Risk factors for the development and outcome of childhood psychopathology

INTRODUCTION

Chapter 1
This thesis is about factors that influence the development and/or persistence of childhood psychopathology, including genetic as well as other familial factors. Risk factors for psychopathology are investigated in two different samples: a large population-based twin sample and a clinical sample of families with children with psychopathology.

Psychiatric disorders run in families. This can partly be explained by genetic factors. Earlier twin-family studies have estimated the heritability for childhood psychiatric disorders to range between 40% (for e.g. depression and anxiety) and 80% (for e.g. attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)) [1-3]. In addition, familial or shared environmental factors, i.e., factors shared by children growing up in the same family, appeared to explain familial resemblance for psychiatric disorders or traits. Shared environmental influences accounted for around 10-30% of the variance in most of the psychiatric disorders or traits measured during childhood [4,5], except for ADHD, for which the effect of the shared environment has consistently been found to be negligible. Not only the resemblance, but also the frequently observed differences between family members can be due to genetic factors, since family members only share part of their genetic material (except for identical twins). Environmental factors that are unique to each member of a family, the so-called non-shared environment, explain the remaining part of the variation in psychiatric disorders.

Although the field of behavior genetics has a long history of twin- and family-studies into childhood psychopathology, several issues that might influence the estimates of genetic and environmental influences remain understudied.

1. Childhood psychopathology is often assessed by external informants, like mothers, fathers, or teachers. Studies on the genetic and environmental causes of individual differences in childhood psychopathology most frequently use either maternal or paternal ratings. However, each rater introduces some kind of rater bias, for example based on his or her own standards or own psychopathology. In twin studies, this so-called rater bias can resemble an effect of the shared environment [6]. Using multiple ratings simultaneously, e.g., both parents for both twins, is also possible [6-22] and results in more reliable estimates of the genetic and shared environmental influences on childhood psychopathology.

2. Different informant do not completely agree. Previous multiple rater studies showed that there are parental differences in the assessment of childhood
psychopathology. The parental agreement about the level of problems in their child (i.e., the correlation between the parental ratings) was not perfect (ranging between r=.60 and r=.75) and mother ratings were often found to be slightly higher than father ratings for internalizing and externalizing problems in their children. Differences in the scores depending on the informant assessing childhood psychopathology may lead to different conclusions in situations where scores are used to screen children for psychiatric disorders. It is still unclear whether differences in means between mother and father ratings depend on the child’s gender or age and whether the mean discrepancies are the result of the gender of the informant or of different reasons, e.g. a different relationship with the child.

3. Age is also a factor that can modify the heritability of psychiatric disorders, which is not always taken into account. Genetic influences are often found to be smaller in childhood and increase with age, whereas shared environmental influences decrease with age [23]. Another issue is the explanation of stability over the ages, i.e. the factors that influence the persistence of psychopathology in childhood into adolescence and adulthood. Epidemiological studies have shown that around 50% of individuals with a childhood psychiatric disorder still fulfil the criteria of a psychiatric disorder in adulthood [24,25]. Earlier genetic longitudinal analyses have shown that for anxiety and depression [26-29], attention problems [30,31], and aggressive behavior [32] the persistence of the psychiatric problems into adulthood is mainly due to genetic effects and not to the shared environment. This has not been studied for other psychiatric symptoms in childhood.

There are also several understudied issues regarding the prevalences of parental psychopathology in families with children referred to a child and adolescent psychiatric outpatient clinic, and the association with the child’s psychopathology, also over time. The significant genetic and shared environmental influences reported in twin-family studies imply that clinicians treating children with psychiatric disorders are likely to come across parents of children experiencing psychiatric symptoms themselves. Studies in clinical samples indeed found that parents whose children are evaluated for psychiatric disorders at a mental health clinic report high levels of internalizing [33-47] and externalizing psychiatric problems themselves [48-52]. The prevalence rates varied between 18% and 68%. Studies also showed that parental psychiatric symptoms influenced the course of childhood psychopathology and outcome of the child’s treatment [47,53-72]. Issues that are understudied are:
1. Resemblance in spouses for psychopathology. Having two parents with psychopathology, as opposed to one, can make the shared environment more unfavorable with a greater impact on outcome [73], but it is unknown whether parents of children referred to a clinic are more often both affected than parents in the general population.

2. The comorbidity of psychiatric disorders. The majority of the earlier research in clinical samples focused on a single psychiatric disorder, but familial resemblance for psychopathology is often not confined to the disorder of the index subjects [74,75]. Assessing a broad range of psychopathology in parents with offspring suffering from various internalizing and externalizing disorders can provide better insight into associations between parent-offspring psychopathology.

3. Paternal psychopathology and father-offspring associations. Although it is known that paternal psychopathology is associated with offspring psychopathology [76,77] as well as with maternal psychopathology for internalizing problems [see for reviews 78,79,80], earlier studies mostly analyzed maternal psychiatric symptoms or included far fewer fathers than mothers.

Data

In this thesis, I investigate genetic and familial risk factors for psychopathology and its outcome in two samples: a large population-based twin sample and a clinical sample of families with children with psychopathology. Both samples are described briefly below. A more extensive description of the clinical data collection procedures, response rates and the measurement instruments used are described in the Appendix.

A. The Twin Sample. Since the establishment in 1987, the Netherlands Twin Register (NTR) has on a regular basis collected information on, among other things, mental health problems in children, adolescents and adults [81-83]. As data have been collected over a period of 27 years, the NTR has come to have a unique large longitudinal twin dataset with information available on psychiatric symptoms across different ages. For my thesis project I analyzed psychiatric symptoms in 12,310 7 year-old, 9,783 9-10 year-old, 6,839 13-18 year-old, and 7,909 19-65 year-old twin pairs, and in 2,784 parents of twins. The NTR has measures available on childhood psychopathology from different informants (i.e. mothers, fathers, teachers and self-reports).
B. The Clinical Sample. Data from families with a child with psychopathology were collected in four different child and adolescent outpatient clinics in Amsterdam and Rotterdam, the Netherlands (de Bascule, GGZ inGeest and UvA Minds in Amsterdam and the Erasmus University Medical Center-Sophia Children’s Hospital (EUMC) in Rotterdam). Data were collected on the child’s, mother’s and father’s psychopathology at time of the first assessment in the clinics (N=1,942 families, N=1,850 mothers and N=1,399 fathers). The same surveys assessing the child’s and parents’ psychiatric symptoms were collected approximately one to five years later for three clinics (N=794 families, N=742 mothers, N=440 fathers). In Appendix I, I describe the part of this data collection that was performed for the NWO TOP project: “Genetic influences on stability and change in psychopathology from childhood to young adulthood.”

Content of this thesis

In this thesis I focus on the outstanding issues described above regarding the influences of genetic and shared environmental factors on childhood psychopathology and the clinical implications. I take into account that data from children are collected from different informants and test for effects of genotype x age interaction. The analyses include one- and two generation designs, using the classical twin design of mono- and dizygotic twins and parent-offspring designs. The first part of this thesis focuses on the heritability and assessment of childhood psychopathology, utilizing the large population-based twin sample from the NTR. The second part of this thesis describes studies into familial factors associated with childhood psychopathology and its outcome, utilizing data from a clinical sample of families with children with psychopathology. In the discussion I will put the results in the context of the implications for psychiatric outpatient clinics treating children with psychiatric disorders and provide recommendations for future research. A brief description of the chapters in this thesis is provided below.

Part I: Childhood psychopathology: assessment and heritability

Chapter 2 presents a twin study which investigates what the influences of genetic and shared environmental factors are on affective, anxiety, somatic, ADHD, oppositional-defiant, conduct and obsessive-compulsive problems in 7-year-olds while analyzing mother and father ratings simultaneously. This chapter also describes differences in parental assessment of their children’s psychiatric problems and whether this depends on gender of the child.
Chapter 3 seeks to answer two questions: 1) whether informant discrepancies depend on the gender or age of the child or on the psychiatric symptoms assessed and 2) whether differences in maternal and paternal reports on childhood psychopathology are due to the gender of the informant. We provide an overview of the informant discrepancies between maternal and paternal ratings, but also between female and male teacher ratings of a broad range of childhood psychiatric symptoms in 5, 7, 10 and 12 year-old boys and girls. If male and female means differ as much as mothers' and fathers', these differences could be due to gender of the informant. It was further tested whether gender of the child interacts with gender of the informant.

Chapter 4 describes the results from a genetic longitudinal analysis which reveals the genetic architecture of childhood and adolescent conduct problems and adult antisocial personality problems when taking into account genotype x age interaction. Conduct problems in children, defined by repetitive and persistent behaviors that violate the rights of others or societal norms or rules [84], are known to be relatively stable and can predict antisocial personality problems in adults and related problems, such as crime and conviction [24,85-87]. We undertook this study to estimate the influences of the genetic, shared and non-shared environmental factors on variation in conduct problems in 9-10 year-olds, 13-18 year-olds and on antisocial personality problems in 19-65 year-olds. We further estimated the contribution of genetic and environmental factors on the persistence of conduct problems from childhood into adolescence and adulthood. Possible gender differences in the etiology of conduct and antisocial personality problems were also examined.

Part II: Aggregation of psychopathology in a clinical sample of children and their parents

Chapter 5 focuses on spousal resemblance, we investigate whether psychiatric symptoms in partners are associated. We evaluate whether parents of children referred to a child and adolescent psychiatric outpatient clinic are more alike in psychiatric symptoms than parents of children in the general population (i.e. the parents of twins registered with the NTR), within and across multiple internalizing and externalizing psychiatric symptoms.

Chapter 6 provides the prevalence rates of several psychiatric symptoms in both mothers and fathers of children that are evaluated for psychiatric disorders at
psychiatric outpatient clinics. In addition, this chapter investigates parent-offspring associations, both within and across internalizing and externalizing symptoms. We seek to address the question whether the parental prevalence rates and associations with their offspring psychopathology are similar in mothers and fathers. The associations are analyzed separately for boys and girls, while controlling for spousal resemblance for psychiatric symptoms.

Chapter 7 reports on a study that aims to identify the parents at the highest risk for psychopathology themselves when their child is evaluated for psychiatric disorders by exploring the predictive validity of various risk factors on multiple parental psychiatric symptoms. We examine whether family (relationship status), parental (e.g. education level, occupational status, age and gender) and offspring characteristics (e.g. age, kind of psychiatric diagnosis and comorbidity) predict depressive, anxiety, ADHD, avoidant personality and antisocial personality symptom scores in mothers and fathers.

Chapter 8 describes the results of a longitudinal analysis which examines the effect of several internalizing and externalizing parental psychiatric symptoms present when their child is evaluated in a psychiatric outpatient clinic on the child’s outcome of psychopathology. We evaluate predictions of the child’s depressive, anxiety, ADHD, oppositional-defiant or conduct problems at follow-up by the parental depressive, anxiety, avoidant personality, ADHD and antisocial personality problems at baseline in a model that also includes the parent-offspring associations at baseline, predictions of parental psychiatric symptoms at follow-up and the child’s symptom score at baseline. Analyses are performed separately for mothers and fathers.

Chapter 9 concludes with a summary of the results of the studies described in this thesis and a discussion on the implications for psychiatric outpatient clinics treating children with psychiatric disorders and recommendations for future research.