

*Risk factors for the development and outcome
of childhood psychopathology*

SUMMARY AND DISCUSSION



Chapter 9

In this chapter I present a summary of the results of the studies described in this thesis followed by a discussion of the research and clinical implications.

Summary

In the first part of my thesis, several issues were addressed that looked at 1) designs in genetics with phenotypes obtained from different raters simultaneously, to obtain more reliable estimates of the influences of genetic and shared environmental factors on childhood psychopathology, 2) the differences between raters or informants in the assessment of childhood psychopathology and 3) the role of genetic and non-genetic factors on childhood psychopathology across ages and how such factors might explain stability over time.

Chapter 2 reports the results of a twin study estimating the role of genetic, shared environmental, and non-shared environmental factors on individual differences in affective, anxiety, somatic, attention deficit hyperactivity disorder (ADHD), oppositional-defiant disorder (ODD), conduct disorder (CD), and obsessive-compulsive (OCD) problems in 7-year-olds. Parents completed a checklist on their twin offspring and agreed to a large extent about the level of problem behaviors in their children (correlations between .6 and .75 for the different problem scales). The correlations between parental assessments did not depend on the child's gender. Differences between parents in the assessment of childhood psychopathology were also observed. Maternal ratings of childhood psychopathology were higher than the paternal ratings for all scales, regardless of the child's gender. Maternal and paternal ratings were analyzed simultaneously in a psychometric model, which decomposes the variances of the mother and father ratings into a part the parents agree upon (the common part) and into two uncorrelated parts reflecting the disagreement (the rater-specific parts). A psychometric model for data from multiple raters provides more reliable estimates of the influences of genes and the shared environment on childhood psychopathology than a model for data from a single rater by estimating the effect of genes on the common plus rater-specific part and the effect of the shared environment solely on the part of the variance the parents agree upon [97]. Genetic factors generally explained around 60% of the variance, except for childhood ADHD in which genes explained around 80% of the variance. For the phenotype which both parents agreed upon, shared environmental influences were significant for affective problems (13%), ODD (13%) and particularly high for CD (37%). Furthermore, as the rater-specific parts of parental ratings were also influenced by significant genetic influences and shared environmental influences, it could be

inferred that both parents assess unique aspects of their child's behavior, which are reliable, as indicated by heritability and maybe biased as indicated by the shared environmental influences.

Chapter 3 of this thesis introduced data from another group of raters, i.e., teachers, and aimed to answer two questions. First, do informant discrepancies depend on the gender or age of the child, or on the psychiatric symptoms assessed? Second, are mean differences in reports from men and women on childhood psychopathology found for parents as well as for teachers? We explored these question for internalizing and externalizing psychiatric symptom scores. Overall, significant mean differences in ratings of childhood psychopathology were observed between mothers and fathers. The paternal ratings for aggressive, attention, anxiety and emotional problems in 5 year-old children were higher than maternal ratings. The opposite was seen in 7, 10 and 12 year-old children, with the maternal scores exceeding paternal ratings for affective, anxiety, somatic, ADHD, ODD and CD problems. The differences between mothers and fathers were present for both boys and girls and for all behavioral domains. In contrast, female and male teacher ratings only differed for 12 year-old boys, with female teachers reporting more problems than male teachers. Gender of the informant thus only consistently influenced parental ratings and not teacher ratings.

Chapter 4 describes a longitudinal genetic analysis of conduct and adult antisocial personality problems. We explored how genetic and non-genetic factors influence individual differences over age and the persistence of the problems from childhood into adulthood. Mean symptom scores differed between males and females at all ages, with males having higher scores. However, the proportions of variance explained by the genetic and environmental factors did not differ between the sexes and the same factors seemed to be of importance in males and females. The effects of genetic and shared environmental factors on individual differences in conduct problems in 9-10 year-olds were similar, both explaining ~44% of the variance. In contrast, in adolescents and adults, the effect of the shared environment was absent and genetic and non-shared environmental effects accounted for 49% and 51% of the differences in adolescents and 43% and 57% in adults. Stable genetic factors mostly explained the persistence of conduct problems into adult antisocial personality problems. The observed longitudinal correlations varied between .20 and .38 and the genetic correlations varied between .39 and .67.

The second part of this thesis addressed issues regarding parental psychopathology in families with children with psychopathology in clinical samples, namely 1) resemblance in spouses for psychopathology in the clinical sample compared to spousal resemblance in the general population, 2) the influence of comorbid disorders on associations between parents and offspring for psychopathology and 3) the comparison of maternal and paternal psychopathology prevalence rates and the associations with their children's psychopathology.

Chapter 5 reports on the spousal resemblance (resemblance between partners) in psychiatric symptoms of parents of children with psychopathology and the spousal resemblance in parents of children from the general population. We analyzed spousal correlations within and across symptoms of depression, anxiety, avoidant personality problems, ADHD, and antisocial personality problems. Almost all spousal correlations were significant within and across the internalizing and externalizing symptom domains in both samples. However, the spousal resemblance was significantly higher, sometimes almost twice as high, in the parents of children with psychopathology. There was significant asymmetry with respect to gender in the clinical, but not in the population-based sample. Paternal ADHD correlated higher with maternal internalizing and externalizing symptom scores than maternal ADHD with paternal internalizing and externalizing symptom scores. Maternal antisocial personality problems correlated higher with paternal internalizing and externalizing symptom scores than vice versa. In addition, parents in the clinical sample had higher mean psychiatric symptom scores than parents in the population-based sample. Overall, these results showed that parents whose children are evaluated at a child and adolescent outpatient clinic were at an increased risk to suffer from a variety of psychiatric symptoms, and were at an increased risk to have a partner with, not necessarily equivalent, psychopathology.

Chapter 6 describes a study on prevalence rates of parental depressive, anxiety, ADHD, avoidant personality and antisocial personality symptom scores and the associations with psychopathology in their offspring. Around 10-15% of the parents had a (sub)clinical score on depressive and avoidant personality problems, around 10% on ADHD problems, and around 24% had a (sub)clinical score on any of the psychiatric symptom scales. These prevalence rates did not differ between mothers and fathers. Maternal anxiety was associated with all offspring problem scores and maternal ADHD problems were associated with offspring ADHD problems. Paternal anxiety was associated with offspring depression and anxiety and paternal ADHD with offspring ADHD and ODD. These associations did not differ

between boys and girls and were not due to spousal resemblance for psychopathology. We also included a large sample of fathers. The prevalence rates for maternal and paternal psychopathology were similar and the associations with offspring psychopathology were in the same order of magnitude for mothers and fathers.

In *Chapter 7* it was investigated whether there are child, parental, or family characteristics that are associated with an increased risk for psychopathology in parents whose child is evaluated in a psychiatric outpatient clinic. We examined whether relationship status of the parents, their education level, occupational status, age and gender and their offspring's age, psychiatric diagnosis, and the presence of comorbidity in the child predicted parental depressive, anxiety, ADHD, avoidant personality and antisocial personality problems. In this large sample of 1,805 mothers and 1,361 fathers from 1,866 children, 35.7% of mothers and 32.8% of fathers scored (sub)clinical for at least one symptom domain, mainly depressive, ADHD or, only in fathers, avoidant personality problems. The parental psychiatric symptoms were generally predicted by unemployment of the parent. Parental depressive and ADHD problems were further predicted by offspring depression and offspring ADHD respectively, in addition to not being together with the other parent. Moreover, parental avoidant personality symptoms were predicted by offspring pervasive developmental disorders. Overall, these findings suggest that parental psychiatric symptom scores are mainly associated with adverse circumstances of the family and with similar psychopathology in their child.

Chapter 8 presents a longitudinal analysis to study the effect of internalizing and externalizing parental psychiatric symptoms on the child's outcome of psychopathology. Parental and offspring psychiatric symptoms were first measured at the time the child was evaluated in a psychiatric outpatient clinic, i.e., baseline, and again at follow-up after a period of on average 1.7 years. Both the offspring's psychopathology as well as the parental psychiatric symptoms decreased over time. Children with parents scoring above threshold for any of the psychiatric symptoms at baseline scored higher at baseline. Although the relative improvement was not smaller in children of parents scoring above the (sub)clinical threshold than in children of parents scoring in the normal range, at follow-up, the children of parents with psychopathology still scored higher. These higher scores at follow-up were not explained by long-term effects of parental psychiatric symptom scores at baseline. Instead, the child's follow-up scores were for the largest part predicted by the child's symptom score at baseline, in addition to predictions of concurrently measured

parental psychiatric symptoms present at time of the follow-up. The magnitude of the parent-offspring associations for psychopathology were of a similar strength for mothers and fathers and remained present when controlling for spousal resemblance. Overall, the higher scores in children at follow-up with parents with psychopathology were explained by a higher severity at baseline in addition to an association with parental psychiatric symptoms at follow-up.

Discussion

In this thesis, I addressed some of the outstanding issues regarding the heritability and assessment of childhood psychopathology in data from twins registered with the Netherlands Twin Register (NTR) [83], and looked at questions regarding familial factors associated with childhood psychopathology and its outcome in data from families with a child with psychopathology evaluated at a psychiatric outpatient clinic.

A major strength of the large population-based twin sample was that it offered possibilities to explore informant effects, effects of genotype x gender and genotype x age interaction, and to estimate the influence of genetic, shared and non-shared environmental factors on childhood psychopathology. Population-based samples have the advantage to be representative for the population, but they include a relatively small proportion of individuals with (multiple) psychiatric disorders. The large clinical sample provided the possibility to examine familial factors associated with childhood psychopathology in families at the extreme end of the distribution, and to study the implications of familial clustering of psychopathology for psychiatric outpatient clinics treating children with psychiatric disorders. A clinical sample, though, includes fewer individuals and may lack the generalizability to the general population. Furthermore, parent-offspring associations in the clinical sample do not allow drawing conclusions about causal influences of the shared environment or genes. Overall, both the population-based and clinical sample were complementary in the quest for finding risk factors for the development and outcome of childhood psychopathology in this thesis.

In all studies I analyzed the DSM-oriented problem scales of the age-appropriate versions of questionnaires belonging to the Achenbach System of Empirically Based Assessment (ASEBA). The questionnaires were originally developed to assess behavioral and emotional problems across a series of empirically defined scales based on exploratory and confirmatory factor analysis [99,175]. In contrast, the items defining the DSM-oriented scales were selected when experienced

psychiatrists and psychologist knowledgeable about ages 6-18 or ages 18-59 judged the item to be highly consistent with the relevant DSM-IV diagnostic category [99,101,175]. While scores on the DSM-oriented scales are associated with the presence or absence of DSM diagnoses [99], they are not the same. On the other hand, the strength of using these questionnaires is that they were designed to measure similar constructs over ages, which makes them especially suitable for studying parent-offspring associations and longitudinal analyses. Moreover, since these scores are continuous measures, they contain more information on the variation in psychiatric symptoms.

Implications for future research and clinical implications

By analyzing maternal and paternal ratings simultaneously, I found that shared environmental influences, corrected for rater bias, were only significant in 7 year-olds for affective, ODD and CD. Contrary to our finding that OCD is not influenced by familial factors, van Grootheest et al. [9], in a multiple informant design, estimated an unbiased effect of the shared environment of 10% on OCD in 7 year-olds. However, the study in this thesis used a larger sample size and analyzed the data with a liability-threshold model, which leads to more accurate estimates of genetic, shared and non-shared environmental effects in skewed data [110]. As significant rater bias in the assessment of a variety of psychiatric symptoms has been reported in children at other ages as well [6-22], I tend to conclude that familial environmental influences reported by earlier studies [102,103] relying on a single parent might have overestimated the effect of the shared environment due to a bias in rating childhood psychopathology.

Our findings confirmed the large role of genetic factors on childhood psychopathology as well as on its stability over age. This underlines the need to identify the genetic variants associated with these phenotypes to shed light on the etiology. The successes to find genetic variants associated with psychiatric disorders like, for example, schizophrenia [263] and, recently, also ADHD (submitted) demonstrate that increasing the sample size is one of the fruitful strategies. Given the high correlations for the genetic factors influencing maternal and paternal ratings, it has been suggested that aggregating multiple raters in molecular genetic studies can also improve power [129]. These studies do need to take into account the systematic mean differences which were observed between maternal and paternal ratings. This can either be done by separate analyses of maternal and paternal ratings

followed by meta-analysis or by correcting for these differences in maternal and paternal scores before performing the genetic association analysis.

Our study on rater differences also raised some questions for further research. Paternal scores were higher than maternal scores of psychiatric symptoms as measured by the Devereux Child Behavior in 5 year-old children, while maternal scores exceeded the paternal scores of psychiatric symptoms in 7, 10 and 12 year-old children as measured by the Child Behavior Checklist (CBCL). An explanation for this contrast besides an effect of age of the child, might be the difference in measurement instrument. Paternal scores exceeded the maternal scores of childhood psychopathology in 4-5 year-olds on the Strength and Difficulties Questionnaire (SDQ) [138,149], however, mothers have also been found to rate the problems as measured by the empirical subscales of the CBCL in their 3 year-old children as more severe than fathers [16]. More insight into parental informant differences determined by the measurement instrument by administering the same set of instruments to parents of a large group of children will resolve these questions.

I furthermore established that gender of the informant could not explain parental informant discrepancies as gender of the informant only consistently influenced parental discrepancies and not the discrepancies between female and male teacher ratings of childhood psychopathology. The question then remains why fathers and mothers differ in their assessment. Does difference in time spent with a child play a role? That would mean that in families where fathers and mothers spent equal time with their children, differences would be smaller. Does it depend on the circumstances the rater is with the child? Teachers observe children in a standardized environment, whereas parents have broader opportunities to interact with their offspring in larger variety of environments. Possibly this may explain why mothers rate their boys' and girls' behavioral problems as more severe than fathers, and also why such differences are not seen for male and female teachers.

Until there is more knowledge on the reasons for the discrepancies between parents, when considering multiple ratings of the same child it is important to keep in mind that ratings from mothers and fathers differ in mean levels, but that there is no "better parent" to consult in the assessment of childhood psychopathology since the genetic epidemiological analyses showed that both parents provide valuable unique information on their child's behavior and both parents are slightly biased in their assessment.

Do the results of our longitudinal analysis on conduct problems imply that the shared environment is not important anymore after childhood? I found a particularly high influence of the shared environment on conduct problems in 7 year-olds (37%) and 10 year-olds (40%). However, the effects of familial factors on conduct problems disappeared in adolescence and on antisocial personality problems in adulthood. If the shared environment is only of temporary influence during childhood this could mean that interventions should focus on other factors. However, family-oriented interventions in which improvement in behavioral problems is achieved by involving parents and children, have been shown to be moderately effective in reducing levels of conduct problems, not only in childhood, but also in adolescence [264,265]. Therefore, I speculate that shared environmental factors that explain differences in conduct problems during childhood may include protective factors that lose their influence during adolescence due to a changed parental role, e.g., different parental monitoring [186]. This could explain the absence of the influence of familial factors on adolescent conduct problems, while at the same time treatment involving the familial environment may reduce adolescent conduct problems. Perhaps future research could shed a light on the impact of parental monitoring on conduct problems in children and adolescents, as this may provide insight into its protective ability and thus may be helpful in the quest for finding effective treatment for conduct and antisocial personality problems.

One of the consequences of the fact that psychiatric disorders can run in families is that family members of individuals assessed for psychopathology are also at an increased risk.

All studies in the second part of this thesis analyzed multiple internalizing and externalizing parental and offspring psychiatric symptoms simultaneously and were therefore able to provide insight into within as well as across symptom associations, while controlling for the frequent comorbidity of psychiatric disorders. Noteworthy is that when we took comorbidity of psychiatric disorders into account, many cross-sectional and longitudinal parent-offspring associations for psychiatric symptoms disappeared. In addition, when taking the concurrent parent-offspring associations into account, i.e. parent offspring psychopathology measured at the same time, we hardly found any longitudinal associations between parental psychopathology at baseline and offspring outcome at follow-up. All in all, findings of parent-offspring associations without controlling for comorbidity may be due to associations between psychiatric symptoms within the individual and findings of longitudinal parent-

offspring associations may be due to parental psychopathology present at time of the follow-up measurement.

The comparisons of paternal and maternal psychopathology prevalence rates and the associations with child psychopathology did not show large differences between mothers and fathers. Overall, the studies in this thesis clearly emphasize the need to also include fathers in both research studies on the aggregation of psychopathology in families as well as in screening and offering subsequent treatment in psychiatric outpatient clinics.

I found that 35.7% of mothers and 32.8% of fathers scored (sub)clinical for at least one symptom domain, mainly depressive symptoms, ADHD or, only in fathers, avoidant personality problems. Parents of a child with psychopathology also more often both experience, not necessarily equivalent, psychiatric symptoms than parents of a child without psychopathology. An increased risk for parental psychopathology was seen in parents who were unemployed or not together with the other biological parent. The longitudinal study showed that children with parents with psychopathology had a poorer prognosis, which was mainly explained by a higher severity at baseline in addition to the presence of parental psychiatric symptoms at follow-up. All these associations do not imply a direction of effect. Parents in the clinical sample could, for example, more often be both affected by psychopathology due to the stress experienced as a consequence of the child's symptoms. It is, however, also likely that it is due to the fact that children of parents who both suffer from psychopathology have a higher risk for psychiatric symptoms and, thus, to be referred to a psychiatric outpatient clinic.

To conclude, these findings indicate that there is a group of children seen in child and adolescent psychiatric outpatient clinics that is especially disadvantaged. Future studies should focus on how the treatment of children with more severe symptoms should be adapted to improve their prognosis. Given the association with parental psychopathology, an obvious question is whether treatment of parental psychiatric symptoms improves the treatment effectiveness and long-term outcomes in the child. This argues for bridging the gap between child psychiatry and adult psychiatry and establishing clinics that provide integrated care for the whole family.