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General introduction



GENERAL INTRODUCTION

Nearly half of my friends grew up in divorced families, some did well and some did very poorly. And I have always wondered, why?

For young children, family disruption is considered the primary agent in shaping their ontogenetic development. As such, children experience family disruption including parental conflict or separation, experience parental hostility or any other form of psychopathology, or were bullied by a sibling. It is actually uncommon to not experience any of these family risk factors to some degree. However, it is unclear in which periods children are vulnerable and in what sequence family events impact them most, and who is most likely to be affected. In this thesis we used different indicators of chronic family disruption such as parental conflict, parental separation, parental hostility, and parental psychopathology with child developmental outcomes. Our focus lies on the chronicity of these processes because continued exposure (in certain periods) can lead to poor developmental outcomes.¹

Therefore, we explored family disruption occurring in the prenatal vs. postnatal period or occurring in both periods and how different exposures interact in relation to developmental outcomes. Importantly, vulnerability is shaped by the occurrence of different risk factors that interact, mediate or simply confound each other. In this thesis we also explore how family disruption becomes behaviorally or biologically embedded.

Imagine two children similar to my friends, Eneda and Estri both 10 years old, sitting in math class waiting for the bell to ring. It is the time when the teacher places your test on your desk, face down. Eneda is engaged and keeps staying focused to complete the test. While Estri tries to stay focused but keeps getting distracted by not feeling motivated, then by the whispering of a classmate, then by the sunny day outside, and then starts constantly moving the chair.

Eneda experienced conflict and family separation. Estri's parents were dealing with anxiety and depression and her mother was hostile. Eneda is doing well and does not have adjustment problems, while Estri not. What happened in their development? In this thesis I take a closer look what underpins the different behavior in these two children. Is it the absence of a parent? The chronicity of conflict or hostility that shapes child behavior? Or is it both long-standing conflict and separation? Why are Eneda and Estri affected by family disruption in different ways? How will their behavior change during development?

In both epidemiologic and animal models, disturbances in child development (both neurological and cognitive) and behavior have been linked to prenatal family risk factors that persist through childhood. Characterization of specific adverse exposures provided evidence supporting the important role that family disruption has in modifying offspring developmental processes.²⁻⁵ Furthermore, prenatal and postnatal environmental factors can both have different effects during distinct stages of child development. Think first of Estri's behavior. What exactly is it about parental conflict and separation that accounts for Estri's emotional and behavioral problems? Is it her age of exposure to parents' conflict itself, or separation that has impact on her behavior? Or is it rather the level of parental conflict?

It is well known that family disruption including poor family functioning or conflict, parental separation, parental anxiety/depression, and different forms of parenting are associated with long-term child emotional and behavioral problems,³ and with lower cognitive abilities and poorer school performance.^{6,7} There is also evidence that simply considering the number of events without considering the nature of disruption,⁸ or ignoring the influence of one disruption on other disruptions,⁹ or not accounting for the timing of the disruption¹⁰ will lead to insufficient understanding of child behavioral problems.

It is also well known that certain brain structures are affected by different types of adversities occurring during child development.¹¹ Both animal and human studies suggest that early-life exposure to stressors may have the most potent impact during specific periods of neurodevelopment in childhood.¹² For example, Romanian high risk children exposed to neglect, and low socioeconomic status during key neurodevelopmental sensitive periods (e.g., over the first five years of life) presented with structural changes in the children's brain.¹³

What brain regions underlie the different behaviors of Eneda and Estri? Their apparently different behaviors are not the result of one brain structure, rather they are the result of a connected brain structures known as total white and gray matter. Preclinical studies suggest that the hippocampus is highly susceptible to stressful experiences during pregnancy and infancy.^{14,15} Circulating glucocorticoids receptors in the hippocampus make this particular structure vulnerable to chronic stressors.¹² As a result children exposed to pre- and postnatal adversities show reductions of hippocampal volumes.¹³ The other brain regions implicated in the response to chronic stress and adversity include limbic and frontotemporal structures of children.¹⁶

While it is clear that research has demonstrated the importance of unidirectional associations between parent and child psychopathology across development for several decades,

relatively few studies investigated bidirectional associations between parent and child, namely the child's impact on changes in parents' psychopathology. Indeed, various studies investigating bi-directionality of dysfunctional parenting and child psychopathology suggest some bidirectional associations,^{17,18} but yet again, the associations of the within and between individuals variation by which parental psychopathology lead to changes in child psychopathology and vice versa remain unclear. Now think of Estri's vulnerability. Is her ability not to stay focused during math test likely to be the result of coping patterns transmitted from her anxious and hostile mother alone, or from both parents' psychopathology? Or is it rather a result of the test pressure, under pressure Estri tends to show more behavior problems than normally? Are Estri's behavioral problems likely to influence her parents' psychopathology?

Thus, any truly transactional model must encompass that not only the parental psychopathology but also the child as it actively participates in its own growth.¹⁹ This understanding requires explanations to the transactional model as equal emphasis must be placed on the bidirectional associations between the child and family environment. In this thesis, we disentangle transactional processes within and between individuals of parent and child psychopathology. Together, persistent effects in development are not some set of psychopathology symptoms but rather the processes by which these symptoms are maintained in the transaction between child and environment.¹

I hope that this thesis will ultimately provide a few answers, and most importantly a clearer picture of the questions lying before us. In chapter 2 we discuss various ways family disruption becomes a risk factor for child behavioral outcomes, and how potential interacting and mediating factors (e.g., family conflict and separation) play an important role in determining the outcomes. The first study of this chapter focuses on the association of family conflict and parental separation from pregnancy onward with child emotional and behavioral problems. It is well known that family conflict could underlie both marital instability and poor parenting and its consequences for children.³ There is also a substantial body of evidence to support the notion that parental separation affects child emotional and behavioral problems.⁹ However, whether parental separation has a negative effects on child problem behavior independent of conflict remains unknown. We therefore introduce a mediation approach that more fully encompasses mediation and interaction of two exposures simultaneously.

The developmental period between childhood and adolescence is a time of substantial cognitive change,²⁰ and may be especially sensitive to family disruption.²¹ In study 2 we further explore to what extent family disruption is associated with school achievement. Specifically, we evaluate whether the associations of prenatal poor family functioning and parental separation with child school achievement are independent and whether the

associations are mediated by childhood non-verbal IQ. This study also assesses whether attention problems explain the associations of poor family functioning and parental separation from pregnancy onward with child school achievement.

The last paper of this chapter focuses on the contribution of parenting practices in early and mid-childhood in the association between parental education and child school achievement. Highly educated parents are more likely to employ more positive parenting practices and thus contribute to higher child school achievement.²² Moreover, child IQ is one of the most important contributors to school achievement.²³ Thus, we evaluated the extent to which parenting practices and child non-verbal IQ in early childhood mediate the association between parental education and school achievement.

Chapter 3 presents an approach to examine bidirectional associations between parent and offspring psychopathology. It has long been acknowledged by proponents of the transactional model that any development in the individual is influenced by the interplay of processes in the individual's context over time.¹⁹ This study included children from the general population over time to test the stability and change of bidirectional associations within and between individuals. We therefore employed an autoregressive latent trajectories approach to understand the variability at the individual level of development.

In the chapter 4, we aimed to investigate the effects of childhood loneliness on long-term mental health disruption in a follow-up study that extends into adulthood. A considerable number of studies has investigated the effects of loneliness in adults with social anxiety disorder^{24,25} and depression.²⁶ However, less is known about the impact of childhood loneliness in light of persistent effects in mental health outcomes. In this prospective-longitudinal, community-representative study, we estimate the effect childhood loneliness and long-term disruption on adult psychiatric disorders (including anxiety, depression, and substance use disorders) while carefully controlling for indicators of other common childhood adversities.

Chapter 5 consists of two studies evaluating the effects of family functioning from pregnancy onward with child brain morphology and well-being. Childhood stress is known to have longstanding consequences. In the first study we obtained parents' assessments of family functioning during pregnancy, and subsequently, ratings of childhood problem behavior and neuroimaging data in preadolescence. Our goal was to investigate to what extent the long-term disruption of poor family functioning associates with preadolescent problem behavior and subcortical brain development.

Microstructural properties related to more efficient neural processing are generally associated with fewer behavior problems, while microstructural properties related to less

efficient neural processing are associated with more problem behavior during development.²⁷ A healthy family environment may lead healthy brain development and low levels of problem behavior. In the last study of this chapter we investigate whether more positive early-life family functioning (reverse-scoring) is associated with more global white matter microstructure.

The final chapter, No. 6, presents a parallel approach to neuroimaging data to further understand determinants of parents' and children's brain morphology. Higher levels of parental hostility are associated with child problem behavior and in particular aggressive behavior.^{28,29} Exposure to parental hostility can have both immediate and lasting effects on physical and psychological health.³⁰ Moreover, in 'at risk families' parents are likely to show the neuroendocrine, immunological, and cardiovascular correlates of persistent stressors.³¹ Many of these physiological and psychological differences potentially explain changes in the brain, such as decreased hippocampus and amygdala volumes.^{32,33} We therefore investigate to what extent parental hostility is associated with differences in maternal, paternal and child brain structure if analyzed together, i.e. as triads that in turn underlie child aggressive behavior.

Thesis objectives

The main goal of this thesis is to explore family disruption factors that we consider of importance to child development psychopathology. We employ various methodological methods to study the associations of specific family disruption from pregnancy onward and child neurobehavioral development. We will also zoom in on bidirectional associations between parent and child psychopathology. In order to do so, the work presented in this thesis is embedded in population-based cohort studies, namely the Generation R Study, which I will introduce in more detail.

The importance of the study setting is best illustrated by including children that have been followed from fetal life onward. The Generation R Study comprised 9,778 pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006.³⁴ Generation R Study is representative of the general population with regard to family risk factors (e.g., 23% parents separated up to 10 years follow-up). More important, the follow-up data collection of the Generation R Study is one of the main advantages for family risk factor research, and in particular the imaging data of children and parents are a strength of this thesis. The follow-up from pregnancy onward render the Generation R Study a valuable tool to map how the various ways of adversity becomes neurobehavioral embedded, and how the timing of such adversity plays an important role in determining behavioral and cognitive outcomes. Of note, the study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants

and from both the parents of minors. Participants gave written informed consent for each phase of the study (fetal, preschool, childhood and adolescence period). From the age of 12 years onwards, children must sign their own consent form, in accordance with Dutch Law. Children received oral information about the study.

The study of childhood loneliness and adult psychiatric disorders was embedded in a prospective-longitudinal, community-representative Great Smoky Mountains Study of 1,420 participants (49% female).³⁵ Childhood predictors of adult outcomes included the following constructs: (1) *DSM*-based traumatic events, psychiatric and substance disorders, and (3) adversities and hardships. All constructs were assessed using the structured Child and Adolescent Psychiatric Assessment (CAPA).^{36,37}

These are the guiding challenges for this thesis:

- To identify periods of specific vulnerability of family disruption to child neurobehavioral outcomes.
- How timing of family exposures interacts with neurobehavioral development during childhood.
- How the vulnerability is shaped by the occurrence of different family factors that interact or mediate with each other in relation to child neurobehavioral outcomes.
- How different family factors becomes behaviorally and biologically embedded.

I do hope that this thesis will take science a few small steps forward. My goal was to understand a bit better how prenatal and childhood family disruption result in shaping the neurodevelopmental vulnerability to emotional, behavioral, and cognitive problems.

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