including the results of a study of Hudziak et al. (2005), in which genetic and environmental influences on maternal Conners Rating Scale-ADHD index scores were estimated using data collected in the Netherlands Twin Registry.

Figure 1 Percentages of total variance explained by additive genetic (A), dominant genetic (D) and non-shared environmental (E) effects in 3, 7, 10, and 12 year old children



Note: CRS=Conners Rating Scale; TRF=Teacher Report Form; DSM=Diagnostic Statistical Manual of Mental Disorders; CBCL=Child Behavior Checklist;

AP=attention problems, HI=hyperactivity, ADHD=attention deficit hyperactivity disorder, CI=cognitive problems-inattention

Genetic influences explain the greatest proportion of Individual differences in parental ratings of attention problems (66-84%). Non-shared environmental effects explain the remaining variance. The heritability of teacher ratings on attention problems is somewhat lower, and ranges between 55-71%. Figure 1 shows that the broad-sense heritability does not vary much as a function of age. For example, the broad-sense heritability of the maternal rated CBCL-AP scale is 77% at age 7, 78% at age 10, and 76% at age 12. The amount of total genetic variance attributable to additive (A) versus dominant (D) genetic effects does vary as a function of age and instrument. At age 3, the genetic variance is mainly explained by D, and to a smaller extent by A. As children grow older, the influence of D decreases, and the influence of A increases. An exception is formed by the DSM-ADHD symptom scores, which were collected by means of a structured clinical interview at age 12. Variation in these symptom scores almost entirely results from dominant genetic effects.

In chapter nine, we investigated the degree to which the genetic and environmental effects are moderated by informant in a sample of 9,689 3-year-old twin pairs. Rater Bias and Psychometric Models were fitted to CBCL/2-3 data obtained from mothers and fathers to determine the genetic and environmental contributions to five CBCL syndromes: aggressive, oppositional, overactive, withdrawn, and anxious/depressed behavior. Parental ratings were found to be influenced by aspects of the child's behavior that are experienced in the same way by both parents and by aspects of the child's behavior that are experienced uniquely by each parent. There is evidence for large genetic contributions to individual differences in all CBCL syndromes. Shared and non-shared environmental influences play significant roles as well. One exception is overactive behavior, which is only influenced by genetic and non-shared environmental influences.

In chapter 10, the genetic and environmental influences on maternal and teacher ratings of Attention Problems (AP) were examined in 7-year-old children. Teachers completed the Teacher Report Form (N=2259 pairs), and mothers completed the Child Behavior Checklist (N=2057 pairs). Higher correlations were found in twins rated by the

same teacher than in twins rated by different teachers. This was explained by a correlated error in same teacher ratings. This correlated error is either the result of i) raters having their own subjective view on which behaviors are appropriate and which are not, or ii) the influence that a rater has on the behavior of the child because of the rater's own personality characteristics. We further found that 41% of the variance in maternal and teacher ratings is explained by a common factor. The broad-sense heritability of this common factor is 78%. The broad-sense heritabilities of the rater specific factors of mothers and teachers are 76% and 39%, respectively. The fact that the rater specific factors are heritable indicates that mothers and teachers assess unique aspects of the child's behavior.

The aim of chapter 11 was to investigate the extent to which individual differences in maternal ratings on three different instruments that assess attention problems and ADHD, reflect the same genetic and environmental influences. The total sample for whom at least one maternal ratings was available consisted of 10916 twins from 5458 families. Child Behavior Checklist (CBCL) ratings were available for 10018, 6565, and 5780 twins at the ages 7, 10, and 12, respectively. The Conners Rating Scale (4887 twins) and the DSM interview (1006 twins) were completed at age 12. Statistical analyses showed phenotypic correlations of the three instruments in the range of .45 to .77. The variances and covariances of the five instruments were mainly explained by genetic influences. The genetic correlations of the data collected at age 12 varied between .61 and 1.00. In conclusion, the genetic overlap between behavior checklist scores and the DSM-IV diagnosis of ADHD is large. This implies that the costs of gene finding studies can be reduced by collecting survey data instead of diagnostic interview data.

The objective of chapter 12 was to investigate the specific environmental influences that play a role for attention deficit hyperactivity disorder (ADHD). A sample of twins was followed longitudinally from birth onwards. Questionnaires were completed by mothers (ages 1, 2, 3, 7, 10, and 12 years), teachers (age 7, 10, and 12 years), and the twins themselves (12 years). Mothers completed a structured clinical interview. From the large longitudinal sample, discordant monozygotic twin-pairs were selected and matched with concordant pairs. The final sample (95 pairs) consists of discordant, concordant-high, and concordant-low twin-pairs. Child-specific environmental influences were

compared between the affected and unaffected twins within the discordant pairs. Environmental factors that are shared by the two members of a twin-pair (e.g., maternal smoking during pregnancy) were compared between the discordant, concordant-high and concordant-low groups. The affected members of the discordant twin-pairs scored higher than the unaffected members on a wide variety of measures of AP, ADHD, and other behavior problems according to the mother, teacher and self. Affected members had lower birth weight and poorer early motor development than unaffected members. Differences between discordant, concordant-low, and concordant-high groups were reported for maternal smoking, sleeping in different rooms, and living with only one of the parents. Maternal smoking was more common in the concordant-high group than in the concordant-low group. The discordant twins did not differ from the concordant twins. Sleeping in separate rooms was more common in discordant pairs than in concordant low pairs at the ages 2-6 years. More concordant-high pairs lived with only one parent than concordant-low or discordant pairs.