Differential susceptibility to parenting: Exploring new approaches

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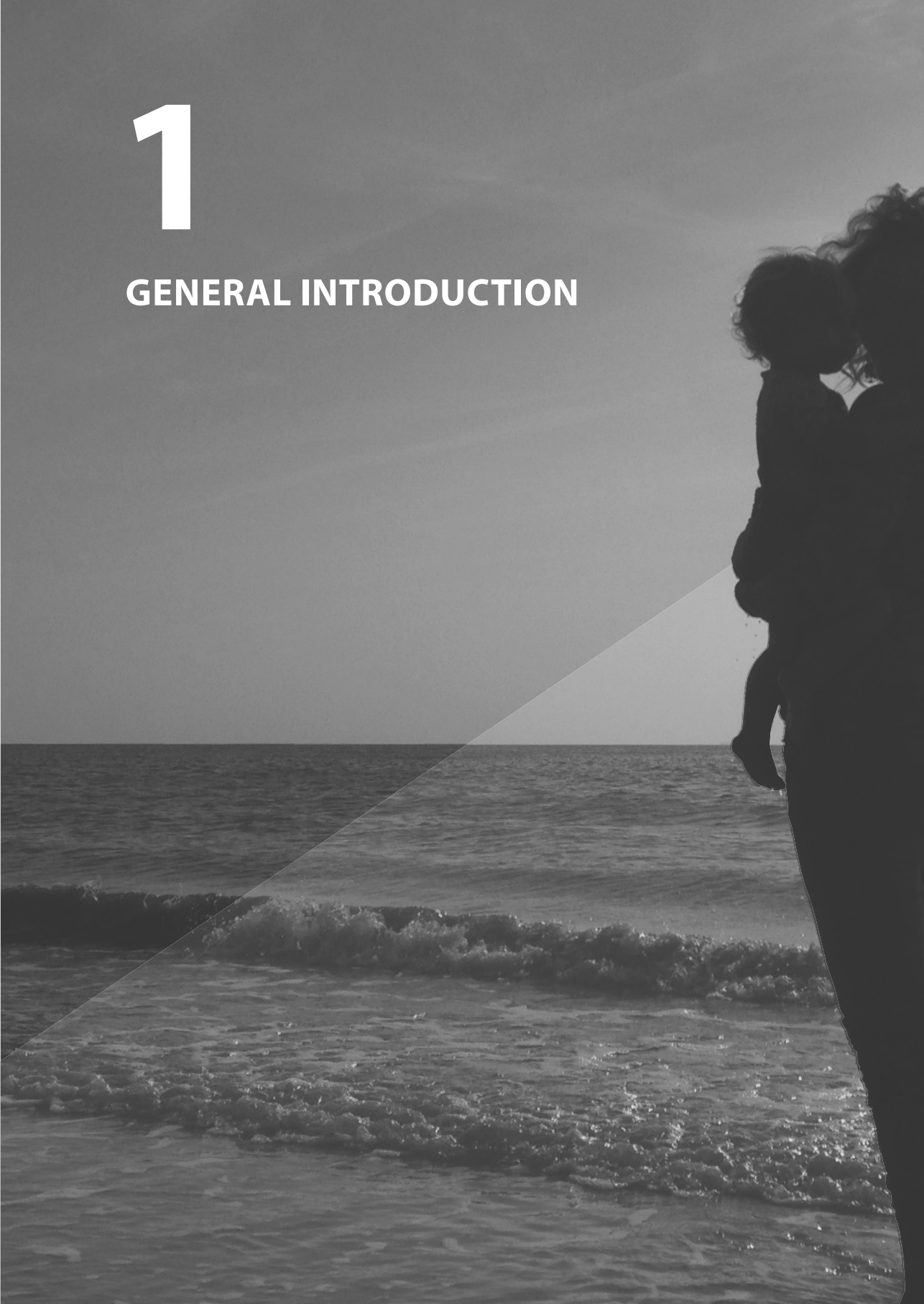
GENERAL INTRODUCTION



INTERPLAY OF BIOLOGICAL AND ENVIRONMENTAL FACTORS IN CHILD DEVELOPMENT

Parenting influences many aspects of child development, including socio-emotional, cognitive, and behavioral outcomes (e.g. Borkowski, Ramey, & Bristol-Power, 2002; Bugental & Grusec, 2006; Hubbs-Tait, Culp, Culp, & Miller, 2002). Yet most such studies report only modest effect sizes. An increasingly likely explanation is that not all children are equally affected by environmental factors, including parenting. The prior debates of nature versus nurture in developmental science have shifted to acknowledge the true complexity of the relationships: nature *and* nurture interact (Keating, 2011). Main effects may be 'hidden' in interactions between parenting and moderating child factors, such as temperament, biological sensitivity, or genetic makeup. In the current thesis, we test the theory of differential susceptibility of children to the effects of parenting. Doing so, we go beyond common methods of testing differential susceptibility.

DIFFERENTIAL SUSCEPTIBILITY THEORY

The first studies investigating the interplay between biological and environmental factors focused on child 'risk' factors and 'risky' environments, consistent with a dual-risk model (Sameroff, 1983) or diathesis-stress model (Zuckermann, 1999). From this point of view, certain endogenous risk factors are thought to make individuals more vulnerable to adverse environments, whereas individuals without these 'risk factors' are considered to be resilient under adverse circumstances. Thus, these models assume that there are vulnerable and resilient individuals, who differ in their response to adverse environments while their responses to supportive environments are (implicitly) assumed to be similar. From an evolutionary theory perspective, these models are problematic. Differential susceptibility theory argues for susceptibility instead of risk, proposing that the same children who are considered most vulnerable in adverse environments, might also profit the most from supporting environments. The origin of differential susceptibility theory is based in evolutionary theory. To that end, two related theories emerged around the same time. The first was labeled the *differential susceptibility hypothesis*, and was first proposed by Belsky (1997, 2005). As the future is uncertain, bet-hedging at the population level ensures the persistence of diverse phenotypes that can endure across a range of environmental circumstances. Natural selection has maintained genetic variants for both conditional and alternative developmental strategies, with variation in susceptibility to the environment as a result. The second theory, labeled *biological-sensitivity-to-context theory,* proposes that individuals in both very supportive and very unsupportive environments develop or maintain high levels of physiological (stress) reactivity as conditional adaptations (Boyce et al.,1995; Boyce & Ellis, 2005). Key to the integrated differential susceptibility theory is that some individuals are more susceptible than others to contextual influences, for better *and* for worse, due to certain susceptibility factors (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van IJzendoorn, 2011). The differential susceptibility model is presented in Figure 1. Great efforts have been put in recent years on supporting the theory of differential susceptibility with empirical evidence.

Susceptibility factors can be subdivided in three categories. The first studies of differential susceptibility in development identified child temperamental factors such as reactivity or negative emotionality as susceptibility factor (Belsky, 1997, 2005; Klein Velderman, Bakermans-Kranenburg, Juffer, & Van IJzendoorn, 2006). Results indicated that negative emotionality and difficult temperament are markers of susceptibility rather than vulnerability, as highly negatively reactive children were also shown to benefit more from supportive rearing environments compared with other children (e.g. Belsky, Hsieh, & Crnic, 1998; Blair, 2002). The second category of susceptibility factors is genetic. Genetic differential susceptibility was first introduced in a study by Bakermans-Kranenburg & Van IJzendoorn (2006). Children carrying a dopamine receptor D4 (DRD4) 7-repeat allele were more susceptible to the effects of both maternal sensitivity and maternal insensitivity: they exhibited greater variation in externalizing behavior as a function of parenting compared with children without this allele. Since then, additional genetic markers have been investigated, with a focus on a group of polymorphic loci in serotonin and dopamine genes that can be labeled as the 'usual suspects' owing to their frequent use in association studies with a wide range of behavioral and other phenotypes. The dopamine system is involved in attentional, motivational, and reward mechanisms (Robbins & Everitt, 1999). The serotonin system is important for sleep, mood, and aggression (Canli & Lesch, 2007; Lucki, 1998; Ursin, 2002). It is through these regulatory mechanisms that dopaminergic and serotonergic genes may exert influence on individual differences in openness to environmental influences. For example, the 7-repeat allele of the DRD4 gene is associated with decreased dopamine receptor efficiency and is implicated in novelty seeking, impulsivity and externalizing behavior (Ebstein, 2006; Schmidt, Fox, Rubin, Hu, & Hamer, 2002). The short allelic variant of the gene coding for the serotonin transporter, 5HTTLPR, is linked with emotionality and stress sensitivity, but also with improved cognitive performance. Overall, the short allele is associated with hypervigilance, which may result in increased sensitivity to environmental stimuli (Homberg & Lesch, 2011). Thus, because dopaminergic and serotonergic polymorphisms are associated with responsiveness to environmental input, they are a logical focus of many studies investigating (genetic) differential susceptibility. The role of these polymorphisms as susceptibility markers has been confirmed meta-analytically (Bakermans-Kranenburg & Van IJzendoorn, 2011, 2015; Van IJzendoorn, Belsky, & Bakermans-Kranenburg, 2012). Another category of susceptibility factors are physiological factors. Physiological susceptibility was described for the first time by Boyce et al. (1995). Highly biologically reactive children, who had increased cardiovascular or immune reactivity to stressors, showed the highest respiratory illness incidences in high-adversity childcare or home environments. Surprisingly, they also showed the lowest illness rates in supportive environments compared with children with low biological reactivity (Boyce et al., 1995). Since then, several physiological measures of the stress systems have been investigated as markers of susceptibility (Obradović, 2012).

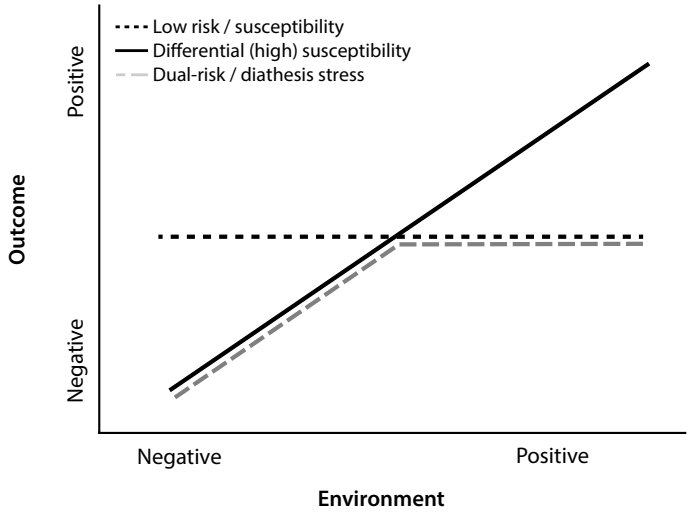


Figure 1 | Differential susceptibility model vs. diathesis stress model. Figure adapted from Bakermans-Kranenburg & Van IJzendoorn, 2007.

THE DEVELOPMENT OF DIFFERENTIAL SUSCEPTIBILITY RESEARCH AND THE CONTRIBUTION OF THE CURRENT STUDY

Since the initial studies on differential susceptibility, the field has continuously expanded and developed. A broad range of susceptibility markers, environmental factors, and outcome measures has been studied in different age ranges and populations (e.g. Bakermans-Kranenburg & Van IJzendoorn, 2015; Ellis et al., 2011). As the number of differential susceptibility studies increases, the methodology develops as well. For instance, for the evaluation of differential susceptibility, researchers have moved from simply eyeballing interaction plots in early studies to stepwise testing of these interactions, to even more extensive statistical methods to distinguish differential susceptibility from other interaction models (Belsky, Pluess, & Widaman, 2013; Roisman et al., 2012; Widaman et al., 2012). Despite the ongoing developments in the field, there are still many unknowns, for example with regard to mechanisms, developmental timing, and specificity of susceptibility (Ellis et al., 2011). In the current series of studies, we describe three important extensions of current research methods to investigate children's differential susceptibility to parenting influences.

First, we investigate differential susceptibility from a developmental perspective. Most studies testing the interplay between parenting and susceptibility factors focus on single measurements of parenting behavior and/or outcomes or combine multiple measures over time. However, interaction effects are not always stable over time (Belsky & Pluess, 2013; Berry, Deater-Deckard, McCartney, Wang,

& Petrill, 2013). Therefore it is crucial, from a developmental perspective, to include *multiple* measures across time.

A second extension is the investigation of gene-environment interplay by taking into account genetic variance across a *set* of genes. The vast majority of studies on gene-environment interactions focus on single polymorphisms and candidate genes. At the same time, the polygenetic nature of complex traits is indisputable. To gain more knowledge about the roles of the genetic pathways in gene-environment interactions, it is necessary to go beyond single genetic markers. In a gene-set approach, genetic variance of multiple polymorphisms within a pre-defined gene-set consisting of functionally of biologically related genes is aggregated (Winham & Biernacka, 2013). This approach enables testing of *joint* effects of the multiple markers within the gene-set. This approach has so far mainly been used in the search for genetic *main* effects. However, it provides promising possibilities for the investigation of gene-environment interplay as well, which is something we undertook in the present thesis.

Finally, we expand the research on mild perinatal adversity as a susceptibility factor. Mild perinatal adversity, defined as late prematurity or low birth weight at full term birth, is associated with increased stress reactivity (Economides, Nicolaides, Linton, Perry, & Chard, 1988; Jones et al., 2006, Wüst, Entringer, Federenko, Schlotz, & Hellhammer, 2005). Mild perinatal adversity was previously shown to act as a susceptibility factor in the cognitive domain, with early literacy as outcome and a computer-based intervention program as the environmental factor (Van der Kooy-Hofland, Van der Kooy, Bus, Van IJzendoorn, & Bonsel, 2012). We extend the research on this prenatal susceptibility factor to a different domain.

TESTING DIFFERENTIAL SUSCEPTIBILITY IN THE GENERATION R STUDY

This study is embedded in the Generation R Study, a prospective population-based cohort study conducted in Rotterdam, the Netherlands. The aim of the Generation R Study is to identify early environmental and genetic determinants of growth, development, and health from fetal life to young adulthood (Jaddoe et al., 2012). Pregnant women living in the Rotterdam area, with an expected delivery date between April 2002 and January 2006 were invited to participate. Questionnaires were filled out by parents reporting on the development of their child. Maternal and paternal demographics were collected at enrolment and during subsequent phases. Additionally, detailed behavioral and physical measurements were obtained in a subgroup of children, the Generation R Focus Cohort. This relatively homogenous subsample consisted of 1,247 children of Dutch origin, meaning that the children, their parents and grandparents were all born in the Netherlands. At the age of 5 to 7 years, all children of the entire Generation R Study and their mothers were invited to the research center for cognitive and behavioral assessments, collection of biological samples, and physical examinations. The broad range of available data, the longitudinal design, and the availability of genome wide genetic data in the Generation R Study provides the opportunity to investigate differential susceptibility in various ways in a sample with sufficient power, in contrast to many of the previous studies that were often

underpowered to examine non-experimental interaction effects (Duncan & Keller, 2011; Ioannidis, 2005). In the studies described in this thesis, we focused on genetic and physiological susceptibility factors. An overview of the main measures used in this thesis is presented in Figure 2.

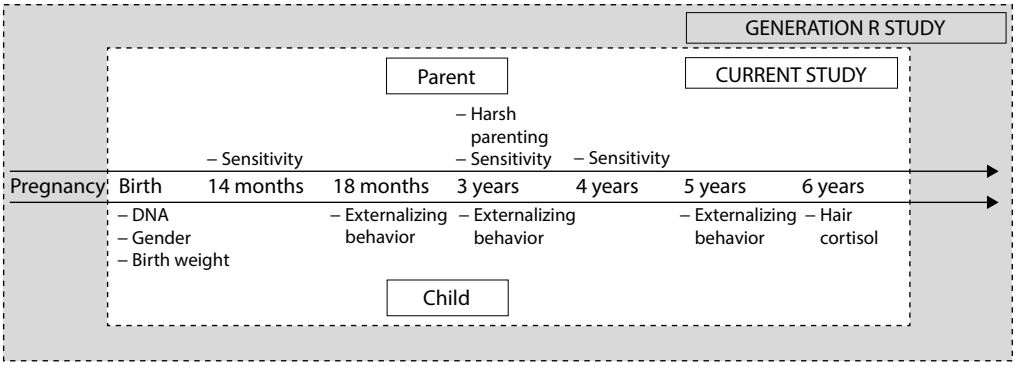


Figure 2 | Overview of the measures used in this thesis

AIM OF THE THESIS

The aim of the studies presented in this thesis is a careful examination of the interplay between parenting and children's biological factors, applying important innovations to current methods in differential susceptibility research. In Chapter 2, we investigate the interaction between DRD4 genotype and maternal sensitivity in the prediction of child externalizing behavior over time. Multiple measures of both maternal sensitivity and externalizing behavior across the first five years of life are included. In Chapter 3, we move beyond single polymorphisms/genes in the study of gene-environment interplay. We use a gene-set approach to test the joint effect of multiple SNPs within a set of dopamine genes on child externalizing behavior while stratifying for harsh parenting. In Chapters 4 and 5 we assess differences in children's hair cortisol levels as a biomarker of chronic stress. The main focus of Chapter 4 is to identify potential confounders, to establish a guideline for future research on hair cortisol and cortisone. In Chapter 5 we examine effects of maternal harsh parenting on hair cortisol levels and we test whether this association is moderated by mild perinatal adversities. Finally, in the general discussion (Chapter 6) the main findings of the empirical studies are reviewed and integrated against the background of differential susceptibility theory. Furthermore, limitations, suggestions for further research, and implications of our findings are discussed.

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