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Familiar scars: an exploration of the biological correlates of child maltreatment in an extended family design

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Chapter 1

General Introduction

Child Maltreatment – The Knowns and the Unknowns

Parents should offer security and protection to their children and parental care is the primary mechanism through which child survival is ensured. Unfortunately, in some situations parents do not or cannot protect their children and in some cases parents are the ones who are causing the harm to children they ideally would protect. Any type of threatening or violent interaction between a parent or caregiver and a minor that (potentially) causes harm to the minor either through action or inaction is described as child maltreatment (Jeugdwet artikel 1; World Health Organization, 2006). We can differentiate child maltreatment along two dimensions (1) active vs. passive, and (2) emotional vs. physical. The active types of child maltreatment are emotional, physical, and sexual abuse and the passive types of child maltreatment are emotional and physical neglect.¹ Child maltreatment affects approximately 2 to 4% of children on a yearly basis (Sedlak, Mettenburg, Basena, Petta, McPherson, et al., 2010; van Berkel et al., 2020) and in most cases it is perpetrated by a parent (U.S. Department of Health & Human Services, 2019).

Experiencing child maltreatment is associated with considerable suffering. Children who experience child maltreatment tend to have more internalizing and externalizing problems (Duprey et al., 2019), be emotionally dysregulated (Weissman et al., 2019), are less likely to be securely attached to their parent (Cyr et al., 2010), are more prone to risk taking behavior (Oshri et al., 2015) and show cognitive delays (Strathearn et al., 2020). Many children carry these negative consequences forth into adulthood. Adults who have experienced child maltreatment are at a higher risk for depression (Humphreys et al., 2020), post-traumatic stress disorder (Kisely et al., 2018), alcohol dependence (Elliott et al., 2014), and have a higher suicide risk (Dube et al., 2001). Child maltreatment is also associated with health risk behavior such as smoking (Elliott et al., 2014), early health risk markers such as obesity (Danese & Tan, 2014), hypertension (Clemens et al., 2018), allostatic load (Widom, Horan, et al., 2015), and lower living standards (Pinto Pereira et al., 2017). In the long term, child maltreatment manifests as increased risk for cardiovascular disease (Basu et al., 2017), diabetes (Duncan et al., 2015), cancer (Fuller-Thomson & Brennenstuhl, 2009) and, ultimately,

¹ In this dissertation, we focus on physical and emotional abuse and neglect. Other types of maltreatment exist. In particular, sexual abuse has been studied extensively (Stoltenborgh et al., 2015). However, the lower prevalence of sexual abuse in combination with its high co-occurrence with the other types of child maltreatment make it difficult to study the unique correlates of sexual abuse (Vachon et al., 2015a; van Berkel et al., 2020). Moreover, sexual abuse is less likely to be perpetrated by a family member than other maltreatment types (Stoltenborgh et al., 2015). For those reasons, sexual abuse is not a focus of this dissertation.

premature mortality (Brown et al., 2009; Chen et al., 2016). It is thus clear that child maltreatment has negative down-stream consequences. Even though there is evidence for a bidirectional causal association between child maltreatment and mental health (Warrier et al., 2021), since there is no direct link between child maltreatment and, for instance, heart disease or depression, the challenge that research is facing currently is understanding through which mechanisms these consequences get embedded (McLaughlin et al., 2016).

What has remained even more elusive is the question of what causes maltreatment to occur in the first place. The etiology of child maltreatment is a complex interplay of multiple factors. However, rather than studying the causes of child maltreatment we tend to study risk factors – factors that increase the likelihood that maltreatment occurs but that are not deterministic. Several risk factors have been identified and confirmed in meta-analyses (Stith et al., 2009; van IJzendoorn et al., 2020). In particular, parent factors such as mental health problems, lack of self-esteem, personal stress and stress physiology, and their own experiences of maltreatment are associated with increased risk of child maltreatment (Madigan et al., 2019; Mulder et al., 2018; Stith et al., 2009; van IJzendoorn et al., 2020). Child factors such as externalizing problems and low social competence may also be related to maltreatment risk (Stith et al., 2009). In addition, factors within the family and the family environment can increase the risk of maltreatment occurring: low SES, family size, interpersonal violence, and lack of family cohesion can put a strain on families (Sidebotham & Heron, 2006; Stith et al., 2009). No individual factor is likely to result in child abuse and neglect on its own, however, risk increases when risk factors accumulate (Mackenzie et al., 2011; Patwardhan et al., 2017). For instance, one study found a quadratic relation between the number of risk factors and the likelihood that maltreatment occurs within a family (Patwardhan et al., 2017). Nevertheless, this study also showed that maltreatment occurred when none of the studied risk factors were present, and there were also families in which four or more risk factors were present and no child maltreatment occurred – illustrating the complexity of child maltreatment. Child maltreatment is an equifinal phenomenon with a multitude of risk pathways. In addition to the accumulation of environmental risk factors, biological vulnerabilities may play a role. This complexity is reflected in the difficulty of predicting and preventing child maltreatment (Euser et al., 2015).

The aim of most research on child maltreatment is to understand why and when child maltreatment occurs and what its consequences are. The assumption is that a better understanding of child maltreatment will be crucial in improving and developing methods of preventing as many cases of child maltreatment as possible, intervening when child maltreatment does occur, and treating negative long-term

consequences. Even though several prevention and intervention programs are rooted in our best theoretical and empirical understanding of child maltreatment, these methods show only modest success and leave much room for improvement (Euser et al., 2015; van IJzendoorn et al., 2020). By exploring the correlates of child maltreatment (what precedes maltreatment, conditions that co-occur with maltreatment, and what can be observed in the aftermath of maltreatment) we hope to discover new targets for intervention. The aim of this dissertation is to shed light on some of the biological correlates of child maltreatment within a family context. We use a three-generational extended family study to investigate intergenerational transmission of child maltreatment (ITCM), the heritability of child maltreatment, resting state connectome similarity in parent-child dyads, glucocorticoids (hair cortisol and cortisone) and body mass index.

Family Matters

Child maltreatment almost exclusively occurs within a family context (U.S. Department of Health & Human Services, 2019; exceptions would be maltreatment by for instance daycare providers, babysitters, family friends or neighbors) and never just concerns one person as at least one perpetrator and one victim are involved. Nevertheless, a lot of research on child maltreatment has been conducted at the level of the individual. To illustrate this, we can have a look at the ten most cited empirical papers in *Child Maltreatment* and *Child Abuse and Neglect*². Of the ten most cited papers in *Child Maltreatment*, only two papers reported on dyadic correlates of child maltreatment (Hibel et al., 2019; Lunkenheimer et al., 2018). Of those in *Child Abuse and Neglect*, only one paper collected data beyond the individual level: this study included twins and mothers in order to control for family confounding (Stern et al., 2018). All of the other 17 studies investigated child maltreatment at an individual level.

Valuable insights can be gained from studies on the individual level. For instance, these studies are well suited to demonstrate the consequences of child maltreatment. However, by investigating child maltreatment at the individual level we cannot draw conclusions on dyadic (or triadic etc.) functioning, how family members influence each other, or on different perspectives of family members. Families are intricate networks of mutual influences. Each member brings their genetic baggage as well as their experiences into the mix. Within families, each

² *Child Maltreatment* and *Child Abuse and Neglect* are the two primary scientific journals for child maltreatment research. Both journals provide a list of the most cited papers published in last three years (*Child Maltreatment*) or since 2018 (*Child Abuse and Neglect*). The ten most cited empirical papers (i.e., excluding meta-analyses and literature reviews) of each journal were reviewed on whether they collected data from more than one family member. This is not intended as an exhaustive literature review but as an example of the wider child maltreatment literature.

family member exerts an influence on every other family member. Parent-child relationships are bidirectional (Paschall & Mastergeorge, 2016). For example, one study found that child externalizing behavior was associated with less positive parenting which in turn exacerbated externalizing problems over time (Serbin et al., 2015). Another study found that maternal negativity at 36 months was associated with lower executive control in children at 54 months. Independently, lower executive control in children at 36 months was associated with more maternal negativity at 54 months, suggesting a bidirectional relationship (Klein et al., 2018). However, not all parenting effects are bidirectional. Maternal warmth, scaffolding, and limit setting were unidirectionally associated with child executive control later on. Generally, the study found more evidence of parenting influencing child outcomes later on than the other way around (Klein et al., 2018). This highlights that families represent one of the most important environmental influences on developing children.

There is also a methodological reason to study child maltreatment in families as opposed to individuals. Multiple perspectives may be relevant when measuring maltreatment. In particular, parents and children may have different perspectives on whether maltreatment has occurred or not. This is reflected in low to moderate convergence between parent- and child-reports as observed in the literature (Chan, 2015; Compier-de Block et al., 2017; Cooley & Jackson, 2020). Each perspective contributes valuable information and is part of a more complete picture. It is increasingly recognized that there is substantial added value of considering *subjective* reports of child maltreatment experiences over apparently objective measures like court records (Baldwin, Reuben, Newbury, & Danese, 2019; Danese & Widom, 2020). However, we know relatively little about the role that differences and overlap in subjective perspectives on child maltreatment between parent and child play predicting long-term consequences of child maltreatment.

The last reason why it is important to take a family perspective to child maltreatment is the finding that child maltreatment runs in families. Several studies have demonstrated that children are more likely to be maltreated if one of their parents has experienced maltreatment: intergenerational transmission of child maltreatment (ITCM) (Berlin et al., 2011; Dixon, Browne, et al., 2005; Pears & Capaldi, 2001b). ITCM is also confirmed by meta-analyses (Assink et al., 2018; Madigan et al., 2019; van IJzendoorn et al., 2020). However, there is considerable variation in effect sizes that may be partially explained by variation in study quality (Assink et al., 2018; Madigan et al., 2019; van IJzendoorn et al., 2020), although Madigan et al. (2019) suggest that this effect would be small. So far, the role of reporter effects in ITCM has not been studied. Moreover, we have an incomplete

understanding of the mechanisms underlying ITCM. In the current dissertation, we use an extended family design to investigate ITCM and the biological correlates of child maltreatment in a family context.

Biology in (Inter-)Action

That child maltreatment is transmitted from one generation to the next may point towards genetic factors that are passed from one generation to the next. There is evidence from twin studies that the risk of experiencing child maltreatment is in part heritable (Fisher et al., 2015; Schulz-Heik et al., 2009; South et al., 2015), however it is unclear whether this depends on the severity of the experienced maltreatment, the type of maltreatment or the socio-economic environment. Recent evidence from a genome-wide association study suggests that there is genetic overlap between different operationalizations of child maltreatment (Warrier et al., 2021). It is also unclear whether perpetrating maltreatment is heritable. There is evidence that the parental genome contributes to the heritability of other parenting behavior (Euser et al., 2020; Klahr & Burt, 2014) – including the use of physical discipline (Wade & Kendler, 2000). Overall, this suggests that genetic effects may play a role in ITCM and that in order to gain a complete understanding of ITCM we need to consider heritability.

However, heritability is not the only plausible explanation for ITCM. Experiences of child maltreatment may get embedded in victims' psychology and biology. It is well established that experiences of child maltreatment are associated with long-term mental and physical health effects including depression (Humphreys et al., 2020) but it is less clear through which mechanisms this occurs (McLaughlin et al., 2016). One common denominator across experiencing child maltreatment, mental and physical health, and perpetrating child maltreatment is stress physiology – in particular HPA axis functioning (Bernard et al., 2017; Bunea et al., 2017; Kennis et al., 2020; Khoury et al., 2019; Manenschijn et al., 2013; Merwin et al., 2015). There is evidence that child maltreatment is associated with long-term alterations in wake-up cortisol levels, cortisol reactivity, and hair cortisol levels – indicating HPA axis dysregulation (Bernard et al., 2017; Bunea et al., 2017; Khoury et al., 2019). However, there are still open questions concerning the direction of this effect and whether cortisol mediates the effect of maltreatment on health outcomes such as body mass index (BMI).

Another pathway through which the consequences of child maltreatment may get embedded is through changes in brain structure and activity (van den Berg et al., 2019; Van den Berg et al., 2018). Experiencing maltreatment appears to change the trajectories of structural and functional brain development. Magnetic resonance

imaging (MRI) research finds evidence of reduced prefrontal cortex volume and thickness as well as hippocampal volume (Gold et al., 2016; Riem et al., 2015) and altered white matter network integrity in children who have experienced child maltreatment (Hanson et al., 2015; Puetz et al., 2017). On a functional level, resting state (RS) functional MRI (fMRI) research suggests that child maltreatment is associated with changes in the connectivity between frontal and limbic regions (implying changes in top-down regulation; Herringa et al., 2013; Marusak et al., 2017; van der Werff et al., 2013). For instance, one prospective study found that maternal aggression during an observational task predicts increased resting state connectivity between the amygdala and other ventro-limbic regions in adolescent offspring four years later (Callaghan et al., 2017). Task-fMRI research suggests that individuals who have experienced child maltreatment process fear and psychosocial stress differently (Hart et al., 2018; Zhong et al., 2020). Moreover, during cognitive reappraisal, maltreated adolescents show greater effort to down-regulate amygdala reactivity when observing negative emotional stimuli (McLaughlin et al., 2015). Meta-analytic evidence also suggests that maltreatment is associated with hyperreactivity to emotional stimuli in the amygdala, the superior temporal gyrus, the parahippocampal gyrus, and the insula (Hein & Monk, 2017). In the long-term, changes in neurobiology that are the consequence of experiencing maltreatment may affect how parents respond to their children. Mothers who have experienced child maltreatment show greater activation in salience and emotion networks when imagining conflictual rather than pleasant interactions with their child compared to mothers who have not experienced maltreatment (Neukel et al., 2018). Little is known about dyadic neurobiological correlates of child maltreatment.

A biological framework of child maltreatment holds promise because it provides an explanation for why stressful events encountered early in life are particularly harmful and have such long-lasting effects (Fox et al., 2011; Nelson et al., 2007; Schalinski et al., 2019). During childhood, the brain develops and changes at a more rapid rate than it does in adulthood (Girault et al., 2019; Knickmeyer et al., 2008; Li et al., 2013; Lyall et al., 2015; Wen et al., 2019) and it has therefore been argued that childhood represents a period of increased sensitivity and plasticity (Humphreys et al., 2019). When adverse environmental circumstances interrupt normative brain development the consequences may be more pervasive than when stress is encountered by a fully developed brain (Luby et al., 2020). Similarly, the stress system develops in childhood and may be more malleable early in life (Gunnar & Donzella, 2002; Tarullo & Gunnar, 2006).

Employing a biological framework is also useful because it allows us to explore interactions between biology and environment. Limiting research to the main

effects of environmental factors may significantly reduce their explanatory power. For one, not everyone is equally affected by child maltreatment. While child maltreatment increases the risk for depression, not every individual who has experienced maltreatment does develop a depression later on (Humphreys et al., 2020). One reason may be differential susceptibility to the environment as a result of, e.g., genetic variation (gene-environment interaction, Ellis et al., 2011; Peyrot et al., 2014). Differential susceptibility could also play a role in explaining why ITCM occurs in some families and not in others. Biological factors may also complement research on other environmental risk factors such as low SES. Low SES has been consistently associated with maltreatment but the predictive value of SES is low: most parents with low SES do not maltreat their children (van IJzendoorn et al., 2020). Low SES in itself is likely not the reason that parents maltreat their children. However, living with the stress of financial insecurity in combination with other factors such as genetic vulnerabilities may trigger the use of inadequate parenting strategies and result in negative parent-child interactions.

Within every interaction between an individual and their social (including family), societal, and physical environment, biological processes are interwoven (Boyce et al., 2021). Biological predispositions such as genetic factors influence how the individual responds to their environment and what types of environments they seek out. Any interaction sets in motion changes in the biology of the individuals such as neural activity and physiology. When two individuals interact with each other, the interaction is shaped by the biological predisposition of both individuals and accompanied by continuous transactional changes within the biological systems on both sides of the interaction. Thus, alongside the correlates of child maltreatment at the level of the family or individual psychology (i.e., behavior, cognition, and emotion) we need to consider biological factors like heritability, endocrinology, and neurobiology and how these levels interact (Beauchaine et al., 2008). Therefore, in this dissertation we investigated the heritability of child maltreatment and whether child maltreatment is associated with resting state connectome similarity, as well as hair cortisol and cortisone.

3G Parenting Study

The ultimate aim of studying child maltreatment is to prevent it whenever possible, intervene when it occurs and to treat its consequences in the most effective way. I believe that in order to do that we need to understand child maltreatment in a fundamental, deep, top-down way – accepting its complexities. Therefore, in order to understand child maltreatment we need to understand its biology in a family context. To achieve this, we collected information on experienced and perpetrated child maltreatment and biological correlates in an extended family

design. In this dissertation I focus on three major biological systems: genetic (heritability), the endocrine system (cortisol and cortisone), and the brain (rs fMRI). The 3G Parenting Study was designed to address gaps in previous research that cannot be filled using data at the level of the individual. We used a cross-sectional extended family design. Extended family designs have been used in the past to estimate heritability of various traits such as cardiovascular health, diabetes, physical activity, schizophrenia, attention deficit hyperactivity disorder (ADHD), and social anxiety (Almgren et al., 2011; Bas-Hoogendam et al., 2018; Gur et al., 2007; Hunt et al., 2002; Mitchell et al., 2003; Sudre et al., 2017). We invited families to participate in this study with at least two generations but ideally three generations. This allowed us to study nuclear families and the influence of growing up in the same family. The extended nature of this design also allowed us to invest a wider variety of (genetic) relationships: grandparent-grandchild, avuncular, half siblings, first cousins, grand avuncular, half-avuncular, and first cousin once removed. Variations in the degree of similarity within and between families can provide insights into heritability and environmental components. During daylong lab sessions, we collected detailed data on experienced and perpetrated maltreatment and several biological measures and specimen: structural and functional MRI, hair for cortisol and cortisone, heart rate, saliva to study immune markers and buccal swabs for DNA. In addition, questionnaires and computerized tasks were used to assess various psychological mechanisms and outcomes such as psychopathology, emotion processing, and resilience.

The 3G Parenting Study was a collaborative and interdisciplinary project. Among a team of senior researchers from the field of pedagogics and clinical psychology, four doctoral students were involved in this study. Findings regarding child maltreatment and (1) heart rate and parent-child interaction are presented in Renate Buisman's dissertation (Buisman, 2020), (2) findings regarding task fMRI and structural MRI are presented in Lisa van den Berg's dissertation (van den Berg, 2021), and (3) findings on emotion processing and parent-child agreement on child maltreatment reports are presented in Laura Compier-de Block's dissertation (Compier-de Block, 2017). Further research, for instance on immunology and molecular genetics, is in progress. This dissertation focuses on three biological systems within a family context: heritability, resting state fMRI, and hair cortisol and cortisone.

This Dissertation

In this dissertation, I will address several of the issues mentioned above. The aim is to integrate biological mechanisms in a family design and perspective. In Chapter 2, I will describe how we used the family design to test intergenerational transmission of abuse and neglect and whether reporter effects play a role. This examination of

reporter effects is only possible in a three-generational family design. In Chapters 3 and 4, we will test a potential mechanism of intergenerational transmission of maltreatment: heritability. We leverage the extended family design to estimate the proportions of variability that are accounted by genetic relatedness, and shared and unique environment. In Chapter 3, we test the heritability of perpetrating child maltreatment. In Chapter 4, we investigate the heritability of experiencing maltreatment. We extend previous research by investigating genetic overlap of abuse and neglect and the moderating role of SES. In Chapter 5, we investigate whether dyadic RS connectome similarity is associated with child maltreatment in in parent-child pairs. The overwhelming majority of neuroscientific research has used one-subject designs. The family design allowed us to apply a dyadic perspective. In Chapter 6, we studied the effects of child maltreatment on hair cortisol and cortisone and whether these endocrinological factors explain the effects of child maltreatment on weight. Cortisol may be one biological mechanism of embedding that has long-term consequences for mental and physical health. Figure 1 summarizes the studies. In Chapter 7, I discuss the results of these studies, their implications for ITCM and potential avenues for intervention. I also consider limitations of this line of research, lessons learned and future directions.

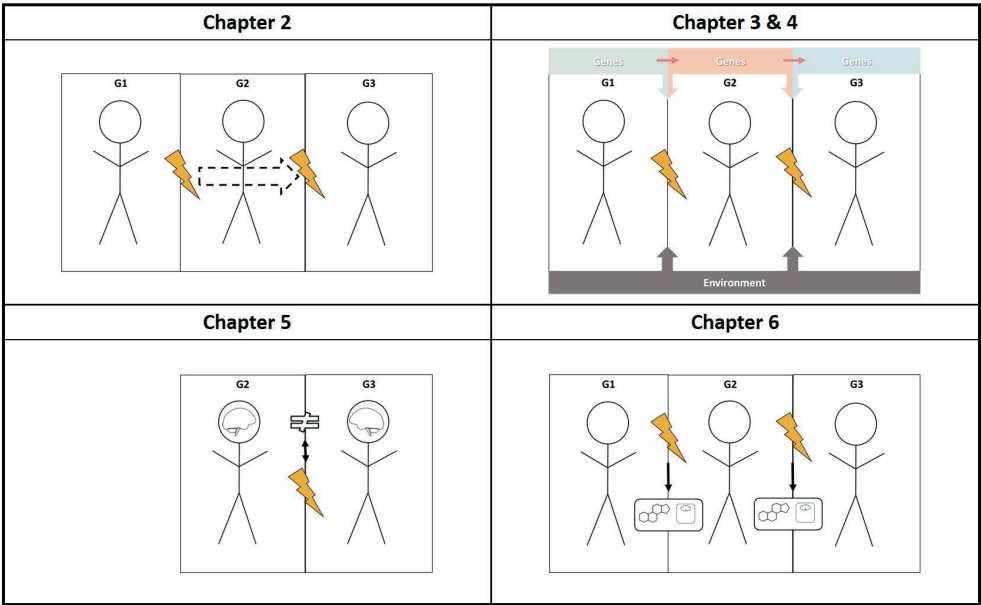


Figure 1: Graphical overview of the empirical chapters of this dissertation. In Chapter 2, we take advantage of the three generational extended family design to test reporter effects on intergenerational transmission of child maltreatment. Chapter 3 and 4, we investigate the heritability and environmental contribution to child maltreatment from a parent and child perspective, respectively. Chapter 5 explores the similarity in the resting state connectomes of parents and children and how this similarity relates to child maltreatment. In Chapter 6, we test the association between experienced maltreatment and hair glucocorticoids and BMI.

Note. The lightning bolt symbolizes child maltreatment.

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