Priska Hubmann

Child Development:

Adaptive Behavior and Biological Embedding

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DEDICATION

To my family and friends for their love, support, and all the shared moments that made me the person I am today.

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Acknowledgements

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Abstract

Childhood seems to represent an important timeline of vulnerability. Previous research indicates that first symptoms of many adult psychopathologies such as depression, anxiety, antisocial personality disorders, etc. can already be observed in early childhood. Therefore, it is crucial to understand the dynamics that lead to maladaptive development, known to pose various challenges on individuals, families, and society. Biological embedding is seen as one underlying mechanism. In this process, early childhood adversities are assumed to result in enduring changes in systems responsible for the physiological stability of an organism, which then may have detrimental consequences for the physical and mental health.

The aim of the present thesis was to provide a different perspective on adaptive child development, and how it is influenced by various risk and protective factors. Moreover, it aims to contribute to a better understanding of underlying biological mechanisms, investigating the associations between stress-related biological parameters and risk and protective factors in early childhood. Two empirical studies were conducted using subsamples of two larger projects.

In the first study, we examined the existence of a general indicator of adaptive child development that is represented by both the absence of problematic and the presence of positive child characteristics. Moreover, we investigated the influence of known contextual risk and protective factors of the home and school environment on this general indicator. Previous studies defined adaptive behavior either as the absence of behavior problems or the presence of positive characteristics. However, as both problematic and positive characteristics seem to be inter-related, a combination of both aspects may provide a better indicator of adaptive child behavior. Data was derived from the first wave of an ongoing population-based multi-cohort longitudinal study called COCON, which aims to investigate the psychosocial development from childhood into adulthood. Primary caregivers and teachers rated six social, cognitive, and personal child characteristics (prosociality, aggression, inhibitory control, attentional focusing, self-efficacy, and anxiety) of 838 preschool children at the age of 6 years, and several risk and protective factors were assessed. Results indicated, that four child characteristics (prosociality, aggression, inhibitory control, and attentional focusing) can be represented by one latent factor, whereas self-efficacy and anxiety are not related to the shared variance of these factors. Findings regarding contextual factors were mostly in accordance with our hypotheses, showing that adaptive development was negatively associated with known risk fac-

tors and positively related to protective factors. Our results provide evidence that although adaptive child behavior cannot be represented by a single global factor, it may be depicted by several aspects of adaptive child behavior, simultaneously involving both problematic and positive child characteristics.

In the second study, we investigated two stress-related parameters (cortisol concentrations in fingernail clippings (NCC) and methylation in the FKBP5 gene) that may play a mediating role in the process of biological embedding of early childhood experiences. High cortisol levels have been associated with behavior problems in preschoolers and higher levels of FKBP5 methylation have been reported in adults and children with a history of child abuse compared to healthy controls. However, so far, few studies have been conducted investigating the role of FKBP5 methylation in child behavior problems, and no study has examined NCC, which could be a promising marker of chronic biological stress, in early childhood. Therefore, we aimed to provide first insights into this new field of research, examining NCC and FKBP5 (intron 7) methylation with regard to child behavior problems and parental sensitivity as a possible protective factor. Moreover, we aimed to investigate the effect of an early intervention program on these two biological parameters. The sample consisted of 142 children and their families from the longitudinal randomized controlled study (ZEPPELIN), which examines at-risk children from birth to adolescence. The intervention group (IG; $N = 77$) received the home visiting program 'Parents as Teachers' (PAT). Parental sensitivity was rated using videotaped interactions at 3 and 12 months postnatal. At 24 and 36 months postnatal, saliva DNA and nail samples were collected, and mothers rated internalizing and externalizing child behavior. In accordance with our expectations, NCC was negatively correlated with FKBP5 methylation. Moreover, parental sensitivity at 12 months positively predicted FKBP5 methylation at 36 months. This association was significantly moderated by group condition with the IG showing a stronger relation. However, FKBP5 methylation was negatively associated with internalizing and (to a lesser extent) with externalizing behavior problems, and was higher in the control group than in the intervention group. No associations with NCC were found. Our results underline the importance of parental sensitivity in early childhood. Nevertheless, high levels of FKBP5 methylation seem not to represent a protective factor per se, and its role in the development of behavior problems has to be further investigated. Meanwhile, NCC seems not to be a useful chronic stress parameter regarding psychosocial factors.

In conclusion, the present thesis provides evidence to examine a combination of both problematic and positive child characteristics when investigating adaptive child development. Moreover, it offers first findings for NCC and FKBP5 methylation regarding central aspects in child development. The novel insights contribute to a better understanding of underlying mechanisms that lead to either maladaptive or adaptive development.

Tables

Figures

Abbreviations

A	Adenine
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit hyperactivity disorder
AUC	Area under the curve
BD	Bipolar disorder
CAPI	Computer-assisted personal interview
CARE-Index	Child-Adult-Relationship-Experimental
CBCL	Child Behaviour Checklist
CBT	Cognitive behavioural therapy
CFA	Confirmatory factor analysis
CFI	Comparative fit index
CG	Control group
CHF	Swiss francs
COCON	Competence and Context – Swiss Survey of Children and Youth
CpG	Cytosine-phosphate-guanine dinucleotides
CRH	Corticotropin-releasing hormone
CSE	Contextual stress exposure
C	Cytosine
DBD	Disruptive behavior disorder
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
fiml	Full information maximum likelihood
FKBP5	FK506 binding protein 5
KEK	Ethics Committee of the Canton Zurich
GR	Glucocorticoid receptor
GRE	Glucocorticoid response elements
G	Guanine
HBS	Heidelberg Stress Scale
HCC	Hair cortisol concentration
HPA	Hypothalamic-pituitary-adrenal
ICC	Intraclass-correlation

IG	Intervention group
ISEI	International Socio-Economic Index of Occupational Status
mlr	robust maximum likelihood
NCC	Nail cortisol concentration
NGS	Next Generation Sequencing
NR3C1	Nuclear receptor subfamily 3, group C, member1
OG-575	Oragene kits for Assisted Collection
PCR	Polymerase chain reaction
PAT	Parents as teachers
PTSD	Posttraumatic stress disorder
PVN	Paraventricular nucleus
RMSEA	Root mean square error of approximation
RNA	Ribonucleic acid
SCC	Salivary cortisol concentration
SDQ	Strengh and Difficulties Questionnaire
SES	Socioeconomic status
SHRP	Stress hyporesponsive period
SNSF	Swiss National Science Foundation
T	Thymine
TRF	Teachers Report Form of the CBCL
ZEPPELIN	Zurich Equity Prevention Project with Parents Participation and Integration
11β-HSD2	11β-hydroxysteroid dehydrogenase

Introduction

Empirical evidence supports the notion of negative developmental cascades, indicating that the presence of one problem behavior in early childhood such as hyperactivity, aggressive behavior, or anxiety increases the risk of developing additional problems resulting in maladaptive development and detrimental long-lasting consequences for physical and mental health (Egger & Angold, 2006; Masten & Cicchetti, 2010). However, the same mechanism is assumed regarding the development of competencies. Positive characteristics such as self-regulation, social competence, and self-efficacy allow children to make positive experiences, which provide them with the opportunity to broaden their competencies, reducing the risk of maladaptive development (Masten & Cicchetti, 2010; Shiner & Masten, 2012). The presence of behavior problems does not exclude the existence of positive child characteristics. Both can be simultaneously present, interacting with each other. Moreover, these interactions have to be understood against the background of a vast amount of influential contextual factors (O'Dougherty Wright, Masten, & Narayan, 2013). Therefore, while adaptive child development can be seen as a combination of various interactions between problematic and positive child characteristics, these characteristics are additionally influenced by several inter-related risk and protective factors. Consequently, this results in an extremely complex model that is far from being completely understood. Many researchers have been examining only single parts of this complex system, focusing on either problematic or positive child outcomes (Masten & Cicchetti, 2010).

The first aim of the present thesis is to contribute to a better understanding of the dynamics that lead to adaptive or maladaptive child development. It is assumed that, instead of investigating either problematic or positive child characteristics, their combination may be more suitable when examining adaptive child behavior. Therefore, preliminary models were developed, testing the existence of an underlying global factor representing adaptive child behavior, involving both problematic and positive child characteristics. Furthermore, the influence of contextual risk and protective factors of the home and the school environment as the most important surroundings for children on this global factor were tested.

The second part of the present work addresses the question if and how child behavior problems in at-risk toddlers are related to FKBP5 methylation and NCC. Moreover, the effects of parental sensitivity and the early intervention program PAT on these two biological parameters are tested. Children living in families that are psychosocially disadvantaged (e.g. low SES, single parenthood) are often at an increased risk of developing behavior problems

that lead to negative long-term consequences (Lanfranchi & Neuhauser, 2013). However, promoting protective factors and supporting the parents may mitigate these negative effects. Parental sensitivity represents one of the most important protective factors in the first years of life and therefore seems to be of special interest (Berry, Blair, Willoughby, Granger, & Mills-Koonce, 2016; Hostinar, Sullivan, & Gunnar, 2014). Moreover, the early intervention program PAT, which is suitable for at-risk children may increase the chance of adaptive development (Neuhauser, 2014). Therefore, behavior problems and the effects of parental sensitivity and PAT are examined with regard to two stress-related biological factors (FKBP5 methylation and NCC). Both FKBP5 methylation and NCC represent hypothalamic-pituitary-adrenal (HPA) axis-related parameters that belong to relatively new fields of research. NCC is considered a promising retrospective marker of chronic biological stress that can be collected more efficiently than basal salivary cortisol levels. Moreover, it is not affected by momentary circumstances such as acute stress, and does not underlie a circadiane rhythm (Ben Khelil et al., 2011; Warnock et al., 2010). To date, only one study investigated NCC in association with psychosocial variables and further research is needed (Warnock et al., 2010). However, findings examining hair, blood, or saliva cortisol indicate that behavior problems in preschoolers are related to higher cortisol levels (Alink et al., 2006; Hartman, Hermanns, de Jong, & Ormel, 2013). Parental sensitivity was reported to be negatively related to cortisol concentrations, emphasizing its role as a protective factor (Ben-Dat Fisher et al., 2007; Letourneau, Watson, Duffett-Leger, Hegadoren, & Tryphonopoulos, 2011). Furthermore, previous early intervention studies were able to effectively reduce basal cortisol levels and normalize diurnal cortisol patterns (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011; Slopen, McLaughlin, & Shonkoff, 2014).

FKBP5 methylation plays a central role in the termination of the stress response, and has recently been discovered as an important underlying mechanism regarding the long-term consequences of child abuse (Klengel et al., 2013). This is in line with the notion of biological embedding that describes enduring changes in biological systems (e.g. HPA axis), which are responsible for maintaining physiological stability. Evidence suggests that such changes can be caused by adverse childhood experiences and may result in detrimental consequences on physical and mental health throughout life (Danese & McEwen, 2012). In fact, previous studies reported associations between adversities in early childhood and various adult physical and mental health disorders (Bayer, Hiscock, Ukoumunne, Price, & Wake, 2008; Kessler et al., 2007). Meanwhile, there is prospective and retrospective evidence indicating that early

child abuse is related to a decrease in FKBP5 methylation, which in turn is associated to adult psychopathologies (Klengel et al., 2013; Tyrka, Price, Marsit, Walters, & Carpenter, 2012). However, no study has been conducted investigating FKBP5 methylation with regard to externalizing and internalizing child behavior problems or parental sensitivity. Only one study investigated the effect of an intervention on FKBP5 methylation in children and the results suggest that treatment responders showed and increase in FKBP5 methylation. Consequently, the second aim of the present thesis is to provide first insights regarding the relations between child behavior problems and the biological stress parameters (FKBP5 methylation and NCC). Moreover, we aim to test the influence of parental sensitivity, and the early intervention program PAT on FKBP5 methylation and NCC.

This thesis consists of three main parts. The first part offers a theoretical background to the research questions of the present thesis and is structured into three chapters. The first chapter introduces and defines the concept of child development and describes central problematic and positive child characteristics that may increase or decrease the chance of adaptive child development. Moreover, the influence of important contextual risk and protective factors from the close environment is depicted. The second chapter introduces the notion of biological embedding of early childhood experiences, which involves the concept of allostasis as a possible mechanism of how early experiences result in long-term consequences for mental and physical health. Next, the function of the HPA axis that represents an important system regarding stress response and allostasis is explained before focusing on the two HPA axis-related parameters of interest: NCC and FKBP5 methylation. NCC has just recently been suggested as a retrospective chronic stress marker and knowledge about the integration of cortisol into the nail is limited. Consequently, for a better understanding of this new stress marker, background information about the structure, growth, and permeabiltiy of the nail is given before summarizing previous findings regarding NCC. Subsequent, an overview of the current literature examining cortisol with regard to the study variables (behavior problems, parental sensitivity, PAT) is given. Similarly, to understand the role of FKBP5 methylation, which represents an epigenetic process, biological background information is provided, explaining the structure of the DNA and describing epigenetic mechanisms. Next, methylation as the most studied epigenetic mechanism is explained and then, the focus is placed on FKBP5 methylation before giving an overview of the current literature on associations between FKBP5 methylation and child behavior problems, parental sensitivity, and intervention programs. In the third chapter, theoretical and empirical findings are integrated and the research questions are presented. The second part of this thesis consists of the results of the two con-

ducted empirical studies. In the third part, the empirical findings are summarized and critically discussed before highlighting methodological strengths and limitations and concluding with an outlook for future research and practice.

PART I: THEORETICAL BACKGROUND

1 Risk and protective factors in adaptive child development

Child development entails a normal life progression with age-dependent physical, emotional, motivational, biological, social, and behavioral changes (Pauen, Frey, & Ganser, 2012). During human development, knowledge, behaviors, and skills are acquired and refined. It is generally accepted that it takes place gradually and in a relatively orderly process. However, interindividual differences are mostly found with regard to how fast and how good the skills are accomplished (Lohaus, Vierhaus, & Maas, 2010; Pauen et al., 2012). The first years are especially important for the development of a child, since developmental processes occur faster than in other life periods. Consequently, children are confronted with various developmental tasks, which they have to manage (Largo, 2001). For example, they start to speak and walk around their first birthday, and they enter school in mid childhood. Early developmental milestones have been defined, enabling observers to evaluate the accomplishment of certain skills in the development. These skills can be subsumed into different domains such as gross and fine motor skills, sensory skills, cognition skills, language skills, emotional skills, and social skills. Normally, developmental milestones are achieved during so-called sensitive periods, and a later achievement is much more difficult (Lohaus et al., 2010). Sensitive periods are thought to be caused by maturational processes in the brain and body. For example, the sensorimotor cortex undergoes maturation between the ages of 2 and 3, supporting the acquisition of motor and sensory skills. Instead, the parietal and temporal cortical regions mature within the first 10 years, enabling language acquisition and spatial attention. On the other hand, the prefrontal cortex develops up to early adulthood, permitting the development of executive functions (Gogtay et al., 2004).

Internal and external challenges constantly increase during development and go along with temporary destabilization and increased insecurity until the milestones are achieved (Pauen, 2011). While these destabilizations and insecurities are part of the normal development, the failure to achieve certain milestones may result in maladaptive development involving later problems or even pathologies. However, maladaptive or adaptive development is an extremely broad concept and has been defined in various ways across different studies. In some studies, the presence of emotional or behavior problems or pathologies served as an indicator of maladaptive development, whereas the absence of these problems or pathologies represented healthy or adaptive development (Benjet, Borges, & Medina-Mora, 2010; Fergusson & Horwood, 2003; Weich, Patterson, Shaw, & Stewart-Brown, 2009). However,

many other studies focused, instead on the development of positive outcomes such as social competence, well-being, academic achievement, etc. (Luthar, 2006; Shiner & Masten, 2012). Most of these latter studies have been conducted within the field of resilience research. Resilience describes "the capacity of a dynamic system to withstand or recover from significant challenges that threaten its stability, viability, or development" (Masten, 2011; p. 494). As the exposure to significant risk that increases the possibility of negative development is one obligatory condition in resilience research, most studies investigated child development after severe adversities such as child physical, sexual, or emotional abuse (c.f. Masten, 2007, 2011). However, in this thesis the interest lies in child development under "normal" or "less severe" circumstances, and therefore, instead of speaking about resilience, the term adaptive child development is used. Evidently, resilience and adaptive child behavior are overlapping constructs, sharing many risk and protective factors.

In this chapter, the focus lies on problematic and positive aspects that have been reported to decrease or increase the chance of adaptive child development. First, the most common early child behavior problems, which involve externalizing and internalizing problem behaviors, are depicted. Children with that show one of these problematic characteristics often show comorbidities. Moreover, comorbidity rates seem to increase during childhood, which possibly leads into a vicious cycle, also called negative developmental cascade, resulting in maladaptive behavior. However, it is assumed that the acquisition of competences works in a similar way with one competence resulting in other competences leading into a positive developmental cascade. Therefore, the notion of developmental cascades is explained before presenting central positive characteristics that can be seen as equivalents to the presented problem behaviors.

1.1 Early child behavior problems

Reports regarding onset dates of psychiatric disorders have shown that many adult mental health problems already start in childhood or adolescence (Kessler et al., 2007; Kim-Cohen et al., 2003). However, it is debatable if preschoolers should be diagnosed with psychiatric disorders since the preschool period involves very rapid physical, behavioral, emotional, and cognitive developmental changes, enhancing the chance of mistaking normal development for psychiatric symptoms. These children, then would be labeled inappropriately (Angold & Egger, 2004). Moreover, there is a relative lack of research on preschool psychopathology compared to studies in older children (Egger & Angold, 2006). Nevertheless, overall preva-

lence rates in preschoolers (ranging from 14%-26%) seem to be similar to the overall rate of disorders reported for older children (for a review, see Egger & Angold, 2006). Furthermore, studies using behavioral checklists show strong evidence of continuity between preschool behavioral and emotional problems and psychopathology in later childhood and even adulthood. Notably, when examining specific disorders, the prevalence seems to vary with age. For example, while attention-deficit hyperactivity disorders (ADHD) show relatively consistent rates across the life span, specific anxiety disorders show remarkable variation in their prevalence (Egger & Angold, 2006). In the following, commonly treated child behavior problems, their prevalence rates, and long-term consequences are presented.

Externalizing and internalizing child behavior problems are among the most commonly treated in mental health settings. Externalizing child behavior problems refer to children's outward negative behavior such as attention deficits, hyperactivity, impulsivity, and aggression, which may result in psychopathologies such as ADHD or disruptive behavior disorder (DBD; including oppositional defiant disorder and conduct disorder) (Campbell, Shaw, & Gilliom, 2000). Internalizing child behavior problems such as depression and anxiety refer to behavior in which children direct feelings and emotions inward (Tandon, Cardeli, & Luby, 2009).

ADHD represents one of the most common diagnosis in early childhood, defined by severe, frequent, or persistent inattention and/or hyperactivity-impulsivity (Wilens et al., 2002). Notably, the definition of the boundaries between normal and clinically significant symptoms is challenging, as the capacity to sustain attention and inhibit behavior is still developing during the preschool years. Overall prevalence rates during preschool range from 2.0% to 5.7% and remain highly stable throughout the life span, with symptoms and impairments extending in over 50% of the cases. However, symptoms of hyperactivity/impulsivity are more common than inattentive symptoms. While the latter remain relatively stable, hyperactivity symptoms show an age-related decline during the early school years (Egger & Angold, 2006; Leopold et al., 2016). DBDs have a prevalence rate between 3.3% and 6.8% (Egger & Angold, 2006). Evidence suggests that oppositional and aggressive symptoms show much higher rates around the ages of two and three, and a decrease during later childhood years (Keenan & Wakschlag, 2000). However, some children maintain a high level of disruptive and defiant behaviors after the age of three. Around 60% of these children still show behavior problems during late childhood, and they are at an increased risk of developing adult disruptive or affective disorders (Alink et al., 2006; Cierpka, 2012; Keenan & Wakschlag, 2000; Shaw, Gilliom, Ingoldsby, & Nagin, 2003).

Concerning internalizing behavior problems, depressive disorders seem to be less common in preschoolers with a prevalence rate up to 2%, increasing from toddlerhood to adulthood (Egger & Angold, 2006). Meanwhile, rates of anxiety disorders vary considerably in different studies, depending on which specific anxiety disorder was investigated. When summarizing these into one variable representing any anxiety disorder, the rates seem to lie between 9% and 10%, similar to school age children and adolescence, whereas prevalence rates in adults were twice as high (c.f. Egger & Angold, 2006).

Usually, adults continue to suffer from the same disorders they have had in childhood or adolescence (homotypic continuity). This seems to be especially true for internalizing behavior problems (Kim-Cohen et al., 2003). However, associations with detrimental long-term consequences are stronger for externalizing behavior problems, whereas relations for internalizing behavior problems can mostly be explained by comorbid externalizing problems or parental socioeconomic status (SES; Evensen, Lyngstad, Melkevik, & Mykletun, 2016; Fergusson, Boden, & Horwood, 2007). Externalizing problem behaviors in childhood are associated with academic underachievement, interpersonal problems, persistent antisocial behavior, incarceration, long-term substance dependence, and employment difficulties in later life (Brumley & Jaffee, 2016; Goldstein & Rider, 2013; Odgers et al., 2008; Reef, Diamantopoulou, van Meurs, Verhulst, & van der Ende, 2011).

1.2 Developmental cascades

While behavior problems can already be observed in early childhood, the risk of developing additional problematic symptoms seems to increase with age. Therefore, early symptoms may represent the beginning of a vicious cycle, in which problematic characteristics lead to other problematic aspects, starting a negative developmental cascade.

In general, comorbidity rates in preschoolers are relatively high. Anxiety is associated with depression, ADHD, and DBD, which in turn are inter-correlated themselves (Keenan, Shaw, Walsh, Delliquadri, & Giovannelli, 1997; Overgaard, Aase, Torgersen, & Zeiner, 2012). Notably, oppositional defiant disorders seem to play a central role, mediating the relations between anxiety and depression, depression and conduct disorder, and depression and ADHD (Egger & Angold, 2006). Studies indicate that around 25% of the children with internalizing disorders show also externalizing disorders and vice versa (Keenan et al., 1997; Overgaard et al., 2012). In the study from Egger and Angold (2006), 8% of the preschoolers showed at least one psychiatric disorder. Within these 8%, 51.6% showed no comorbidities,

whereas 25.8% had two types of disorders and 22.6% three types of disorders. Importantly, the proportion of children showing comorbidities increased about 1.6 times each year from age 2 (18.2%) to 5 (49.7%), reducing the chance of positive adjustment while precipitating a cascade of adverse outcomes into adulthood (Egger & Angold, 2006; Goldstein & Rider, 2013).

Developmental cascades are defined as cumulative consequences for development, which result out of various interactions and transactions in developing systems, spreading across levels, domains, and systems. The function in one domain is assumed to influence the function in other domains, and therefore, adaptive and maladaptive functions can spread over time, promoting or undermining development (Masten & Cicchetti, 2010). For example, inattention, hyperactivity, and impulsivity can quickly lead to underachievement, low self-esteem, and interpersonal difficulties or even social rejection and neglect (Barkley, Fischer, Edelbrock, & Smallish, 1990; Milich, Landau, Kilby, & Whitten, 1982). In turn, these problems increase vulnerability for depression and anxiety, and reduce opportunities to develop appropriate social interactions, keeping up a vicious cycle (Goldstein & Rider, 2013).

However, it is assumed that developmental cascades can also be positive, in that competence begets competence, resulting in adaptive behavior (Masten & Cicchetti, 2010). For example, early cognitive abilities were associated with later fluid intelligence (Fry & Hale, 1996), and indirect associations between early behavior and later intellectual functioning were reported (Bornstein et al., 2006). Therefore, it seems important not only to look at problematic aspects that could challenge adaptive development, but also to investigate positive characteristics that may prevent negative developmental cascades or even lead into positive cascades.

1.3 Positive child characteristics

The achievement of key developmental tasks seems to play a central role in developmental models of competence (Masten, Burt, & Coatsworth, 2006). The capacity of self-regulation, the ability to build positive relationships, and the belief in one's own capacities represent key developmental tasks that have been reported to result in less negative and more positive developmental outcomes. These positive child characteristics are assumed to represent equivalent aspects to the aforementioned behavior problems. While self-regulatory competences such as inhibitory control and attentional focusing can be seen as opposite endings of ADHD symptoms, prosociality may be the counterpart of aggression, and self-efficacy may represent

a central aspect that is missing in anxiety. In the following chapter, the role of these three positive aspects on adaptive child development will be described.

One of the most important key developmental tasks in the first years of life is the ability of self-regulation (Lewis, Zimmerman, Hollenstein, & Lamey, 2004). Self-regulation not only refers to the ability to regulate bodily functions such as sleep and urinary excretion, but also to the ability to control automatic behavioral response tendencies by inhibiting undesirable and exhibiting alternative behaviors (inhibiting control), and to maintain, direct, and focus attention (attentional focusing; Smith-Donald, Raver, Hayes, & Richardson, 2007). Inhibitory control and attentional focusing are often summarized into one dimension that is called "effortful control" (Stevens, Bardeen, & Murdock, 2015), or integrated into the concept of executive functioning. Together with other cognitive factors such as working memory, executive functioning plays a role in goal-oriented behavior (Garon, Bryson, & Smith, 2008). Effortful control seems to develop from the age of 2 to 7 (Kochanska, Murray, & Harlan, 2000; Rothbart, Ahadi, Hershey, & Fisher, 2001). It is negatively related to anxiety, anger, peer conflict, and externalizing problem behaviors, but positively related to rule-abiding behavior, low antisocial solutions to hypothetical dilemmas, and delay of gratification. Moreover, it predicts long-term quality of social competence, with higher sociability, better communication, and more assertiveness in peer relations (Acar, Rudasill, Molfese, Torquati, & Prokasky, 2015; Muris, van der Pennen, Sigmond, & Mayer, 2008; Valiente, Smith, Fabes, Guthrie, & Murphy, 2003).

Another important dimension in early child development is the ability to build positive social relationships (Pauen, 2011). Newborns are already able to regulate closeness and distance in relationships. After the age of one, children start to realize that others have different needs and wishes, and initial prosocial behaviors can be observed (Warneken & Tomasello, 2006). Prosociality refers to behaviors that benefit other persons such as sharing and helping others. It often involves increased perspective taking, interactional skills, empathy, and emotional regulation (Eisenberg, Fabes, & Spinrad, 2006; Griese & Buhs, 2014). During middle childhood, peer relationships become more central and prosocial children are less likely to be victimized by peers. Moreover, children showing prosocial behavior were found to be able to establish adaptive peer relationships despite victimization or aggression (Griese & Buhs, 2014). Furthermore, prosocial children were seen as more attractive, felt less lonely, and were more likely to show positive self-concepts and greater self-efficacy (Eisenberg et al., 2006; Griese & Buhs, 2014; Laible & Carlo, 2004). Eisenberg et al. (2006) argue that children with

positive self-concepts and higher self-efficacy feel better about themselves, which leads to less self-focused and more other-oriented behavior, having more resources to assist others.
Self-efficacy can be generally defined as personal beliefs in one's one capabilities. It is grounded in the social cognitive theory proposed by Bandura (1986), which assumes that individuals are self-organizing, proactive and self-reflecting organisms influenced by the environment or inner impulses. Self-efficacy beliefs determine how people feel, think, behave, and motivate themselves, and consequently are involved in every aspect of people's lives. Self-efficacy positively predicts academic performances, work and life satisfaction, and mental health outcomes (Judge & Bono, 2001; Pajares, 2005; Wille, Bettge, Ravens-Sieberer, & BELLA study group, 2008). In contrast, people who doubt their own capabilities have low aspirations, draw back from difficulties and show weak commitment to their own goals. Low self-efficacy has been found to be related to depression, anxiety, and ADHD (F. Klasen et al., 2015; Major, Martinussen, & Wiener, 2013; Tahmassian & Moghadam, 2011).

1.4 Summary

Development in early childhood seems to be of special importance, as it happens very fast and goes along with sensitive periods indicated by maturational processes in the brain. Every child has to acquire various competencies and skills to achieve the expected milestones, leading to an adaptive and healthy development. However, challenges and responsibilities increase with age and some children show difficulties in this adaptational process.

Although it is especially challenging in early childhood to distinguish between normal development and psychopathology, externalizing and internalizing behavior problems are unmistakably already present during preschool years. They may lead to deleterious long-term consequences posing various challenges for individuals, families, and society. DBDs and anxiety disorders seem to be common in preschoolers with DBD showing a peak around two to three years, which is also called the "terrible two's" or "the terrible three's" (Keenan & Wakschlag, 2000). Meanwhile, ADHD rates seem to be relatively stable throughout life, whereas depression rates are low during the preschool years and increase into adulthood.

Moreover, externalizing and internalizing behavior problems are highly comorbid, with increasing comorbidity rates into middle and late childhood, supporting the notion of negative developmental cascades. However, developmental cascades can be positive or negative, leading to maladaptive or adaptive behavior, respectively. On the one hand, externalizing symptoms such as impulsivity, inattention, and aggression, and internalizing symptoms such as

depression and anxiety increase the risk of maladaptive child development. On the other hand, positive factors such as effortful control, including inhibitory control and attentional focusing, prosociality, and self-efficacy increase the likelihood for adaptive child development, possibly leading to a virtuous cycle.

1.5 Contextual risk and protective factors

In the previous chapter, the focus has been on the child as an individual, who can display various problematic or positive characteristics, indicating adaptive or maladaptive development. However, development is influenced by numerous environmental factors that interact with child characteristics. Consequently, when investigating adaptive child behavior, these contextual factors have to be considered.

According to Bronfenbrenner (1979), environmental factors can be divided into several social subsystems: microsystem, mesosystem, exosystem, macrosystem, and chronosystem. The microsystem refers to the close surrounding of an individual, and mostly involves interactions with family members, people at school or at work. Instead, the mesosystem describes interrelated surroundings of the microsystem such as the relationship between the parents and the school or teacher. The exosystem refers to surroundings and relationships that are not directly linked to the individual, but can have indirect effects; as for example, friends of the parents, who can influence parental behaviors. The macrosystem involves values and other aspects of the society, culture, and subculture an individual is living in. Finally, the chronosystem indicates that all subsystems are interrelated and are constantly developing. Consequently, child development should be viewed against the background of all these subsystems, which themselves are constantly changing. However, due to the high complexity of the whole system and the many influential factors to control for, most of the studies in this area have focused on the microsystem, as it is the closest subsystem to the individual (Lohaus et al., 2010). Therefore, the following chapter concentrates on the microsystem. As the family and school environment often represent the most constant and important surroundings for young children, an overview of known risk and protective factors is given. However, investigating all of them would result in a model too complex to be tested. Therefore, some of the most studied and central risk and protective factors (socioeconomic status, parental conflicts, harmonious parental relationship, strict parenting, peer victimization, and classroom climate) have been selected, describing their influence on adaptive child behavior.

1.5.1 Home environment

A vast amount of risk and protective factors within the family has been identified. Table 1 presents some of these factors assembled from Lohaus et al. (2010), O'Dougherty Wright, Masten, and Narayan (2013), and Olsson, Bond, Burns, Vella-Brodrick, and Sawyer (2003).

Table 1. Risk and protective factors of the home environment

Risk factors	Protective factors
• Constant family or parental conflicts including partner violence • Frequent changes of the attachment figure • Mental or physical disorders of the parents, or high levels of stress • Problematic parenting styles (e.g. authoritarian, laissez-faire) • Low socioeconomic status (low income, low parental education, crowded living conditions, big family) • Parents unemployment • Parents criminality • Single parenthood • Loss of a parent (separation, divorce, death) • Mother employed before 12 months postpartum • Age-intervals to siblings less than 18 months • Disabilities of siblings • Young mother (Primipara < 20 years) • Unwanted pregnancy • Placement (e.g. institution, foster care) • Frequent relocations • Physical, sexual, emotional child abuse	• Cohesion and care within the family • Harmonious parental relationship • Secure attachment • Parental sensitivity • Healthy parents • Positive parenting style (authoritative, non-blaming, structured) • Socioeconomic advantages (above-average income, postsecondary education) • Positive parent-child relationship (warmth, encouragement, assistance) • Positive sibling relationships • Daily routines and structures • Social support • Faith, religious affiliation

It becomes clear that the distinction between risk and protective factors is not always obvious. The absence of a risk factor is sometimes seen as a protective factor and vice versa (e.g. criminality of a parent). Moreover, risk and protective factors can often be seen as opposite poles of the same dimension (Lösel & Bender, 2014). For example, while low socioeconomic status (SES) represents a risk factor, above-average SES functions as a protective factor. A vast amont of research has been conducted examining the influence of low SES, which seems to have a direct effect on child development. Other relevant chronic risk and protective factors

known to be directly linked to child development are parental relationship quality and parenting styles.

SES refers to a broad concept that depicts the placement of a person or family with regard to its capacity to create or consume goods, which are valued within the corresponding society (Miech & Hauser, 2001). Low SES affects different areas of social life and goes along with decreased access to education and health care. Evidence suggests that socioeconomically disadvantaged children are at increased risk of developing mental health disorders and show higher mortality rates (for systemic reviews, see Reiss, 2013; Russell, Ford, Williams, & Russell, 2016). Moreover, the development of mental health problems were two to three times more likely in children and adolescents with low SES compared to children with high SES, and stronger in younger children than in those aged 12 or above. More frequent exposure to poverty was associated with greater risk of mental health problems (Najman et al., 2010). Furthermore, a decrease in SES was associated with an increase in mental health problems, and an increase in SES was related to a reduction of mental health problems and subsequent remission. These associations were stronger and more robust with regard to externalizing disorders than internalizing disorders (Amone-P'Olak et al., 2009; Boyle & Lipman, 2002; Davis et al., 2010).

In contrast, other studies have found higher stronger relations between low SES internalizing disorders (Vollebergh et al., 2006; Wight, Botticello, & Aneshensel, 2006), or no differences at all (Tonge, Hughes, Pullen, Beaufoy, & Gold, 2008). When examining specific types of disorders, studies showed a negative association with depression, anxiety, antisocial behavior, conduct disorders, and ADHD. Moreover, children with low SES were more likely to show comorbidities than peers with high SES (c.f. Reiss, 2013). It should be noted, that SES is often conceptualized differently, with the majority of the studies independently examining household income, parental education levels, and occupation status. Other studies have been looking at relative poverty, defined as lower than the average income level of the corresponding country, the receipt of welfare benefits, or a calculated index of SES, involving income, education, and occupation (Reiss, 2013). Nevertheless, findings are relatively consistent despite the heterogeneity of the assessment of SES. Differences have been found regarding the effect sizes, with household income and parental education showing stronger relations than parental unemployment or occupational status (Reiss, 2013).

Parental conflicts are known to have detrimental effects on children (for a review, see Sarrazin & Cyr, 2007). In many cases, children not only are witnesses to their parents' conflicts but also get trapped into harmful dynamics, often leading into conflicts of loyalty, caus-

ing feelings of anxiety and guilt. Higher frequency of parental conflicts has been found in children and adolescents showing maladaptive development. Affected children show inferior academic results and social skills, higher levels of depression and anxiety, of delinquency, antisocial behavior, disobedience, and aggression (c.f. Sarrazin & Cyr, 2007). In contrast, the extent to which parents engage in positive interactions with each other has been associated with child well-being and adaptive child development (Berger & McLanahan, 2015; Goldberg & Carlson, 2014). Children may learn positive ways of interaction, observing their parents. Moreover, marital relationship quality was found to be positively related to the quality of parent-child interactions, indirectly influencing child well-being (c.f. Goldberg & Carlson, 2014). In two recent studies, higher parental relationship quality was negatively associated with internalizing and externalizing child behavior problems in married or cohabiting families with biological fathers or stepfathers (Berger & McLanahan, 2015; Goldberg & Carlson, 2014). Moreover, an increase in supportiveness within the marital relationship was related to a decrease in behavior problems (Goldberg & Carlson, 2014). However, effect sizes were small and associations are assumed to vary over the course of development, since the children's understanding of their parents' relationship changes over time (O'Brien, 2005). It is expected, that parental relationship quality shows greater effect on younger children, whereas, child behavior influences parental relationship quality, as the children grow older (Goldberg & Carlson, 2014). Further research is needed to clarify relations and causalities. Notably, high relationship quality was found to go together with higher parenting quality, particularly in fathers (Carlson, Pilkauskas, Mclanahan, & Brooks-Gunn, 2011).

Parenting styles play a crucial role in child development, as they are part of the direct parent-child interaction, and also due to their assumed mediating or moderating role on the effects of several other influential factors such as SES or parental relationship quality. Evidence suggests that self-reported parenting styles were able to explain 44% of the variance in externalizing behaviors (Rinaldi & Howe, 2012). There are two main dimensions, parental acceptance/responsiveness and demandingness/control, which are generally accepted and can be combined into four parenting styles: authoritative (high responsiveness & high control), permissive (high responsiveness & low control), authoritarian (low responsiveness & high control), and uninvolved (low responsiveness & low control) (Baumrind, 1967; Grolnick, 2003). While the authoritative parenting style has proven to have beneficial effects for the child, all other parenting styles are related to less positive outcomes such as increased internalizing and externalizing behavior problems (Aunola & Nurmi, 2005; Booth-LaForce & Oxford, 2008; Rinaldi & Howe, 2012). Acceptance/responsiveness generally is seen as a posi-

tive characteristic, but its effect on child development seems to depend on the amount of exerted control on the child. Both, too much or too little control seems to have negative effects. As early childhood represents a period marked by autonomy growth, exploration, emotion regulation, etc., monitoring or control in terms of clear, but flexible boundaries, may provide support to the children, giving them structure and guidance (Rinaldi & Howe, 2012). In fact, monitoring and autonomy support were found to be negatively related to externalizing behavior problems in adolescents such as alcohol abuse (Donaldson, Handren, & Crano, 2016; Rinaldi & Howe, 2012). In contrast, extreme or strict parental control involving a lack of reasoning was associated with both internalizing and externalizing problems (Aunola & Nurmi, 2005; Ozer, Flores, Tschann, & Pasch, 2013; Rinaldi & Howe, 2012).

1.5.2 School environment

Next to the home environment, kindergarten or school also represent constant and important environments for children. Various research has been conducted examining risk and protective factors (for an overview, see Goldstein & Brooks, 2013a). As children grow older, peers get more important, and the influence of the parents decreases. On the one hand, peer interactions enable the acquisition and improvement of social skills and peers may be seen as guiding models. On the other hand, negative group dynamics and negative peer relationships increase the risk of maladaptation (Lohaus et al., 2010).

Bullying and victimization pose serious challenges to teachers and schools. Bullying includes a range of destructive behaviors such as hitting, kicking, threatening, destroying others' belongings, harassing, disparaging, or verbal abuse (Lösel & Bender, 2014). In an average classroom, one out of every seven children reports being bullied, often responding with self-imposed isolation (National School Savety Center, 2006; Taub & Pearrow, 2013). Social exclusion, name-calling, and spreading rumors even increase in middle and high school (Taub & Pearrow, 2013). According to a US large-scale survey with children in grades three to five, around 13% tried to start a fight, 27% hit someone, 15% of the children had been sent to the office for disciplinary problems, and 12% stated being threatened by a knife or a gun in the past week (Embry, Flannery, Vazsonyi, Powell, & Atha, 1996). Children exposed to peer victimization have been reported to feel more anxious, insecure, depressed, lonely, and to possess lower self-respect compared to their non-exposed classmates (Buhs & Ladd, 2001; Yoleri, 2015). Moreover, they face more problems adjusting to school, enjoying school less, developing negative attitudes towards school, and being more inclined to absenteeism

(Kochenderfer-Ladd & Wardrop, 2001; Yoleri, 2015). Some children that have been exposed to victimization also display negative behaviors such as aggression, and may even themselves start bullying (Goldstein & Brooks, 2013b). Notably, victimization can already happen in kindergarten. In a recent study, victimization in preschoolers was found to be positively associated with hostile and aggressive behavior, anxiety and fear, and hyperactivity-distractibility, while it was negatively associated with school adjustment (Yoleri, 2015). Externalizing behaviors at the beginning of school in turn increases the probability of later peer victimization (Pettit, Bates, & Dodge, 1997).

In contrast, good school and classroom climates increase the chance of adaptive child development (Cohen, 2013; Doll, 2013; Taub & Pearrow, 2013). Classroom emotional climate refers to a global classroom atmosphere, which is supportive and functions harmoniously (Wilson, Pianta, & Stuhlman, 2007). Positive classroom environment was found to facilitate the development of emotion regulation and social skills (Howes, 2000; Pianta, la Paro, Payne, Cox, & Bradley, 2002). It shows positive relations with social competence, cognitive performance, and quality of child-teacher relationship, and negative associations with externalizing problems rated by both mothers and teachers (Yan, Zhou, & Ansari, 2016). Moreover, a positive classroom climate protects children with risks for reading disabilities and those with problem behaviors such as disruptive behavior, anxiety, and loneliness from peer rejection (Avant, Gazelle, & Faldowski, 2011; Kiuru et al., 2012), and protects aggressive children from school failure (Downer, Rimm-Kaufmann, & Pianta, 2007).

1.5.3 Summary

Child characteristics play a central role in child development. However, they are constantly influenced by a broad range of contextual factors. Most research has focused on the microsystem and identified several risk and protective factors within the home and the school environment. Concerning the home environment, SES, the relationship of the parents, and parenting styles have proven to be important indicators of adaptive or maladaptive child development. While low SES, parental conflicts, and strict parenting control were found to be related to both externalizing and internalizing behavior problems, above-average SES, high parental relationship quality, and low strict control seem to promote adaptive behavior. Regarding the school environment, victimization is of great concern, as it may already start in kindergarten, occurs frequently, and often leads to maladaptive child development. In contrast, a good classroom climate enhances social competences, and protects children at risk from possible social rejection and school failure.

2 Biological Embedding

As described above, childhood seems to represent an important timeline of vulnerability and adaptive development. There is convincing evidence from prospective and retrospective studies that early childhood experiences have long-lasting consequences on health. Childhood adversities were shown to be significantly associated with adult mental and physical health problems such as depression, anxiety, auto-immune disorders, cardiovascular diseases, etc. (Danese & McEwen, 2012; Gluckman, 2008; Mersky, Topitzes, & Reynolds, 2013; Provençal & Binder, 2014; Shonkoff, Boyce, & McEwen, 2009). This may be due to the fact that childhood consists of sensitive periods for brain development represented by elevated region- and neuron-specific plasticity (Gröger et al., 2016). Chronic stress and early adverse experiences are assumed to lead to enduring changes in biological systems, which are responsible for maintaining physiological stability (for a review, see Danese & McEwen, 2012). This process is called biological embedding and has been suggested as an underlying mechanism explaining how early experiences 'get under the skin' resulting in long-term consequences for mental and physical health (Danese & McEwen, 2012). The process of biological embedding relies on the concept of allostasis, which is described in the following chapter.

2.1 Allostasis

Allostasis refers to the process of maintaining stability (homeostasis) of key physiological variables through physiological and behavioral changes (McEwen, 1998). Key physiological variables such as body temperature and energy balance are relatively stable and only narrow variations are compatible with life. However, humans and animals are in constant interaction with the environment, which itself underlies constant changes, threatening homeostasis. Therefore, biological processes themselves underlie changes in order to maintain stability and ensure survival. This involves the ability to detect contextual and internal variations and to activate specific adaptive responses (Sterling, 1988). Biological systems that are known to have the ability to mediate allostatic processes are the nervous, the immune, and the endocrine systems, which are highly interrelated. At birth, these systems are not fully matured and undergo substantial changes during childhood which seem to be highly regulated by early experiences (Danese & McEwen, 2012; Del Giudice, Ellis, & Shirtcliff, 2011; Hostinar et al., 2014).

In response to psychosocial stress, alertness and attention to the environment is increased and the sympathetic nervous system is activated, leading to a fight or flight response. This involves physiological changes such as an increase in catecholamines, heart rate, blood pressure, breathing frequency, the dilatation of the pupils, vasoconstriction, and a reduced secretion of saliva. Moreover, inflammation is triggered as an immune response to prevent infection of possible tissue damage (Bierhaus et al., 2003). Furthermore, a neuroendocrine stress response is induced, stimulating the hypothalamic-pituitary-adrenal (HPA) axis (described in detail in chapter 2.2). While these systems seem to promote short-term adaptation to environmental changes, chronic or repeated exposure to psychosocial stressors has been associated with a prolonged activation of nervous, immune, and endocrine systems, leading to allostatic load or even overload with detrimental physiological consequences (McEwen, 1998; McEwen & Wingfield, 2003).

It is suggested that in addition to such chronic stressors, stress experienced in sensitive developmental windows may induce similar biological changes (biological embedding), which modify the responsiveness of the nervous, immune, and endocrine systems, leading to long-term effects on physical and mental health (Danese & McEwen, 2012; Del Giudice et al., 2011; Gunnar & Quevedo, 2007; Hostinar et al., 2014). For example, previous research found that maltreated individuals show structural and functional abnormalities in the prefrontal cortex, which in turn have been related to behavioral disorders such as ADHD, conduct problems, and antisocial behavior (Moffitt et al., 2008) and to depression and posttraumatic stress disorder (PTSD) (Nanni, Uher, & Danese, 2012). Moreover, elevated inflammation levels and a stronger inflammatory stress response were found in victims of maltreatment (for a review, see Danese & McEwen, 2012). Concerning the endocrine system, children and adults with a history of childhood maltreatment showed chronic activation of the HPA axis (e.g. Carpenter et al., 2004; Carrion et al., 2002; Cicchetti & Rogosch, 2001). In contrast, no HPA axis abnormalities were found in adults without a history of child abuse, who suffered from current psychopathology, compared to healthy controls (Heim et al., 2000; Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008). Interestingly, adults that stayed healthy despite having experienced maltreatment in childhood exhibited similar HPA axis changes as healthy children with a history of child abuse (Carpenter et al., 2007, 2009). Danese and McEwen (2012) pointed out that while maltreated individuals with or without current psychiatric disorders exhibit chronic activation of the HPA axis, they seem to differ in HPA axis response to psy-

chosocial stressors. Maltreated individuals with current psychiatric disorders seem to show a blunted response to stressors, whereas those without current psychiatric disorders seem to show a heightened stress response.

In conclusion, the nervous, immune, and endocrine systems contribute to the adaptation and stability of key bodily functions. However, when facing extreme circumstances such as child maltreatment or chronic stress, these adaptations, although protective in the short-run, can lead to profound functional impairments throughout the life-course (Danese & McEwen, 2012). One of the most studied systems within the framework of allostasis is the HPA axis, and its end product cortisol has been found to play a central role in various mental and physical disorders throughout life (Alink et al., 2006; Del Giudice et al., 2011; Herane Vives et al., 2015).

2.2 Hypothalamic-Pituitary-Adrenal Axis

The HPA axis represents one of the primary physiological stress response systems among humans and animals. It interconnects the central nervous system with the periphery via hormonal signaling (Nawroth & Ziegler, 2001). When cortico-limbic and brain stem structures are activated, they stimulate the hypothalamus. The hypothalamus is responsible for the integration and regulation of somatic, endocrine, and vegetative processes (Nawroth & Ziegler, 2001). Once activated, a hormonal cascade starts: The paraventricular nucleus (PVN) in the hypothalamus releases the corticotropin-releasing hormone (CRH), which induces the secretion of the adrenocorticotropic hormone (ACTH) from the anterior pituitary. Via bloodstream ACTH reaches the cortex of the adrenal gland, where it stimulates the production and secretion of the lipophilic glucocorticoid cortisol (Ehlert, 2013). Released cortisol binds to the intracellular glucocorticoid receptor (GR), a protein, which is distributed throughout the brain and body, causing the GR to translocate into the nucleus. There it binds to specific DNA sequences on cortisol-responsive genes, called glucocorticoid response elements (GREs), and regulates the expression of a variety of genes (Kadmiel & Cidlowski, 2013; Magee, Chang, Stormo, & Milbrandt, 2006). Multiple feedback mechanisms are involved in the regulation of the HPA axis activity. In a short feedback loop, ACTH signals back to the PVN, inhibiting further release of CRH. Moreover, in two long feedback loops, cortisol from the adrenal gland inhibits further release of ACTH in the pituitary, and reduces the secretion of CRH in the PVN (Fritsch & Kühnel, 2005).

2.3 Cortisol in child development

There is a vast amount of literature showing that stress leads to an activation of the HPA axis, and therefore to an increased level of its end product cortisol (Böhmelt, Nater, Franke, Hellhammer, & Ehlert, 2005; Gaab et al., 2003; Hammerfald et al., 2006; Kirschbaum, Pirke, & Hellhammer, 1993; Kudielka & Wüst, 2010; Wirtz et al., 2007). Cortisol regulates numerous basal processes such as fat and glucose metabolism, blood pressure, inflammatory and immune responses. Moreover, it helps the organism maintaining a circadian rhythm with its secretion showing a peak in the morning and a decrease over the day (Kudielka & Wüst, 2010).

Research examining cortisol in adult and child mental health disorders show many inconsistencies. Regarding child behavior, positive and negative as well as no associations have been found (for a review, see Alink et al., 2006). Therefore, the role of cortisol in adaptive child behavior is still unclear and more research is needed. As psychosocially disadvantaged children are exposed to many risk factors that may reduce the chance of adaptive behavior, special interest lies on the question if protective factors have a positive effect on the HPA axis activity, possibly reducing negative outcomes. One of the most important protective factors in the first year of life represents parental sensitivity (Berry et al., 2016; Hostinar et al., 2014). Moreover, early intervention in these children may prevent negative biological embedding by reducing risk factors and promoting protective factors, enabling them an adaptive development (Neuhauser, 2014). Therefore, in this chapter, the role of cortisol in child behavior problems is described before presenting empirical findings concerning the association between cortisol and parental sensitivity. Finally, prior research investigating the effect of intervention programs on cortisol is described. However, as cortisol can be derived from various tissues, important methodological aspects have to be considered first.

Cortisol concentrations can be measured in blood, saliva, and urine. However, measurements from those three tissues represent momentary cortisol concentrations within minutes (blood/saliva) to hours (urine) at the time of sampling. Moreover, the cortisol levels are influenced by timing, the collection method, and various situational factors such as contextual stressors, sleep patterns, diet, mood, etc. (Hansen, Garde, & Persson, 2008). Therefore, it is difficult and time consuming to assess chronic stress in terms of long-term cortisol levels. In the last decade, keratinized structures such as hair and nails have been increasingly investigated as an alternative approach for cortisol measurement. Hair and nails are assumed to provide

retrospective information of stress over several months that is not affected by diurnal or momentary changes in HPA axis activity (Stalder & Kirschbaum, 2012; Warnock et al., 2010). For example, cortisol is assumed to enter the hair via blood, sebum, and sweat, staying there as the hair grows. Considering the average hair growth of 1cm per month, the first proximal 5cm of a hair strand is thought to represent stress during the first to the fifth previous months (Russell, Koren, Rieder, & Van Uum, 2012). Regarding the aforementioned need of finding a biological marker that represent chronic stress, both hairs and nails can be seen as promising parameters, helping identify individuals at risk for maladaptive developmental outcomes. However, while several studies have been investigating hair cortisol concentrations (HCC), only one study has been conducted examining nail cortisol concentrations (NCC) in relation with psychosocial variables (Warnock et al., 2010). For a better understanding of this promising new chronic stress marker, background information about the structure, growth, and permeability of the nail is provided before investigating its role in the aforementioned psychosocial variables.

2.3.1 Nail structure and growth

The nail plate consists of 80-90 layers of compacted keratinized epithelial cells, and can be divided into three histochemically different plates: the dorsal, the intermediate, and the ventral nail plate (Figure1). The dorsal plate is physically hard and provides some water resistance due to the high phospholipid and calcium content. In contrast, the intermediate plate has little phospholipids and calcium. Finally, the ventral plate, which is only one or two cells thick, seems to be a variable entity (for a review, see de Berker et al., 2007). In contrast to hair, which consists of 'hard' keratin only, nail was found to contain both 'soft' and 'hard' keratin. 'Hard' or 'hair-type' keratin has many cysteine disulfide cross-links between the keratinized cells, which reduce its flexibility. However, 'soft' or 'skin-type' keratin contains few disulfide links. It can be stretched but returns back to the normal state upon relaxation of tension (Heid, Moll, & Franke, 1988). The different layers of the nail plate are mainly produced by different regions of the nail matrix, in which cells become larger and paler as their nucleus disintegrates. These so-called onychocytes are then flattened and elongated. The matrix is protected by the nail fold, but often can be seen in the thumbs and big toes. The visible part of the matrix is called lunula or half-moon. Once the matrix is damaged, it is difficult to repair it (de Berker et al., 2007). However, while approximately 79% of the nail plate is produced by the

matrix, 21% is formed by the underlying nail bed (Johnson, Comaish, & Shuster, 1991). The nail bed is firmly attached to the nail plate and contains many blood vessels, giving it a pink color (de Berker et al., 2007).

Average linear fingernail growth rates lie between 2-3 mm per month, which corresponds to 1/3rd of the average hair growth (Gupta et al., 2005). However, there are differences in nail growth rates depending on the digit that is examined. The biggest linear growth rates were found for the middle fingers, whereas the little fingers grew the slowest. Additionally, nails on the right hand were found to grow faster than those on the left hand (Gupta et al., 2005). This may be because the majority of people are right-handed. They use their right hand more than their left hand, which leads to higher blood circulation in the right hand. High blood circulation in turn is assumed to increase nail growth, whereas a strongly diminished blood flow leads to the production of pathogenic keratin, which may cause discoloration and fungal infections (Raab, 2012). Low blood circulation also seems to be the cause of the growth rates in toenails, which grow at half the pace of fingernails (1-1.5mm per month).

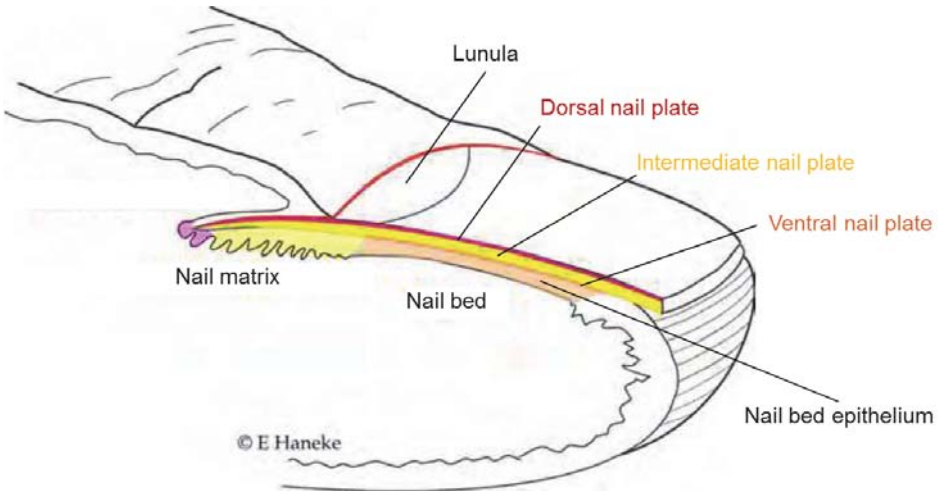

Figure 1. Longitudinal cross-sectional anatomy of the nail apparatus

Adapted version with friendly permission from Haneke (2012), p. 144.

Furthermore, age and gender differences in nail growth have been observed. In their study with 153 Indians, Gupta et al. (2005) found that fingernail growth rate was high during adolescence and childhood, whereas it constantly decreased during adulthood. Moreover, fingernails of all ten fingers grew faster in women than in men. This contrasts the study of (Hamilton, Terada, & Mestler, 1955), who found faster linear nail growth rates in men up to

the age of 19. Afterwards, their levels gradually diminished until the age of 69, when women's nails grew faster. However, when nail growth volume was measured instead of linear growth rates, men continued to have higher nail growth throughout life. As suggested by Hamilton, Terada, and Mestler (1955), nail growth volume should be measured by multiplying thickness, breadth, and growth length per day in mm. As the nail plate gains thickness and density as it grows distally (Johnson et al., 1991), the assessment of the volume is assumed to be more appropriate than the linear growth rate. However, it is more difficult to assess.

The influence of temperature on nail growth is less clear. Bean (1974) investigated his own nail growth and found that his nails grew faster during the warm seasons. However, these seasonal variations diminished with age, which was probably also caused by his movement from Iowa to Texas, where seasonal contrasts are reduced. Likewise, slow nail growth rates were observed during a stay in the Arctic (Geoghegan, Roberts, & Sampford, 1958). Nonetheless, no evidence for slower nail growth was found in subsequent studies conducted in the Antarctic (Donovan, 1977; Gormly & Ledingham, 1983).

Other factors that are assumed to increase nail growth rates are pregnancy, minor traumas such as caused by nail biting, a variety of diseases such as psoriasis, onycholysis, hyperthyroidism, hyperpituitarism, brittle nail syndrome, and medications such as calcium, oral contraceptives, and biotin. On the other hand, lactation, acute infections such as mumps or fever, chronic diseases, malnutrition, smoking, yellow nail syndrome, antimitotic agents, retinoids, lithium, etc. are assumed to reduce nail growth (for a review, see de Berker et al., 2007).

2.3.2 Nail cortisol concentrations

To date, a whole range of substances can be detected in nails: e.g. drugs such as amphetamine, benzodiazepines, cannabinoids, cocaine, and morphine, trace elements such as aluminum, arsenic, copper, iron, and zinc, and sexual hormones such as testosterone and estradiol (for a review, see Daniel, Piraccini, & Tosti, 2004). However, only little is known about the incorporation of these exogenous and endogenous substances into the nail plate (Palmeri, Pichini, Pacifici, Zuccaro, & Lopez, 2000).

Only very few studies have been looking at NCC. In their pilot study, Warnock et al. (2010) measured cortisol and dehydroepiandrosterone (DHEA) in 33 university students (26 females, 7 males) between the ages of 18 and 24. Nail samples were collected twice during one semester; once in August when the stress-level was expected to be low and once in De-

cember, prior to the exams. The students were asked to cut their nails two weeks before data collection, to ensure that the samples represent two weeks of accumulated stress. Exclusion criteria involved significant physical health problems, psychiatric disorders, pregnancy, nail diseases, and medication that may interfere with the HPA axis activity. Results showed that cortisol and DHEA were significantly related to each other at both measurement time points, and that the cortisol-to-DHEA ratio increased significantly from the first to the second measurement time point. However, this result seems rather be due to the changes in DHEA levels, as DHEA decreased significantly, while no significant increase in cortisol was found.

One year later, Ben Khelil et al. (2011) collected nails of the right thumbs of 10 adult women to determine cortisol, cortisone, DHEA and DHEA sulfate (DHEAS), which were all significantly interrelated. Compared to Warnock et al. (2010), DHEA concentrations were much higher, which led to lower cortisol-to-DHEA ratios. Moreover, cortisol-to-DHEA ratios were lower than in serum and saliva, whereas cortisol-to-DHEAS ratios were higher than in serum and saliva. Interestingly, cortisol-to-cortisone ratios were higher than in saliva but lower than in serum, showing most similarities to free urinary cortisol-to-cortisone ratios. Notably, cortisol concentrations were higher than previously reported in hair, whereas cortisone concentrations were similar (Raul, Cirimele, Ludes, & Kintz, 2004).

Differences in these results compared to those of Warnock et al. (2010) could be due to different sample characteristics or may have been caused by methodological differences. While Warnock et al. (2010) used an enzyme immunoassay, Ben Khelil et al. (2011) used an ultra-performance liquid chromatography tandem mass-spectrometry that resulted in much higher average NCC. Notably, Warnock et al. (2010) tested two different extraction methods. For the first method, they used only 50 mg of the grounded nail powder, whereas in the second method, they used the whole nail powder. The two extraction methods did not show significantly different levels of cortisol or DHEA. They suggested using the whole nail powder, as it is in a solid phase, in which homogeneity can hardly be attained. However, Ben Khelil et al. (2011) reported that 1mg of nail powder was enough to determine cortisol, cortisone, DHEA and DHEAS.

As for the reported differences in ratios, Ben Khelil et al. (2011) suggest that permeability of the nail plate may play a crucial role. The nail plate represents a hydrophilic gel membrane with low permeability for big, hydrophobic, and ionic molecules (for a review, see de Berker et al., 2007). It is approximately a thousand times more permeable to water than the skin and contains about 7-12% water and only 0.1-1% lipids. This nail barrier and the nail's innate immune system not only protect the nail but also pose various challenges in the treat-

ment of nail diseases, as certain medicaments are barely able to diffuse into the nail. DHEA has a lower molecular weight (288.42 g/mol^{-1}) than cortisol (362.46 g/mol^{-1}), and therefore may show a different incorporation, leading to changes in the ratios. Nonetheless, DHEAS and cortisone share similar molecular weights as cortisol (Ben Khelil et al., 2011). Ben Khelil et al. (2011) suggest that the higher NCC could be due to a bigger wash-out effect of cortisol in hair (Clemens Kirschbaum, Tietze, Skoluda, & Dettenborn, 2009). However, this finding contrasts results in forensic research that showed lower drug concentrations in nails than in hair (Palmeri et al., 2000).

Nevertheless, subsequent research on NCC indicated its validity as a biological stress marker, as associations with other cortisol measurements were found. In the study of Izawa et al. (2015), NCC was found to be moderately associated with HCC. Moreover, saliva cortisol (area under the curve; AUC) was significantly related to NCC collected four and five months later, but not to NCC collected one, two, three, and six months later. This indicates, that measured NCC like HCC may represent HPA axis activity during a specific retrospective (four to five month) time period (Izawa et al., 2015). However, this is the only study that simultaneously assessed hair, nail, and saliva cortisol in humans, and further research is needed to clarify the exact time period of HPA axis activity. Notably, forensic research has shown that drugs can be detected in the distal nail plate sooner than expected by the growth rate alone. It is assumed that substances may also enter the nail plate via the nail bed, making it difficult to determine a specific retrospective time frame (Palmeri et al., 2000).

To date, no study compared NCC in different fingers or toes. However, drug concentrations were found to be higher in toenails than in fingernails (Palmeri et al., 2000). This finding may be due to the much slower growth rates in toenails, which emphasizes nail growth as an important factor regarding substance concentrations in nail plates (Palmeri et al., 2000). Moreover, a recent Japanese study examined NCC between the left and the right hand in right-handed adult participants. The authors built left-to-right ratios and defined values over 1.2 or below 0.8 to indicate differences between left and right. According to this criteria, no difference was found for NCC with a mean of 1.05 (SD = 0.12) and a range from 0.83 to 1.27 (Higashi et al., 2016).

Finally, the influence of other important factors regarding nail growth such as gender, age, pregnancy, or temperature, or external factors such as air pollution, nail lacquer, etc. have not been investigated. However, two animal studies investigating NCC have been conducted. In the first study, cortisol concentrations in hooves of 32 calves were examined. Results showed that cortisol levels were significantly higher in newborn calves with 0-30 days of age

than in those with 31-60 days and 61-120 days of age. Furthermore, cortisol concentrations were lower in soaked hooves (put into water for 72 hours) than in the same dry samples, indicating a wash-out effect (Comin et al., 2014). The second study examined cortisol levels in coat and claws of 165 newborn puppies. Coat and claw cortisol levels were highly correlated, and no differences were found with regard to tissue, gender, body size, and coat color.

NCC may provide a promising retrospective marker of chronic biological stress, representing stress during the past four to six months. The collection is easy and noninvasive, and therefore especially suitable for working with children. Moreover, it is not influences by momentary circumstances. So far, no study has been conducted examining NCC in children. However, findings from HCC and SCC could provide valuable information. Evidence from saliva and blood cortisol suggests that there is a stress hyporesponsive period (SHRP) in early childhood, starting approximately six months postpartum and extending over the years (Gunnar & Quevedo, 2007). During this period, basal cortisol levels are assumed to remain low, whereas they increase during late childhood and adolescence (for a review, see Gunnar & Vazquez, 2001). In a cross-sectional study of 1482 healthy children between 2 days and 18 years, serum cortisol concentrations showed a high variance at birth that decreased abruptly after one year and started to increase again in late childhood (Bailey et al., 2013). A similar pattern was found for HCC, with HCC decreasing from two to ten years and then starting to increase again (Dettenborn, Tietze, Kirschbaum, & Stalder, 2012).

2.3.3 Cortisol and child behavior problems

In adolescents and young adults between 12 and 21 years of age, HCC was positively related to perceived stress, symptoms of depression and neuroticism. No association was found with extraversion (Rietschel et al., 2016). Moreover, HCC was higher after school entry, especially in fearful children (Groeneveld et al., 2013). These findings are in line with a meta-analysis that showed higher cortisol levels in saliva, serum, and urine in depressed children and adolescence compared to non-depressed controls with a global standardized mean difference of $d = 0.20$. Notably, differences in basal cortisol levels with regard to age and sex were less robust than group differences in cortisol reactivity, indicating that dysregulation in stress response does not necessarily translate to basal HPA axis dysregulation (Lopez-Duran, Kovacs, & George, 2009).

It has been suggested that internalizing problems are associated with HPA axis hyper-activation, whereas externalizing problems are related to HPA axis hypo-activation (Hartman et al., 2013). Several studies showed that elevated morning cortisol was related to internalizing problems, whereas low basal cortisol was associated with externalizing problems such as disruptive behavior and conduct problems (Alink et al., 2008; Cicchetti & Rogosch, 2001; Laurent et al., 2013, 2014; Laurent, Vergara-Lopez, & Stroud, 2016; McBurnett, Lahey, Rathouz, & Loeber, 2000; McBurnett et al., 2005; Pajer, Gardner, Rubin, Perel, & Neal, 2001).

Several explanations for this inverse relation have been suggested. First, lower autonomic arousal may lead to frequent stimulation-seeking, for example by fighting, which in turn may result in a habituation and blunted stress response (van Goozen, Fairchild, Snoek, & Harold, 2007). Second, high levels of externalizing behavior may be associated with less sensitivity to stress and therefore less physiological arousal, which results in low levels of anxiety and more engagement in externalizing behavior (fearlessness theory; Raine, 1996). And third, early prenatal and postnatal stressors (domestic violence, parental substance abuse and depression, low SES, etc.) may cause enduring changes in the HPA axis activity, heightening the risk for externalizing behavior problems (for a review, see McBurnett, King, & Scarpa, 2003).

However, a meta-analysis based on 72 studies with 5'480 subjects showed that the effect size for basal cortisol and externalizing behavior is smaller than previously assumed (Alink et al., 2008). In some studies, basal cortisol levels showed positive (Hart, Burock, London, Atkins, & Bonilla-Santiago, 2005; van Bokhoven et al., 2005), or no (Hartman et al., 2013) associations with externalizing behavior. Notably, age represented the only significant moderator in the meta-analysis (Alink et al., 2008). In preschoolers, cortisol levels and externalizing behavior were positively associated, whereas in school-aged children they were negatively associated. In addition, no relation was found in adolescents. The authors suggest that this effect may be due to developmental differences in externalizing behavior, as aggression is more normative in early childhood with a peak at approximately four years of age (Alink et al., 2006; Tremblay, 2002, 2003). However, if the high levels of stress continue, it causes allostatic load, which in turn may downregulate the HPA axis resulting in lower cortisol levels (Fries et al., 2015; Gunnar & Vazquez, 2001). Therefore, high stress during early childhood may first lead to higher cortisol levels and more externalizing behavior before a downregulation of the HPA axis takes place at school age resulting in lower cortisol levels (Alink et al., 2008).

2.3.4 Cortisol and parental sensitivity

It is presumed that sensitivity and responsiveness of the primary caregivers are especially important early in life, when high levels of regulatory support is required (Berry et al., 2016; Feldman, 2007; Hostinar et al., 2014). Parental sensitivity refers to the caregiver's ability to interact and communicate with the child in a sensitive way. This requires a) that behavioral signals of the child are perceived, and b) interpreted adequately, c) that the response of the caregiver to the child's behavior is prompt, so that the child can link the reaction of his caregiver to its own behavior, and d) that the caregiver's reaction is appropriate with regard to intensity (Ainsworth, Bell, & Stayton, 1974). Sensitive parenting has been found to be related to secure attachment relationships, promoting a sense of trust and security, leading to behavioral independence, and higher social and cognitive development in children (Ainsworth et al., 1974; Bretherton, 2011; De Wolff & van IJzendoorn, 1997). Moreover, the social buffering hypothesis suggests that maternal sensitivity may mitigate the effects of early childhood adversity (Hostinar et al., 2014).

To date, three studies examined the relation between parenting and HCC, reporting inconsistent findings. Palmer et al. (2013) showed that child HCC was positively correlated with mothers' reports of parenting stress and the use of negative parenting practices measured with the Parenting Stress Index Short Form (Abidin, 1995). In contrast, poor parenting was negatively associated with HCC in the study of Ouellette et al. (2015). Moreover, it moderated the relation between HCC of the mother and HCC of the daughter, in that the association became stronger as parenting quality became poorer. This moderation effect appeared to be especially relevant in mothers with high HCC, indicating that parenting quality is particularly important in highly stressed mothers (Ouellette et al., 2015). Notably, poor parenting reflected an aggregated measure involving recoded positive parenting characteristics such as sensitivity, supportive presence, confidence, and positive affect, and negative parenting characteristics such as hostility, intrusiveness, negative affect, indulgence, and coercion. Such multiple indices of maternal sensitivity were often found to be unrelated to SCC (e.g. Letourneau et al., 2011; Philbrook et al., 2014).

Finally, in the study of Flom, St. John, Jerrold, and Amanda (2016), no associations were found between HCC and maternal parenting stress, motherese (proportion of time spent using infant-directed speech), maternal intrusiveness (proportion of time spent taking a toy away from the infant), and maternal negative or positive affect.

Findings from studies investigating basal cortisol levels in saliva showed that maternal sensitivity was associated with lower basal SCC, lower AUC, and a steeper diurnal slope (Ben-Dat Fisher et al., 2007; Berry et al., 2016; Blair et al., 2013; Letourneau et al., 2011; Philbrook et al., 2014). Moreover, negative parenting has been linked to higher basal SCC (Blair et al., 2013; Taylor et al., 2013). In contrast, no association between maternal sensitivity and SCC was found in the study by Vergara-Lopez et al. (2016).

Notably, maternal sensitivity was operationalized differently across studies. Nonetheless, most of the studies investigating SCC suggest that maternal sensitivity is related to lower basal cortisol levels. Therefore, NCC is expected to be also negatively associated with maternal sensitivity. Further studies are needed to investigate these relations.

2.3.5 Cortisol in early intervention studies

As adverse childhood experiences can be associated with enduring changes in the physiological stress-systems, it is important to know whether these changes can be reversed through interventions. To date, there are no studies investigating the effect of an early intervention on NCC or HCC. However, two intervention studies with adults indicate that HCC may be altered through intervention and may be used as a predictive biological marker for psychological outcomes. In one study, the effect of guided imagery on HCC in adult patients undergoing a total knee replacement was tested. They found that HCC was significantly lower at six months after surgery than at three weeks before surgery in the intervention group, but not in the placebo-control group (Jacobson et al., 2016). The other study examined the effect of a one-year cardiac rehabilitation program in subjects with coronary artery disease and showed that higher HCC levels at baseline predicted less improvement in verbal memory performance (Saleem et al., 2013).

In contrast, significantly more early intervention studies have been conducted assessing SCC (for a systemic review, see Slopen, McLaughlin, & Shonkoff, 2014). Many of these early intervention studies were examining children living in institutions, receiving interventions that involved social and educational enrichment, and/or training for caretakers or parents after the children entered new placements. One study found that institutionalized children in the intervention group had lower noon-time SCC (Carlson & Earls, 1997). Moreover, SCC in foster children entering an enriched placement were comparable to those of a community sample, while controls receiving regular foster care showed increasingly flattened morning-to-evening cortisol activity (Fisher, Gunnar, Chamberlain, & Reid, 2000; Fisher,

Stoolmiller, Gunnar, & Burraston, 2007). These findings were replicated in a subgroup of children, who had one placement change during the intervention (Fisher, Van Ryzin, & Gunnar, 2011). Furthermore, foster children, whose parents received help in encouraging regulatory capacities in their children, showed similar SCC patterns as community controls, whereas children, whose parents were trained in promoting their children's language skills, had significantly lower SCC (Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008). Taken together, early interventions in foster children seem to influence SCC in a positive way, normalizing the diurnal HPA axis activity. Notably, the age of the children at baseline assessment ranged from 2 months to 5.4 years across the studies. However, children's age may be of importance regarding sensitive developmental periods. Accordingly, a recent study showed that intervention effects on the HPA axis were only evident for children that were placed before 24 months into foster care (McLaughlin et al., 2015).

Besides studies with foster children, other studies investigated at-risk children and found similar results. Maltreated children became indistinguishable from community controls with regard to SCC after an attachment-based intervention (Cicchetti, Rogosch, Toth, & Sturge-Apple, 2011), and at-risk children receiving a one-year intervention program showed lower SCC compared to controls and a significant decline in SCC (Bugental, Schwartz, & Lynch, 2010). Moreover, children of polydrug-using mothers had lower SCC levels after intervention compared to controls and similar levels as the community-based comparison group (Field, Scafidi, & Pickens, 1998). No direct but a mediating effect was found in parentally bereaved youth, with the adolescents in the Family Bereavement Program experiencing less negative life events and more positive parenting, leading to lower externalizing symptoms, which was negatively related to SCC (AUC; Luecken et al., 2014). However, in families receiving an intervention with children high in externalizing behavior, AUC levels differed only from controls in children with the dopamine receptor D4 7-repeat allele (Bakermans-Kranenburg, van Ijzendoorn, Mesman, Alink, & Juffer, 2008), indicating a relevant gene x environment effect.

No intervention effects on SCC were found in children with depressed mothers, receiving home-based peer support (Letourneau et al., 2011), and in siblings of youth adjudicated for delinquency, receiving home visits to improve parenting practices and preschoolers competence (Brotman et al., 2007). Finally, children from low-income women at risk of depression during the second trimester, who received a cognitive behavioral stress management training, showed lower SCC at 6 months postpartum. However, at 18 months postpartum no differences were observed (Urizar & Muñoz, 2011).

2.3.6 Summary

Overall, NCC seems to be a valid biological marker of HPA axis activity, as it is associated with HCC and SCC. However, to date, there is only one study that examined NCC with relation to a psychosocial variable (stress), and the results showed that NCC did not change from a low to a highly stressful period (Warnock et al., 2010). Therefore, the applicability of NCC as a biological stress marker in psychology still has to be tested. So far, very little is known about NCC. The retrospective time frame represented by NCC cannot be estimated clearly, because substances may enter the nail plate also via the nail bed. Additionally, there are large intra- and interindividual differences in nail growth, which in turn are influenced by many internal and external factors such as gender, age, pregnancy, temperature, blood circulation, sweat, etc. Moreover, the nail barrier should be taken into account. On the one hand, cortisol is poorly water-soluble and has a quite high molecular weight, which may make it difficult for it to enter the nail plate. On the other hand, these characteristics may reduce a possible wash-out effect. Notably, permeability may differ between the three nail plates.

Although to date, no studies have been examining NCC in children, many studies regarding HCC or SCC have been conducted that could provide valuable information. Findings concerning internalizing and externalizing child behavior showed some inconsistencies regarding HCC and SCC with positive, negative, and no associations found. Moreover, age seems to play a crucial role regarding the relation between externalizing behavior problems and SCC. However, taken together, findings suggest that both internalizing and externalizing behavior seem to be positively related to cortisol when preschoolers are investigated.

Parental sensitivity is an established protective factor that seems to be able to mitigate the effects of adverse childhood experiences. Findings predominantly suggest negative relations with SCC. Studies examining HCC showed inconsistent results. However, there have been only three studies and the conceptualization of maternal sensitivity differed considerably.

Finally, despite the heterogeneity of the intervention studies with regard to age, selection criteria, intervention design, follow-up duration, and SCC assessment (AUC, single cortisol assessment, differences in slope, individual components of diurnal measures), most of the studies show significant lower SCC after the intervention compared to controls. Moreover, in many studies a normalization was observed, in that children of the intervention group showed similar SCC patterns as healthy controls, whereas those of the control group showed elevated

SCC. Notably, although some studies did not find significant effects, there was no study showing increased basal SCC.

2.4 FKBP5 methylation in child development

Besides cortisol, HPA axis activity is influenced by other factors such as FKBP5 methylation that is known to play a central role in the termination of the stress response (Binder, 2009). Empirical findings suggest that high FKBP5 methylation represents a protective factor against the detrimental long-term consequences of child abuse (Klengel et al., 2013). However, its part in the biological embedding just recently started to be investigated and only few studies have conducted prospective studies in children. Further research is needed to elucidate its role in adaptive child development. Therefore, equivalent to the chapter 2.3 regarding cortisol in child development, previous research investigating FKBP5 methylation with regard to behavior problems, parental sensitivity, and effects of intervention programs is reported in this chapter. Again, biological background information is given first, for a better understanding of FKBP5 methylation. As methylation represents an epigenetic process, the structure of the DNA and mechanisms of epigenetic processes are explained before describing the role of the FKBP5 gene in HPA axis activity.

2.4.1 The DNA

Genetic information is stored in the deoxyribonucleic acid (DNA). The DNA double helix consists of two single deoxy nucleotide strands that are bound together through hydrogen bonds. Each nucleotide is composed of a nucleobase, a five-carbon sugar, and a phosphate (or phosphate group). There are four deoxy nucleobases: adenine (A), guanine (G), cytosine (C), and thymine (T). The nucleobases form complementary base pairs (bp) – each nucleobase on one strand is bound to just one type of nucleobase on the other strand – with T bound to A, and C bound to G. The human genome consists of over 3 billion bp within estimated 20’000-25’000 genes located on 23 chromosome pairs in the cell nuclei (International Human Genome Sequencing Consortium, 2004). Long strands of DNA, which are wrapped around histones, form the typical shape of the chromosome.

2.4.2 Epigenetics

The term *epigenetic* describes phenotypic variations that are not caused by underlying genetic variations, but rather due to non-genomic effects that influence gene expression (Champagne, 2010). During gene expression, a protein is synthesized according to the information in the DNA. This complex process is based on two steps, the transcription and the translation. In the transcription phase a DNA section is copied into a ribonucleic acid (RNA), which then is translated into sequences of amino acids (Ehlert, La Marca, & Abbruzzese, 2013). Notably, only a very small fraction of the genome (approximately 1.5%) consists of protein-coding regions (mostly represented by exons). During transcription, introns are removed, whereas exons are joined together in the messenger RNA (mRNA). However, introns play a central role in gene expression as they allow for alternative splicing, permitting a single gene to encode many different proteins (Bicknell, Cenik, Chua, Roth, & Moore, 2012). Additionally, all genes contain promotor sequences that regulate gene expression. Transcription factors such as the RNA polymerase recognize promotor regions and bind to them to initiate transcription (Alberts et al., 2002). However, transcriptional activity depends on the accessibility of these transcription factors to the DNA, and the accessibility can be reduced or enhanced by multiple post-translational modifications of histone proteins including, acetylation, methylation, phosphorylation, and ubiquitation (Peterson & Laniel, 2004).

2.4.3 Methylation

DNA methylation is the most widely studied epigenetic mechanism and is considered to induce relatively stable and enduring changes in gene expression (Champagne, 2010; Koch, Metz, & Kovalchuk, 2013). During methylation, a methyl group ($–CH_3$) binds to a C that is linked to a G by a phosphate bond (CpG) in the nucleotide sequence, converting it into 5-methylcytosine. This process is mediated by methyltransferases such as DNMT1 or DNMT3 and reduces the probability of transcription. Moreover, methylated DNA attracts other methyl-binding proteins (e.g. MeCP2), which further reduce the accessibility of the gene (Champagne, 2010). In mammals, between 60%-90% of the CpG sites are methylated with the majority of methylated CpG sites found within the gene body and less than 3% found in promoter regions (Maunakea et al., 2010; Tucker, 2001). However, while methylation of gene promoters is linked to silencing, the role of intragenic methylation is less clear. Transcription not only initiates between genes, but also within the gene bodies. While there are few tissue-

and cell-specific methylation in the promoter regions, intragenic methylation seems to play a major role in regulation cell- and context-specific alternative promoters within the gene body (Maunakea et al., 2010). Notably, during cell division, not only the DNA is passed to the daughter cells, but also the methylation patterns (Fukuda & Taga, 2005).

Taken together, DNA methylation may reduce the probability of a gene to be transcripted and consequently to be expressed. Therefore, it is highly important for normal development, cell proliferation, and proper maintenance of genome stability (Weber & Schübeler, 2007). Despite its heritability, epigenetic changes remain sensitive to environmental influences and can be reversed throughout life (Jones & Liang, 2012). However, findings suggest that epigenetic regulation of gene expression is particularly important during early stages of development (c.f. Champagne, 2010; Karsten & Baram, 2013).

2.4.4 FKBP5 methylation

FKBP5 is located on chromosome 6 and represents a co-chaperone of the GR cellular complex. It influences the effect of the chaperon HSP90, which is an important regulator of GR sensitivity (Binder, 2009). FKBP5 has a mediating role in the negative feedback mechanism of the HPA axis in that it facilitates termination of the stress response. In this ultra-short feedback loop, FKBP5 is rapidly induced following cortisol-induced GR-activation. It binds to the GR itself and therefore blocks it for cortisol. Therefore, elevated FKBP5 levels reduce the binding of cortisol, and consequently the translocation of the GR into the nucleus, limiting cortisol-induced transcription (Binder, 2009). Methylation of FKBP5 reduces FKBP5 expression and hence increases systemic GR-sensitivity to cortisol (Klengel et al., 2013; Tyrka et al., 2012). Cortisol has been found to induce FKBP5 demethylation in neuronal progenitor cells (Klengel et al., 2013) and was found to be negatively related to FKBP5 methylation (Weder et al., 2014; Yehuda et al., 2013, 2015) and positively associated with FKBP5 expression (Lee et al., 2011; Sarapas et al., 2011). However, findings differ with regard to cortisol measurement and specific CpG sites. While wake-up cortisol was negatively related to FKBP5 methylation, no association was found for bed-time cortisol in the study from Yehuda et al. (2015). Moreover, no relation with cortisol (AUC) was found in the study of Monk et al. (2016), and relations in the study of Yehuda et al. (2013) were CpG site-dependent. Therefore, it is assumed that variation in methylation at specific CpG sites may underlie differential effects of stress on HPA axis activity (Kertes et al., 2016).

In the past two decades, methylation in several stress-related genes such as NR3C1, FKBP5, CRH, CRHBP, and 11β-HSD2 has been investigated in relation with early psychosocial factors (Kertes et al., 2016). The CRH gene, which codes for the corticotrophin-releasing hormone, and the CRHBP gene, which codes for the corticotrophin-releasing hormone binding protein are both involved in the initial HPA axis activation and have been related to chronic stress and war trauma (Kertes et al., 2016). In contrast, the nuclear receptor subfamily 3 group C member 1 (NR3C1) gene, coding for the GR, and the FKBP5 gene, coding for the FK506 binding protein 51, which are negatively associated, are jointly involved in the downstream effects of cortisol at target tissues (Kertes et al., 2016). To date, most studies focused on NR3C1 methylation, for which the majority of the studies reported increased methylation in association with early-life adversity and parental stress (for a review, see Turecki & Meaney, 2016). In contrast, only few studies have been conducted investigating FKBP5 methylation patterns in child development.

2.4.5 Methylation and child behavior problems

Several studies have investigated the relation between placental methylation in the 11β-hydroxysteroid dehydrogenase Type 2 (11β-HSD2) gene and newborn neurobehavior, which is an assumed predictor of long-term developmental outcome (Lester, Conradt, & Marsit, 2014). Methylation in the 11β-HSD2 gene is assumed to represent a valid marker of prenatal stress as 11β-HSD2 converts maternal cortisol into cortisone and its methylation results in greater exposure of the fetus to maternal cortisol (Conradt et al., 2016). Findings indicate that higher 11β-HSD2 methylation, and therefore an increased exposure of cortisol in utero, has a negative effect on the infant's motor control and smoothness of movements (Marsit, Maccani, Padbury, & Lester, 2012). This relation seems to be influenced by mood disorders of the mothers, as infants who had anxious mothers and high levels of 11β-HSD2 methylation were more hypotonic (low muscle tone) than infants with mothers without anxiety (Conradt, Lester, Appleton, Armstrong, & Marsit, 2013). Similarly, infants with depressed mothers and high placental NR3C1 methylation (indicating reduced cortisol's transcriptional activity) showed more hypotonia and lethargy, while simultaneously displaying poorer self-regulation. Therefore, these children, like their mothers, showed depression-like behavior (Conradt et al., 2013). However, in a previous study, opposite relations were found in that higher NR3C1 methylation was positively associated with infant quality of movement (Bromer, Marsit, Armstrong, Padbury, & Lester, 2013). Likewise, FKBP5 methylation was found to be posi-

tively related to infant arousal, a risk factor involving fussiness and spontaneous movements (Paquette et al., 2014). Moreover, FKBP5 methylation mediated the association between maternal stress and fetal coupling, a factor composed of fetal movement and heart rate that is related to mature neural integration at birth. Maternal stress was associated with higher placental FKBP5 methylation, which in turn was related to lower fetal coupling (Monk et al., 2016).

Taken together, results show inconsistencies given that in some studies high 11β-HSD2 and high NR3C1 methylation are related to poorer neurobehavioral outcomes, whereas in other studies, low NR3C1 and high FKBP5 methylation were associated with poorer neurobehavioral outcomes. Paquette et al. (2014) suggest that the FKBP5 hypermethylation (and therefore probably also low NR3C1 methylation) may increase cortisol activation of placental GR, which results in an over-active cortisol pathway at birth. This over-active cortisol pathway in turn could increase the risk of developing stress-related disorders.

Notably, the presented findings represent prenatal and in utero influences on child behavioral outcomes (fetal programming) that are relatively untouched by postnatal experiences (Lester et al., 2014). Since the functioning of the placenta itself is very complex and not fully understood, examining methylation in the placenta may result in different associations than if blood or salivary methylation in the children themselves would have been examined. To date, there are only two recent studies that investigated the relation between child behavior problems and methylation. The first study examined 241 children between the ages of 4 and 16 years, who were referred for the treatment of behavioral and/or emotional problems. Higher levels of internalizing problems were related to higher NR3C1 methylation in both blood and saliva samples. Moreover, NR3C1 methylation predicted higher salivary morning cortisol levels, and there were site-specific positive associations between NR3C1 methylation and severity of internalizing symptoms. Concerning externalizing symptoms, no association was found for the overall NR3C1 methylation. However, methylation at two CpG sites positively predicted externalizing symptom severity in saliva samples but not in blood samples (Dadds, Moul, Hawes, Mendoza Diaz, & Brennan, 2015). The second study investigated 171 preschoolers between the ages of 3 and 5 years, who had experienced early adversities such as maltreatment in the past six months. NR3C1 methylation was examined at different exons (1_D, 1_F, and 1_H) and compared to child behavior problems reported by the parents. Methylation at 1_D and 1_F was positively associated with internalizing behavior problems, whereas no associations were found for exon 1_H and regarding externalizing behavior problems. Moreo-

ver, NR3C1 methylation was positively related to early adversity and mediated the effect of early adversity on internalizing behavior problems (Parade et al., 2016).

2.4.6 Methylation and parental sensitivity

The relation between methylation and parental sensitivity was first discovered from Weaver et al. (2004) in an animal study. The authors found that lower maternal caregiving represented by low licking and grooming was found to be related to higher NR3C1 methylation levels (hippocampal GR exon 1_7 promoter region) in the rat offspring (Weaver et al., 2004). Notably, at the first day postpartum, all rats exhibited hypermethylation at the binding site for the transcription factor NGFI-A (nerve growth factor-inducible protein A), which was consequently reduced only in those rats that received high levels of licking and grooming (Liu et al., 1997). Subsequent animal studies found that low licking and grooming during infancy was associated with higher methylation in the promoter region (1_B) of the estrogen receptor alpha (ERα) gene (Champagne & Meaney, 2006) and lower methylation in the promoter region of the glutamic acid decarboxylase (GAD1) gene (Zhang et al., 2010). The GAD1 encodes the GAD enzyme, which catalyzes the decarboxylation of glutamate to γ-Aminobutyric acid (GABA), the main inhibitory neurotransmitter in the central nervous system (Bruxel et al., 2016).

Meanwhile, several human studies have been conducted following the publication of Weaver et al. (2004), focusing on the effect of childhood adversities, mostly abuse and maltreatment, on NR3C1 of FKBP5 methylation (Klengel et al., 2013; Turecki & Meaney, 2016; Yehuda et al., 2015). However, only two studies have directly investigated maternal sensitivity in relation with methylation. Both studies examined NR3C1 methylation in the $GR1_F$ promoter region, which is the homolog of the exon 1_7 in the rat (McGowan et al., 2009). In the first study, maternal sensitivity and child cooperativeness were measured using the CARE-Index (Crittenden, 2004). But while a negative relation was found between NR3C1 methylation and, child cooperativeness during play, there was no association with maternal sensitivity (Schechter et al., 2015). In the second study, maternal responsiveness represented by appropriate touch during face-to-face play was positively related to NR3C1 and 11β-HSD2 methylation (Conradt et al., 2016). Moreover, significant interaction effects with maternal depressive symptoms were found. While children with high levels of NR3C1 or 11β-HSD2 methylation had less responsive and more depressive mothers, no differences in methylation were found among those infants whose mothers were responsive, regardless of depressive symptom se-

verity. These findings support the notion of the social buffering hypothesis, in that maternal sensitivity may buffer the negative effect of maternal depression on the infant development. However, only one (appropriate touch) out of three subscales (accepting, responsiveness) representing maternal sensitivity showed a relation with NR3C1 methylation. Concerning 11β-HSD2 methylation, there was an additional association with the subscale accepting with no significant interaction found (Conradt et al., 2016).

2.4.7 Methylation in intervention studies

To date, there has been only one study investigating the effect of a family-centered prevention program on changes in methylation (Brody, Yu, Chen, Beach, & Miller, 2016). In this longitudinal intervention study, a subsample of 399 families who participated in the Strong African American Families (SAAF) program was examined. At the age of 11, the participants had been assigned randomly to the control (CG) or the intervention group condition (IG). The SAAF program involved seven consecutive meetings (two hours weekly), at which parents learned about instrumental and emotional support, monitoring and control, etc. Methylation was assessed from blood samples when the children were 20 years old. From these methylation levels, epigenetic age was calculated. Comparing the epigenetic age with the chronological age resulted in residuals, which served as a measure of epigenetic aging. The authors found a significant interaction between depressive symptoms of the parents and group condition on epigenetic age. Young adults in the CG, whose parents had high levels of depressive symptoms, showed accelerated epigenetic aging, whereas the other three groups did not differ from one another. However, no main effect of the intervention program was reported (Brody et al., 2016).

Although no other family-centered intervention study was found, there have been two recent studies examining the effect of cognitive behavior therapy (CBT) on methylation in children suffering from anxiety disorders (Roberts et al., 2014; Roberts et al., 2015). In the first study, methylation in the serotonin transporter gene (SERT) in 116 children between 6 and 13 years of age were examined. The children were classified into responders (defined by the absence of primary anxiety or all anxiety diagnoses) or non-responders at post-treatment and at 6 months follow-up. There was no difference between pre- and posttreatment at any CpG site when analyzing both groups together or when using the average methylation change across the whole region. Moreover, no differences in methylation levels were found between responders and non-responders when they were split up at post-treatment. However, when the

children were split up at 6 months follow-up, responders showed an increase in SERT methylation at one specific CpG site, whereas non-responders showed a decrease in SERT methylation at this CpG site (Roberts et al., 2014).

Similar results were found in the second study, which investigated the effect of CBT on FKBP5 methylation in 1152 children aged 5-18 years with anxiety disorders (Roberts et al., 2015). This time, treatment response was defined as the change in primary anxiety disorder severity from pre-treatment to follow-up (3, 6, or 12 month after post-treatment). Again, there were no differences in methylation levels between pre- and post-treatment, and pre-treatment methylation was not associated with treatment response. Nevertheless, responders showed a decrease, whereas non-responders showed an increase in FKBP5 methylation. Importantly, this was only true for risk allele carriers (rs1360780). In contrast, protective allele carriers showed CpG specific effects with either no significant changes or changes leading into opposite directions (an increase in responders and a decrease in non-responders). In adults, similar intervention effects on FKBP5 methylation were found, although the genotype was not assessed. In combat veterans suffering from posttraumatic stress disorder, responders to prolonged exposure psychotherapy showed a decrease in the number of methylated sites, whereas non-responders showed an increase (Yehuda et al., 2013). The authors suggest that changes in FKBP5 methylation may be only related to changes in HPA axis activity, in association with changes in symptom severity, and therefore do not simply reflect an upstream regulation of cortisol. Moreover, Roberts et al. (2015) suggest that children carrying the risk allele may be more vulnerable to changes in methylation, be it for better or for worse.

2.4.8 Summary

FKBP5 represents one of several HPA axis-related genes such as NR3C1, CRH, 11β-HSC2. It mediates the negative feedback mechanism of the HPA axis by facilitating the termination of the stress response. Methylation in FKBP5 leads to reduced FKBP5 expression, which in turn increases cortisol induced GR-activity. To date, few studies have been conducted investigating FKBP5 methylation in childhood. However, findings from other stress-related genes can provide valuable insights. Regarding child behavior, several studies have examined placental methylation in 11β-HSD2 and NR3C and newborn neurobehavioral outcomes. However, the results are inconsistent and are assumed to represent fetal programming rather than postnatal development. Studies examining postnatal methylation levels are scarce but suggest a negative relation between NR3C1 methylation and internalizing behavior problem. This may indi-

cate that FKBP5 methylation would be positively related to internalizing behavior problems, as methylation of NR3C1 and FKBP5 are inversely related to each other. Externalizing behavior problems seem to be also positively associated with NR3C1 methylation, but only at specific CpG sites. Regarding parental sensitivity, research in animals suggests that it plays an important protective role in biological embedding. However, research in humans is scarce and findings are inconsistent. Only two studies investigated maternal sensitivity in relation with methylation with one study showing a negative relation with NR3C1 methylation and the other study showing no significant association. More research is needed to clarify the role of maternal sensitivity as a protective factor that may be able to buffer the effect of adverse experiences on an epigenetic level. Studies examining intervention effects indicate that alterations in methylation levels can be achieved. However, the underlying mechanism remains unclear. Methylation seems to represent a moderator that increases or decreases the effect of the intervention. Change in methylation was found to be related to treatment response rather than to treatment itself. While methylation increases in responders it decreases in non-responders or vice versa. Moreover, children carrying a risk allele seem to be especially prone to changes in methylation levels, may it be for better or for worse.

3 Conclusions, research questions, and hypotheses

The general aim of the present thesis was to provide new insights into adaptive early child development and associated contextual and biological factors. For this reason, two studies were conducted using subsamples from two different longitudinal projects.

Adaptive child development is of special interest, as the origins of various adult psychiatric illnesses can be traced back into childhood and adolescence (Hiscock, Ukoumunne, Price, & Wake, 2008; Kessler et al., 2007; Ries Merikangas, Nakamura, & Kessler, 2009). Externalizing and internalizing behavior disorders account for the most treated child psychopathologies. Symptoms of ADHD, DBD, depression, and anxiety may already start to develop during preschool years, probably leading into a vicious cycle that increases the probability to develop comorbid disorders. Such negative developmental cascades are often associated with deleterious long-term consequences throughout life. A similar mechanism is assumed regarding the development of positive child characteristics such as cognitive ability, social competence, and self-esteem. As competence begets competence, the development of positive characteristics may lead into a virtuous cycle, possibly mitigating the adverse effects of problematic characteristics, and increasing the chance of adaptive development. Moreover, positive and problematic child characteristics are influenced by a broad range of contextual risk and protective factors. A central role is given to the home and the school environment, as they describe the most consistent and influential surroundings. Evidence suggests that low SES, parental conflicts, a parenting style that consists of strict control, and peer victimization at school increase the risk of developing externalizing and internalizing behavior problems. In contrast, above average SES, high parental relationship quality, a parenting style that consists of monitoring but not strict control, and a good classroom climate seem to reduce behavior problems while at the same time promoting social competence and academic success.

Taken together, problematic and positive child characteristics seem to be interrelated, constantly influencing each other, while at the same time they are influenced by contextual factors. Nonetheless, most studies did not combine problematic and positive aspects, defining adaptive development either as the absence of problematic or the presence of positive child characteristics. However, a combination of both aspects may explain better, why some children stay healthy while others get stuck in a vicious cycle.

Therefore, in the first study, we aimed to investigate, if adaptive child behavior in preschoolers can be represented by a global factor involving both the absence of problematic and the

presence of positive child characteristics. Moreover, we aimed to test the influence of known risk and protective factors in the close environment on this global factor, integrating all of them into the model.

The aim of the second study was to examine possible underlying mechanisms of adaptive child behavior in at-risk toddlers. There is increasing evidence that long-term consequences of early childhood experiences are caused by enduring changes in biological systems that help to maintain the stability of key bodily functions. While these allostatic systems aid the organism to adapt to environmental changes, chronic activation can lead to allostatic overload and significant impairments. The HPA axis represents one of the most important physiological stress systems and its influence in the development of mental and physical disorders is well established. In preschoolers, cortisol has been positively associated with child behavior problems. As children living in psychosocially disadvantaged families are exposed to many risk factors, the focus is placed on protective factors that may reduce negative outcomes such as parental sensitivity as a central protective factor and intervention programs. Previous studies showed negative associations between cortisol and parental sensitivity. However, few research has been conducted and no study has investigated child developmental factors in association with NCC that may represent a promising chronic stress marker. Similarly, few studies have been conducted investigating FKBP5 methylation, and its relation to child behavior or protective factors remains unclear. In this study, we aimed to examine the roles of FKBP5 methylation and NCC, as recently discovered HPA axis-related markers, in early child development, investigating their associations with behavior problems, parental sensitivity, and an early intervention program.

PART II: EMPIRICAL STUDIES

4 The influence of contextual risk and protective factors on adaptive child behavior in preschoolers

4.1 Introduction

Both retrospective and prospective research indicate that various adult psychiatric illnesses can be traced back into adolescence and childhood (Bayer, Hiscock, Ukoumunne, Price, & Wake, 2008; Kessler, 2008; Ries Merikangas, Nakamura, & Kessler, 2009). At the same time, evidence suggests increasing prevalence of mental health problems among adolescents, posing various challenges for individuals, families, and society (Collishaw, Maughan, Goodman, & Pickles, 2004). Community surveys of young children showed 16.8% externalizing (attention deficits, hyperactivity, impulsivity, aggression) and 9.4% internalizing (anxiety, depression) disorders with rates of comorbidities increasing about 1.6 times each year from age 2 (18.2%) to 5 (49.7%; for a review, see Egger & Angold, 2006).

These increasing rates of comorbidities support the notion of developmental cascades defined as cumulative consequences for the development across different domains, which result out of several inter- and transactions in complex living systems (Masten & Cicchetti, 2010). Developmental cascades are assumed to begin in the preschool years and extend into adolescence. They can be negative or positive, resulting in either maladaptive or adaptive behavior. However, the conceptualization of adaptive or maladaptive behavior differs considerably between studies. Whereas some researchers have focused on the absence of problematic behavior as an indicator of positive adaptation, other studies concentrated on the development of positive outcomes instead (Shiner & Masten, 2012). In the present study, adaptive behavior is assumed to be represented by both the absence of problematic and the presence of positive social, cognitive, and personal child characteristics such as prosociality, aggression, inhibitory control, attentional focusing, self-efficacy, and anxiety.

4.1.1 Adaptive child behavior

Well-known problematic child behaviors are inattention and impulsivity, which represent difficulties reported in attention-deficit/hyperactivity disorders (ADHD). Children suffering from ADHD are at an increased risk for learning disabilities, peer rejection, and lack of self-efficacy (for a review, see Spira & Fischel, 2005). At the same time, they show higher comorbidity rates with anxiety and aggressive symptoms (Sonuga-Barke, Cortese, Fairchild, &

Stringaris, 2016), which in turn are related to negative long-term consequences. Childhood anxiety constitutes a strong risk for anxiety and depressive symptoms in adolescence and adulthood (Kim-Cohen et al., 2003), whereas aggressive symptoms are related to substance abuse, delinquency, antisocial behavior, incarceration, academic underachievement, and employment difficulties (Brumley & Jaffee, 2016; Evensen, Lyngstad, Melkevik, & Mykletun, 2016; Goldstein & Rider, 2013).

In contrast, positive child characteristics such as self-efficacy, prosociality, and effortful control have been linked to mental health (O'Dougherty Wright et al., 2013; Shiner & Masten, 2012; Stevens et al., 2015). Self-efficacy is negatively related to depressive symptoms, anxiety, social avoidance, and worry (Klasen et al., 2015; Tahmassian & Moghadam, 2011). Moreover, an increase in self-efficacy was associated with a decrease in depressive symptoms (Klasen et al., 2015). Prosocial behavior is linked to increased empathy, emotional regulation, positive self-concepts, greater self-efficacy, more positive peer interactions, and less ADHD symptoms (c.f. Griese & Buhs, 2014; Lösel & Bender, 2014). Furthermore, effortful control is defined as the abilities to inhibit automatic response tendencies (inhibitory control) and to control attention (attentional focusing), which both help regulating emotions and behaviors (Stevens et al., 2015). While effortful control is negatively related to anxiety, externalizing behaviors, and peer conflict, positive associations with sociability and assertiveness in peer relations were found (Acar et al., 2015; Muris et al., 2008; Valiente et al., 2003).

4.1.2 Contextual risk and protective factors

While adaptive child behavior seems to involve problematic and positive child characteristics simultaneously, it is also influenced by a variety of contextual risk and protective factors that have been identified over the past 50 years (O'Dougherty Wright et al., 2013; Olsson et al., 2003). Special attention has been given to the home and school environments, as they often represent the most important and constant surroundings for young children.

Low socioeconomic status (SES), parental strict control, and parental conflicts are considered risk factors of the home and family environment (Fergusson & Horwood, 2003; Zolkoski & Bullock, 2012). Children with low SES are more likely to develop mental health problems such as internalizing and externalizing problem behavior (for reviews, see Reiss, 2013; Russell, Ford, Williams, & Russell, 2015). Moreover, a decrease in SES was associated with an increase of mental health problems. Furthermore, above-average SES had a direct protective effect against violent behavior (Loeber, Farrington, Stouthamer-Loeber, & White,

2008). Similarly, parental strict control is linked to substance abuse, anger and fear dysregulation, and depressive symptoms, whereas autonomy support has been associated with effective emotion regulation skills (Donaldson et al., 2016; Ozer et al., 2013; Roth, Assor, Niemiec, Deci, & Ryan, 2009). Finally, parental conflicts are associated with child depression and anxiety, inferior academic results, poor social skills, aggression, and disobedience (for a review, see Sarrazin & Cyr, 2007), whereas harmonious inter-parental relationships are seen as protective factors (O'Dougherty Wright et al., 2013).

Besides the home environment, another branch of research has examined risk and protective factors of the school environment (c.f. Goldstein & Brooks, 2013a). There are estimations that in an average classroom approximately one out of every seven children reports being bullied, often responding with self-imposed isolation (National School Savety Center, 2006). Long-lasting peer rejection in children with conduct problems, in turn, is significantly related to aggressive responding and even bullying itself (Goldstein & Brooks, 2013b). On the other hand, peer acceptance has been found to be positively related to prosocial behavior and negatively correlated to externalizing and internalizing problem behavior (Henricsson & Rydell, 2006). School intervention studies aiming to improve school/classroom climate found that a positive classroom climate can reduce school bullying and may be a protective factor against later violence (Cohen, 2013; Lösel & Farrington, 2012).

There is a vast amount of risk and protective factors influencing adaptive behavior, which in turn can be defined in different ways, either by the absence of problematic or the presence of positive child characteristics. However, the distinction between risk and protective factors or problematic and positive child characteristics is not always clear. Often they can be seen as opposite poles of the same dimension (Lösel & Bender, 2014). For example, low SES represents a risk factor, whereas above-average SES functions as a protective factor. Analogously, high inhibitory control is seen as a positive child characteristic, while low inhibitory control can be considered as high impulsivity, which represents a problematic child characteristic.

In the present study, it is assumed that adaptive behavior is represented by both the absence of problematic and the presence of positive child characteristics. Therefore, we first tested, if adaptive child behavior can be represented by a global factor involving problematic and positive child characteristics such as prosociality, aggression, inhibitory control, attentional focusing, self-efficacy, and anxiety. Second, we examined the effects of contextual factors on the developed latent factor model (Figure 2). Regarding the home environment, SES and harmonious parental relationship were expected to be positively related to the latent fac-

tor, whereas parental conflicts and parental strict control were assumed to show negative associations. Concerning the school environment, a negative relation with victimization and a positive relation with classroom climate were presumed.

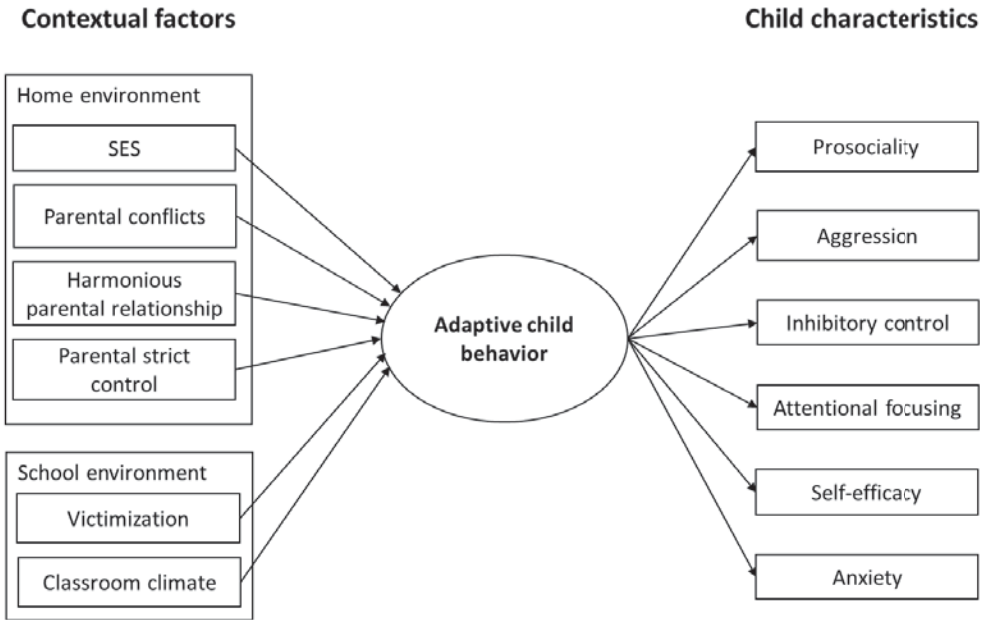

Figure 2. Conceptual model of adaptive child behavior

Adaptive child behavior represented by the absence of problematic and the presence of positive child characteristics, and the influence of contextual risk and protective factors of the home and school environment.

4.2 Methods

4.2.1 Participants and procedure

Data were derived from the first wave (collected in 2006) of the youngest cohort (6 years old children) of the Swiss Survey of Children and Youth – Competence and Context (COCON). COCON is an ongoing population-based multi-cohort longitudinal study, representative for the German- and French-speaking parts of Switzerland, which aims to investigate the psychosocial development from childhood into adulthood (Buchmann & Fend, 2004). According to the current regulations in the canton of Zurich, Switzerland, no ethic approval was required for this non-invasive survey (c.f. Malti, Gummerum, Keller, Chaparro, & Buchmann, 2012).

In a two-step process, 131 communities were selected and children were randomly sampled on the basis of information provided by the community's official register (see Buchmann et al., 2007; www.cocon.uzh.ch). After parents had given written informed con-

sent, a computer-assisted personal interview was conducted with the primary caregiver – defined as the person most responsible for the child's socialization. Primary caregivers and kindergarten teachers completed additional questionnaires regarding the psychosocial child development.

Of the 1275 participating children, 437 were excluded; 60 because they did not attend kindergarten (53 had already entered school, 7 were still at home), and 377 due to missing teacher ratings (no parental agreement to contact the teacher or teacher did not participate). The excluded children did not differ from the retained sample in age, gender, annual family income, or education of the primary caregiver. The final sample consisted of 838 children (50% boys; M_{age} = 6.16; SD_{age} = 0.20). Primary caregivers (94% mothers, M_{age} = 37.72; SD_{age} = 4.68) were predominantly Swiss (76%) or members of the European Union (8%). The families, of which 19% were living in rural areas, were socioeconomically heterogeneous, with family income ranging from below CHF 20'000 to over CHF 150'000 per year (median CHF 75'000 – CHF 99'999). Kindergarten teachers (97% female; M_{age} = 39.72; SD_{age} = 11.75) had 15.37 years (SD = 10.18) of working experience on average.

4.2.2 Measures

As COCON is conducted in the German- and French-speaking parts of Switzerland, all measures were translated into French and back into German by bilingual native speakers. To ensure adequacy and age-appropriateness of the questions, pilot studies were conducted and if necessary, items were adapted (Buchmann et al., 2007).

Adaptive child behavior

All child characteristics were rated on a Likert-type scale ranging from 1 (strongly disagree) to 6 (absolutely agree) by both the primary caregivers and the kindergarten teachers. The items were introduced by the sentence: How characteristic are the following behaviors for your/the child?

Prosociality and **aggression** were assessed with the German version of the Strength and Difficulties Questionnaire (SDQ-Deu; Klasen, Woerner, Rothenberger, & Goodman, 2003); e.g. prosociality: "My/The child is helpful if someone is hurt, upset or feeling ill"; aggression: "My/The child has temper tantrums or hot tempers". Whereas primary caregiver ratings showed relatively low Cronbach's α using four (α = .61) and three (α = .51) items,

respectively, kindergarten teacher ratings were acceptable and good using three (α = .78) and seven (α = .86) items, respectively.

Effortful control was operationalized as inhibitory control and attentional focusing, which were assessed with the Children's Behavior Questionnaire (Rothbart et al., 2001); e.g. inhibitory control: "My/The child has trouble sitting still when s/he is told to do so (at movies, church, etc.)"; e.g. attentional focusing: "My/The child shows strong concentration when drawing or coloring in a book". Again, primary caregiver ratings showed low Cronbach's α using three items each (α = .51; α = .54), while kindergarten teacher ratings were acceptable using three items each (α = .72; α = .75).

Anxiety was rated by the primary caregivers with five items (α = .69) using the German version of the California Child-Q-Sort (Göttert & Asendorpf, 1989); e.g. "My child is fearful and anxious". Teacher ratings were based on the German version of the Teachers Report Form (TRF) of the Child Behavior Checklist (CBCL) developed by the Arbeitsgruppe Deutsche Child Behaviour Checklist (1993), consisting of three items (α = .75); e.g. "The child is afraid to make mistakes".

Self-efficacy was rated using four items (primary caregivers: α = .71; teachers: α = .72) of the Scales for the Assessment of Teacher and Student Characteristics (Schwarzer & Jerusalem, 1999); e.g. "My/The child finds ways and means to assert him/herself if confronted with drawbacks".

Contextual factors

Socioeconomic status of the primary caregivers was measured using the International Socio-Economic Index of Occupational Status (ISEI) as introduced by Ganzeboom, De Graaf, and Treiman (1992). This index is based on international data regarding income and education for different occupations.

Parental conflicts were rated by primary caregivers on a 6-point Likert scale from 1 (never) to 6 (always) using three items (α = .74) developed by Schneewind and Ruppert (1992); e.g. "Within your partnership, how often does an uncomfortable atmosphere result out of trivialities?".

Harmonious parental relationship was rated by primary caregivers on a 6-point Likert scale from 1 (never) to 6 (always) using three items (α = .76) developed by Furman and Buhrmester (1985); e.g. "How often does your partner like you the way you are?"

Parental strict control was rated by primary caregivers on a 6-point Likert scale from 1 (never) to 6 (always) using four items (α = .50) developed by Engfer (1984); e.g. "Even if my child has different plans, it must ultimately do what I want".

Victimization was rated by kindergarten teachers on a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree) using three items (α = .76) developed by Alsaker (n.d.); e.g. "Sometimes the child is excluded by other school children".

Classroom climate was rated by kindergarten teachers on a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree) using four items (α = .74) developed by the Government of Canada (n.d.); e.g. "During group activities, the children are easily distracted by the disruptive behavior of a few".

4.2.3 Data analysis

As child characteristics were rated by both the primary caregivers and teachers, first analyses were conducted to address the question of dealing with multi-informants. Inconsistencies between parent and teacher ratings arise often and could be due to rater bias or the fact that the expression of a child's behavior can vary strongly across different settings (Hunsley & Mash, 2007). Zero-order correlations (Spearman's Rho) between primary caregiver and teacher ratings revealed low but significant relations for all child characteristics ranging from r_s = .22, p < .000 (self-efficacy) to r_s = .27, p < .000 (aggression). To allow for an overall impression of the children's behavior, the two ratings were combined. All scales were standardized to ensure an equal contribution of both informants before building the mean of the two ratings. Cronbach's alphas for combined reports ranged between .62 (attentional focusing) and .81 (aggression).

Statistical analyses were conducted using the R package lavaan (Rosseel, 2012). Full information (fiml) and robust (mlr) maximum likelihood estimations were chosen to deal with missing values and the non-normality of the data. First, the existence of a global underlying latent factor representing adaptive child behavior involving the aforementioned child characteristics was tested with a confirmatory factor analysis (CFA). Second, the contextual risk and protective factors of the home and school environment were integrated into the developed model to examine their influence on the latent factor. Finally, a post-hoc multi-group analysis was carried out to determine whether the relations among the variables in the model operate similarly for girls and boys. As primary goodness-of-fit statistics, the overall chi-square value

(Bollen, 1989), the root mean square error of approximation (RMSEA, Browne & Cudeck, 1993), and the comparative fit index (CFI, Bentler, 1990) were used. Good model-fit is generally assumed to be indicated by a non-significant chi-square test, an RMSEA less than .05, and a CFI ≥ .95 (see Byrne, 2009).

4.3 Results

Descriptive statistics and zero-order correlations for the study variables are depicted in Table 2. First, a confirmatory factor analysis (CFA) involving all the internal factors was conducted to determine the best-fitting model. The one-factor model (Figure 3a) fit poorly (χ^2 (9) = 427.30, p = .000; RMSEA = .24, 90%CI = [.22, .25]; CFI = .59). Loadings for self-efficacy (β = .19; p = .001) and anxiety (β = -.03; p = .540) were small and modification indices suggested a large increase in model-fit (χ^2 (8) = 190.47) when adding a covariance between those two variables, possibly indicating a two-factor latent model (Figure 3b).

Again, this second model fit poorly (χ^2 (8) = 152.08, p = .000; RMSEA = .15, 90%CI = [.13, .17]; CFI = .86), and one latent factor was under-identified (Adaptive child behavior 2 consisted of only two manifest variables). A third multiple indicators and multiple causes (MIMIC) model was tested (Figure 3c) with self-efficacy and anxiety predicting adaptive child behavior. An additional covariance was added between inhibitory control and attentional focusing as they both represent effortful control. The model resulted in a similarly poor model-fit (χ^2 (7) = 177.81, p = .000; RMSEA = .17, 90%CI = [.15, .19]; CFI = .85). However, modification indices suggested that both self-efficacy and anxiety were directly related to the other four child characteristics. Therefore, the one-factor structure was retested with prosociality, aggression, inhibitory control, and attentional focusing predicted by self-efficacy and anxiety (Figure 4). This model showed an excellent fit (χ^2 (1) = .30, p = .591; RMSEA = .00, 90%CI = [.00, .07]; CFI = 1.00). Effect sizes for regressions were between R^2 = .26 (attentional focusing) and R^2 = .59 (aggression). The covariance between inhibitory control and attentional focusing was significant, indicating that these variables share additional variance that cannot be explained by the latent factor. Aggression was neither significantly predicted by self-efficacy nor by anxiety. Finally, although self-efficacy and anxiety were negatively correlated, both showed positive associations with prosociality, inhibitory control, and attentional focusing.

Table 2. Descriptive statistics and zero-order correlations (r_s) for study variables

Measure	*N*	*M*	*SD*	1	2	3	4	5	6	7	8	9	10	11
Internal factors														
1. Prosociality	838	0.24	0.66	-										
2. Aggression	838	-0.12	0.74	-.40 ***	-									
3. Inhibitory control	838	0.22	0.68	.42 ***	-.52 ***	-								
4. Attentional focusing	838	0.13	0.71	.32 ***	-.24 ***	.41 ***	-							
5. Anxiety	838	-0.03	0.80	.01	.01	.03	-.01	-						
6. Self-efficacy	838	0.10	0.18	.24 ***	.03	.11 **	.28***	-.52 ***	-					
Family environment														
7. ISEI	805	44.61	15.52	.06	-.07	.04	.09**	-.04	.12**	-				
8. Parental conflicts	680	2.43	0.90	-.10**	.18***	-.13**	-.06	.06	-.06	.03	-			
9. Harmonious parental relationship	677	5.23	0.62	.18***	-.09*	.15***	.15***	-.01	.14***	-.00	-.38***	-		
10. Parental strict control	838	3.83	0.89	.-.02	.15***	-.04	.02	.03	.06	-.05	.01	.05	-	
School environment														
11. Victimization	838	1.86	1.04	-.26***	.38***	-.32***	-.20***	.21***	-.20***	-.08*	.09*	-.05	.01	-
12. Classroom climate	838	4.50	0.92	.10**	-.10**	.16***	.10**	-.05	.08	.03	.00	-.06	-.02	-.17***

Note: Child characteristics represented by the mean of standardized primary caregiver and teacher ratings. *M* = Mean; *SD* = standard deviation; ISEI = International Index of Socio-Economic Index of Occupational Status. *** = p < .001; ** = p < .01; * p < .05.

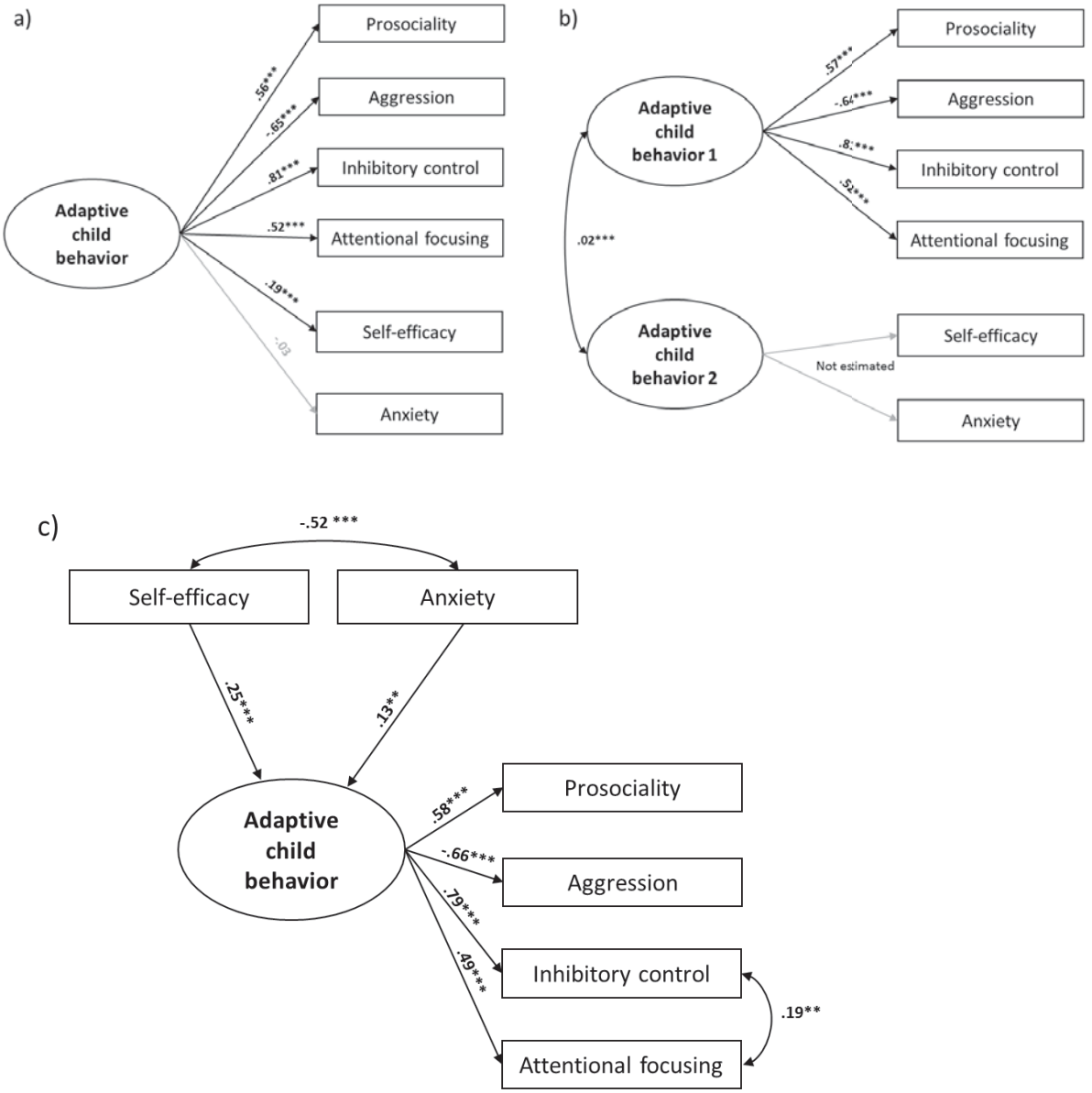

Figure 3. Tested models of adaptive child behavior I

Tested models with poor model-fit. Standardized coefficients of a) the one-factor model, b) the two-factor model, and the c) multiple indicators and multiple causes (MIMIC) model. b) Loadings for adaptive child behavior 2 could not be estimated, since this factor was under-identified. Significant regressions and correlations are depicted as black lines, whereas grey lines represent non-significant associations. ***= $p < .001$; **= $p < .01$; *= $p < .05$.

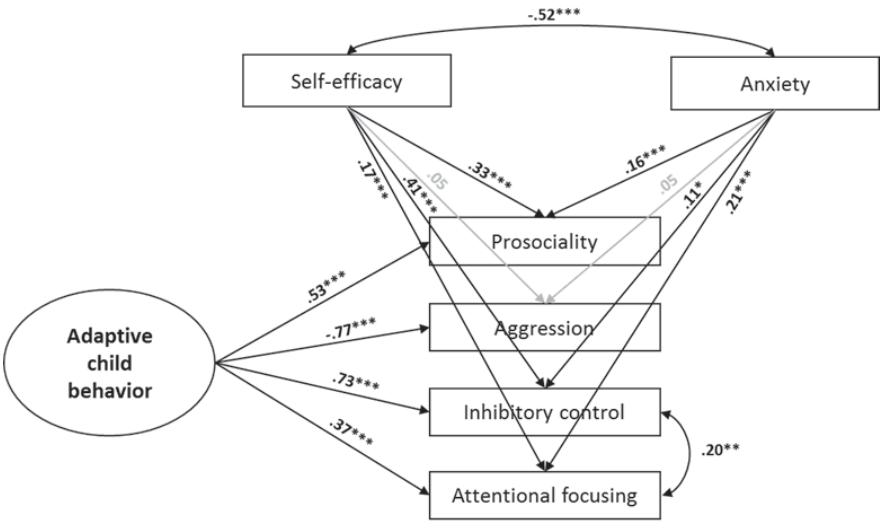

Figure 4. Tested models of adaptive child behavior II

Standardized coefficients of the tested model representing adaptive child behavior showing good model-fit. Significant regressions and correlations are depicted in black lines, whereas grey lines represent non-significant associations. ***= $p < .001$; **= $p < .01$; *$p < .05$.

Next, the effect of the contextual variables onto the developed model was examined (Figure 5). All variables of the home and school environment were integrated at once, allowing for intercorrelations. The model showed a good fit (χ^2 (19) = 28.25 p = .079; RMSEA = .024, 90%CI = [.000, .041]; CFI = .993). Except for ISEI, all the external factors predicted adaptive child behavior, with victimization showing the highest regression weight. Notably, victimization was the only external factor associated with anxiety.

As the internal factors revealed significant differences between boys and girls (Table 3), post-hoc analyses were conducted to test for sex differences. The developed model representing adaptive child behavior (Figure 4) was tested for invariance with respect to a) factor loadings and b) regression coefficients and covariates, leaving intercepts noninvariant. Regarding the factor loadings, no differences between girls and boys were found. Nevertheless, after additionally setting regression weights invariant, the model difference was significant ($\Delta\chi^2$ (8) = 16.97; p = .030) indicating sex differences of at least one parameter. To identify the source of invariance, regressions and covariates were stepwise set noninvariant. The final model (χ^2 (11) = 15.00, p = .182; RMSEA = .03, 90%CI = [.00, .06]; CFI = .99; $\Delta\chi^2$ (6) = 10.48; p = .106) showed that boys and girls differed regarding two regression coefficients.

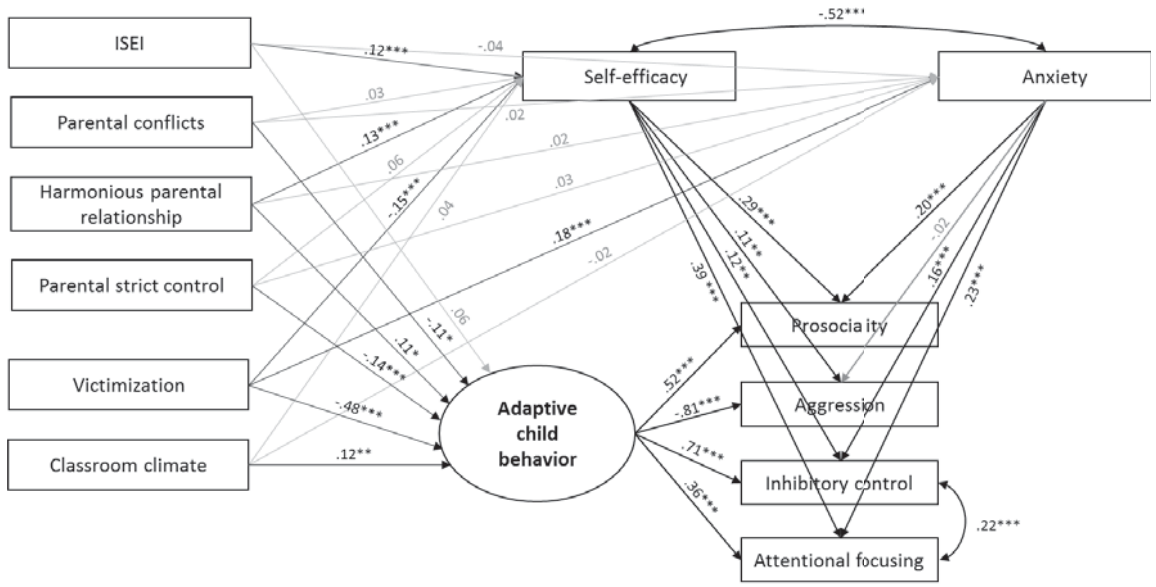

Figure 5. Influence of contextual risk and protective factors on adaptive child behavior

Standardized regression coefficients depicting the influence of contextual risk and protective factors on adaptive child behavior. Significant regressions and correlations are depicted in black lines, whereas non-significant regressions are depicted in grey. ISEI = International Index of Socio-Economic Index of Occupational Status. ***= p < .001, **= p < .01, *= p <.05.

Table 2. Sex differences in child characteristics

	Mdn girls / boys	*U*	*p*
Prosociality	.33 / -.16	-8.94	**.000**
Aggression	-.24 / -.05	-3.74	**.000**
Inhibitory control	.29 / -.13	-7.37	**.000**
Attentional focusing	.19 / .03	-3.72	**.000**
Anxiety	-.07 / -.13	-0.53	.595
Self-efficacy	.18 / -.02	-.4.03	**.000**

Note. *Mdn* = Median (from combined standardized primary caregiver and teacher ratings); *U* = Mann-Whitney-U. Significant results in bold.

In girls, anxiety did not predict aggression (B = .004, SE = .05, β = .004, p = .936), whereas in boys it was positively associated (B = .106, SE = .05, β = .100, p = .036). Moreover, the positive relation between attentional focusing and anxiety was stronger in girls (B = .264, SE = .05, β = .294, p = .000) than in boys (B = .141, SE = .05, β = .124, p = .008). Furthermore,

boys and girls differed with respect to the covariance between inhibitory control and attentional focusing. While for girls no correlation was found (r = .108, p = .143), boys showed a positive association (r = .271, p = .000). Finally, the external factors were added into this partially invariant model. The resulting model showed a good fit (χ^2 (48) = 58.45 p = .144; RMSEA = .023, 90%CI = [.000, .040]; CFI = .992) and therefore all the additional regressions were set invariant to test for sex differences regarding the external factors (χ^2 (66) = 80.09 (girls: 41.46; boys: 38.63), p = .114; RMSEA = .023, 90% CI = [.000, .038]; CFI = .989). The two models did not differ significantly ($\Delta\chi^2$ (18) = 21.64; p = .249), indicating that the relations were not gender-specific.

4.4 Discussion

Adaptive child behavior results out of complex interrelations between several risk and protective factors. However, there have been many different conceptualizations of adaptive child behavior, and risk and protective factors can often not be distinguished clearly from each other. In the present study, we first tested a latent factor model assuming that adaptive child behavior can be represented by both the absence of problematic and the presence of positive child characteristics. The developed model showed that prosociality, low aggression, inhibitory control, and attentional focusing loaded on one latent factor, whereas self-efficacy and anxiety did not. Yet, self-efficacy and anxiety were positively related to the other four child characteristics. Second, the integration of contextual risk and protective factors into the developed model demonstrated that all of the contextual factors, except for ISEI, predicted adaptive child behavior, with victimization showing the highest regression coefficient. Post-hoc analyses revealed different relations between boys and girls regarding child characteristics. Whereas in boys positive relations between anxiety and aggression and between inhibitory control and attentional focusing were found, in girls those variables showed no associations. Instead, the positive relation between anxiety and attentional focusing was significantly stronger in girls than in boys.

Testing the underlying factor structure revealed that there is no global latent factor involving all child characteristics. However, four variables previously known to be inter-related (c.f. Eisenberg et al., 2001) loaded on one latent factor: prosociality, aggression, inhibitory control, and attentional focusing. This supports our assumption that problematic and positive child characteristics may be integrated as equivalent variables when investigating child adaptive behavior. Moreover, despite the fact that girls scored higher on prosociality, inhibitory

control, and attentional focusing, whereas boys scored higher on aggression, the factor loadings did not differ between the genders, indicating that adaptive behavior is represented by the same amount of shared variance for girls and for boys.

However, self-efficacy and anxiety were not related to the latent factor and possibly represent conceptually different child characteristics. As aggression and low effortful control are seen as externalizing behavior problems (Egger & Angold, 2006), we suggest that the latent factor in our study mostly represents adaptive externalizing behavior. Instead, anxiety is defined as an internalizing behavior problem (Egger & Angold, 2006) and may contribute with self-efficacy to a second latent factor, representing adaptive internalizing behavior. However, as the latent factor representing adaptive internalizing behavior (see Figure 3b) was under-identified, such a model would have to be tested involving more variables. Nevertheless, our results suggest that externalizing and internalizing behavior should be treated as separate but overlapping indicators of adaptive child behavior, which is in line with prior research (e.g. Brumley & Jaffee, 2016; Evensen et al., 2016).

Furthermore, inhibitory control and attentional focusing shared variance that could not be explained by the latent factor. This may be due to methodological aspects, as both characteristics were assessed with the same questionnaire. Another explanation may be that while prosociality and aggression contribute to the social aspect of adaptive behavior, effortful control may contain an additional cognitive aspect. This seems plausible as executive functioning is related to ADHD (Russell A Barkley, 1997). Therefore, child adaptive behavior may also be best represented by three conceptually different but overlapping aspects: a) social (e.g. prosociality and aggression), b) cognitive (e.g. inhibitory control and attentional focusing), and c) personal (e.g. anxiety and self-efficacy) aspects. More research is needed to test this assumption.

Post-hoc analyses revealed that inhibitory control and attentional focusing were correlated only in boys. No prior study was found concerning effortful control that confirmed this gender difference. Instead, a possible explanation could be drawn from the research regarding ADHD, which showed that females have fewer impulsive and more inattentive symptoms compared to males (for a review, see Gershon, 2002). Furthermore, Skogli, Teicher, Andersen, Hovik, and Øie (2013) found higher levels of co-existence between internalizing symptoms and ADHD in females compared to males, which is in line with our finding of a stronger relation between anxiety and attentional control in girls.

However, anxiety was positively associated with attentional focusing and inhibitory control. Although most prior research indicates that anxious children are less able to ignore distractions and therefore demonstrate negative associations with effortful control (for a review, see Nigg, 2006), one study found a positive association with internalizing behavior (Murray & Kochanska, 2002). The authors discuss that, despite assumed methodological issues, inhibited or over-controlled children may be more cautious and therefore more vigilant, feeling distressed more easily by novel stimuli and consequently being at an increased risk for future anxiety. At the same time, we hypothesize that these children may be more prosocial to avoid conflicts, which may be a possible interpretation of the positive relation between anxiety and prosociality in the present study. This would be in line with a recent study that examined joint development trajectories of prosocial and problem behavior and found that prosociality can co-occur with both low and high anxiety (Nantel-Vivier, Pihl, Côté, & Tremblay, 2014).

Although no relation was found between anxiety and aggression, post-hoc analyses revealed that the association was significantly positive only in boys. This may be due to the lower aggression levels in girls, which is in line with prior research (e.g. Nivette, Eisner, Malti, & Ribeaud, 2014). But while boys show more physical, proactive, and reactive aggression, girls are assumed to more likely use other, more indirect forms of aggression such as relational, indirect, and social aggression, which involve spreading slanderous rumors or social exclusion (Marshall, Arnold, Rolon-Arroyo, & Griffith, 2015). Future studies should integrate different forms of aggressive behavior when examining gender differences.

As expected, self-efficacy was positively related to prosociality, inhibitory control and attentional focusing, whereas it was negatively correlated with anxiety. However, while no association was found between self-efficacy and aggression in the developed model (see Figure 4); the relation became positive when contextual risk and protective factors were integrated. It should be noted that in this study, general self-efficacy was assessed, which is an extremely broad concept. Prior research revealed that domain-linked or specific measures of self-efficacy work better in predicting behavior (Bandura, 1989). As Perry, Perry, and Rasmussen (1986) suggested, aggressive adolescents often see aggression as a normal response, believing it to result in positive outcomes, and feel confident about their capacity to carry out aggressive behavior. Future research should distinguish different forms of self-efficacy.

Regarding the contextual risk and protective factors, adaptive behavior was positively predicted by harmonious parental relationship and classroom climate, while negatively predicted by parental conflicts, parental strict control, and victimization. These results were in

line with our expectations. Notably, victimization revealed the highest loadings, emphasizing its role as a relevant risk factor for adaptive child behavior. However, ISEI was not related to adaptive child behavior. Although measurements of SES are heterogeneous, prior findings concerning child mental health are consistent, in that they show a negative relation. Moreover, stronger associations have been found with externalizing disorders than with internalizing disorders (Reiss, 2013). The lack of association in this study could be due to the fact that SES was measured with the ISEI of the primary caregiver (mostly the mother) only, excluding the partner. However, the ISEI of both parents may be more representative.

Several limitations have to be considered. First, the number and the choice of the problematic and positive child characteristics and the contextual risk and protective factors are selective. There are numerous other variables known to be relevant for adaptive child development (e.g. depression, mental and physical health of the parents, maternal sensitivity, child-teacher relationships, neighborhood and societal factors), which have not been considered in this study. Second, primary caregiver and teacher ratings were investigated while not examining child-reports. Furthermore, primary caregiver and teacher ratings were combined, knowing that informant's reports commonly disagree. However, informant discrepancies may display meaningful information, as the expression of a child's behavior can vary strongly in different settings (De Los Reyes et al., 2015). Third, internal consistencies for primary caregiver ratings were relatively small (Cronbach's α ranged from .51 to .69), which could be due to the small number of items. Similar values for small number of items rated by caregivers were found in a study by Guion, Mrug, and Windle (2009). Fourth, although many associations became significant, effect-sizes were relatively small (e.g. $R^2 = .29$ for adaptive child behavior, $R^2 = .05$ for anxiety, $R^2 = .06$ for self-efficacy). As the p value is likely to be significant if sample size is big, the significant effects in this study could be mainly driven by the big sample size (Sullivan & Feinn, 2012). Fifth, generalizability of our results is reduced to preschool children living in Switzerland. Finally, surveys of mental health problems in children are thought to be susceptible to nonresponse bias, as parents may be reluctant to report child problems. This could be also used as a possible explanation of the many missing teacher ratings in this study.

Because of the vast amount of risk and protective factors, many studies build cumulative risk factors, adding up the single variables, to reduce complexity (for a review, see Browne, Plamondon, Prime, Puente-Duran, & Wade, 2015). Although this proofed to be a useful approach, in these models all risk factors are treated as if each variable would have the same influence on the outcome. As some variables such as victimization tend to have a

stronger impact, we suggest that different indicators of adaptive child behavior (e.g. social, cognitive, and personal aspects) may be also depicted as latent factors represented by both, problematic and positive child characteristics entered individually. Future studies should compare these latent factors models with other outcome measures such as the recently developed Diagnostic Adaptive Behavior Scale (Tassé et al., 2016). Furthermore, latent indicators of adaptive child development should be examined longitudinally, analyzing latent change and examining trajectories.

5 FKBP5 methylation in toddlers at risk: associations with parental sensitivity, child behavior problems, and early intervention

5.1 Introduction

Childhood adversities have been associated with a variety of adult mental and physical health disorders such as depression, anxiety, auto-immune disorders, cardiovascular diseases, diabetes, and premature mortality (for a review see Danese & McEwen, 2012; Provençal & Binder, 2014). One explanation for these associations is that sensitive periods for brain development involving elevated region- and neuron-specific synaptic plasticity represent timelines of vulnerability and resilience (Gröger et al., 2016). There is increasing evidence that childhood represents a critical window during which adverse experiences may cause enduring negative changes in the biological systems responsible for maintaining physiological stability (Danese & McEwen, 2012).

The hypothalamic-pituitary-adrenal (HPA) axis represents one of the primary biological stress response systems. Aberrations in the HPA axis may be due to an impaired number and function of glucocorticoid receptors (GRs). Stress exposure activates the HPA axis, resulting in the secretion of glucocorticoids (e.g. cortisol), which bind at the intracellular GRs. This induces translocation of the GRs into the nucleus, where they bind to glucocorticoid response elements (GREs) activating systems necessary for an adaptive response to acute stressors. To shut down the stress response, HPA axis activity is inhibited by negative feedback mechanisms at the hypothalamic and pituitary level (Kadmiel & Cidlowski, 2013).

The FK506 binding protein 5 (FKBP5) is known to have a mediating role in these negative feedback mechanisms. Cortisol-induced GR activation leads to a rapid induction of FKBP5, which binds to the GRs itself, blocking them for cortisol. Hence, high FKBP5 expression decreases systemic sensitivity to cortisol. Gene expression, in turn, is influenced by epigenetic mechanisms such as DNA methylation (Klengel et al., 2013). During methylation, a methyl group binds to cytosine-phosphate-guanine (CpG) dinucleotides, blocking the binding of transcription factors through which gene expression is inhibited (Klengel, Pape, Binder, & Mehta, 2014). Consequently, lower FKBP5 methylation leads to increased FKBP5 expression, which in turn reduces GR-mediated negative feedback (Klengel et al., 2013; Tyrka et al., 2012).

Although social epigenetics is a relatively new field of research, the body of literature in this area is growing exponentially. Besides FKBP5, other HPA axis-related candidate genes have been identified, such as the corticotropin-releasing hormone (CRH) gene and the nuclear receptor subfamily 3 group C member 1 (NR3C1) gene (Kertes et al., 2016). However, while findings regarding childhood adversities are relatively consistent for NR3C1 (Turecki & Meaney, 2016) and FKBP5, the results regarding the relation with psychosocial stress and psychopathology show inconsistencies. Particularly regarding FKBP5, very few studies have been conducted linking FKBP5 methylation to early child behavior or treatment effects.

5.1.1 FKBP5 methylation and childhood adversities

Recently, Klengel et al. (2013) found an interaction effect between genotype and early trauma on FKBP5 methylation in intron 7. As CPGs in intron 7 are located in proximity to or within GREs and have direct contact with the FKBP5 transcription start site, methylation of these sites is assumed to affect FKBP5 expression. Adults with a history of childhood abuse who are carriers of the rs1360780 risk allele showed an average decrease in methylation of 12.3% compared to controls without childhood abuse and carriers of the protective allele. Moreover, this decrease was related to a decrease in GR sensitivity but was not associated with serum cortisol levels. Interestingly, no associations were found with trauma exposure in adulthood. Likewise, Yehuda et al. (2015) found a negative association between FKBP5 methylation and childhood abuse in risk allele carriers but a positive association in protective allele carriers. Finally, reduced FKBP5 methylation in maltreated children was reported in two prospective studies from Tyrka et al. (2012) and Weder et al. (2014), although in the latter study, a 450K methylation array was used, which does not include intron 7.

Beyond maltreatment, additional childhood adversities have rarely been examined. Non et al. (2016) found a negative correlation between time spent in institutional care at an average age of 30 months and FKBP5 methylation at the age of 12. This association disappeared when analyzing later measurement time points (at the ages of 42 months, 54 months, 8 years, 12 years). Moreover, Tyrka et al. (2012) examined lifetime and past-month contextual stress exposure (CSE; e.g. frequent change of residence, homelessness, etc.) in impoverished preschoolers. While a negative relation at a trend level was found for lifetime CSE, there was no association for past-month CSE. In contrast, Needham et al. (2015) found that low childhood SES and persistent low SES into adulthood were associated with increased methylation.

5.1.2 FKBP5 methylation and child behavior

To date, no study has investigated postnatal FKBP5 methylation in relation to child behavior. However, two studies examined infant behavioral outcomes in relation to placental FKBP5 methylation, possibly reflecting effects of fetal programming.

Monk et al. (2016) found that maternal perceived stress was positively associated with placental methylation, which in turn was negatively related to fetal coupling (fetal movement and heart rate associated with mature neural integration at birth). The indirect effect was significant. The second study found a positive association between placental FKBP5 methylation and infant arousal, which represents a prenatal risk factor involving fussiness and spontaneous movements (Paquette et al., 2014). The authors argued that hypermethylation may lead to an increased cortisol activation of GRs in the placenta, resulting in an over-active cortisol response pathway at birth. In turn, this may promote hypervigilance and hyperarousal and increase the risk of developing stress-related disorders such as anxiety, depression or PTSD.

5.1.3 FKBP5 methylation in intervention studies

Roberts et al. (2015) examined FKBP5 methylation in response to cognitive behavior therapy (CBT) in children (aged 5-18 years) suffering from anxiety. No differences were found in methylation between pre- and post-treatment, and methylation at pre-treatment was not associated with treatment response. Nevertheless, within risk allele carriers, treatment-responders showed a decrease in FKBP5 methylation, whereas non-responders revealed an increase. Similarly, Yehuda et al. (2013) found a significant group by time interaction in adult combat veterans with PTSD who received prolonged exposure psychotherapy. Responders showed a decrease in the number of methylated sites, while non-responders showed an increase. Additionally, the number of methylated sites at 3-month follow-up was positively correlated with post-treatment PTSD severity.

Hence, FKBP5 methylation seems to be related to changes in HPA axis activity, in association with changes in symptom expression, rather than reflecting an upstream regulation of cortisol (Yehuda et al., 2013). This assumption is supported by the finding that cortisol was negatively related to FKBP5 methylation within but not across measurement time points (Yehuda et al., 2013). However, higher variability in FKBP5 methylation does not seem to represent a protective factor per se. The children who demonstrated greater variability in methylation changes were those carrying the risk allele (Roberts et al., 2015). These children

showed both positive and negative treatment outcomes, along with either decreased or increased methylation, leading the authors to suggest that they may be more vulnerable to any changes, be they for better or for worse.

In summary, evidence suggests that childhood adversities lead to lower FKBP5 methylation levels. In contrast, problematic child behavioral outcomes, although solely based on placental methylation, seem to be related to FKBP5 hypermethylation. Moreover, an increase in methylation was associated with better treatment outcomes.

However, so far, prospective studies are scarce and underlying mechanisms are far from being understood. Moreover, most studies have focused on physical, sexual, and emotional child abuse in relation to FKBP5 methylation. No previous study has investigated protective factors. Research on social buffering processes suggests that the effects of early adversities on the HPA axis may be mitigated by parental sensitivity and responsiveness (for a review see Hostinar, Sullivan, & Gunnar, 2014). To date, no research has been conducted regarding parental sensitivity and FKBP5 methylation. However, maternal sensitivity has been associated with methylation levels of other stress-relevant genes such as the 11β-hydroxysteroid dehydrogenase (11β-HSD2) gene and the glucocorticoid receptor (NR3C1) gene (Conradt et al., 2016).

The present study includes a subsample of a longitudinal, randomized controlled intervention study conducted in children living in psychosocially at-risk families in Switzerland. The aim is to investigate FKBP5 methylation, cortisol concentrations, and their variations in relation to 1) parental sensitivity 2) child behavior problems, and 3) the early intervention program *Parents as Teachers* (PAT).

5.2 Method

5.2.1 Participants and procedure

This study is part of the ZEPPELIN project (Zurich Equity Prevention Project with Parents Participation and Integration), a longitudinal, randomized controlled early intervention study aiming to enhance educational opportunities for psychosocially at-risk children in the long term (Lanfranchi & Neuhauser, 2013; Neuhauser et al., 2015). The study was approved by the Ethics Committee of the Canton of Zurich (Ref. Nr. KEK-ZH 2013-0278) in Switzerland.

Families were recruited before or shortly after giving birth by an interdisciplinary network of parent counseling offices and medical and psychology professionals, at three project sites in the Canton of Zurich, Switzerland. A self-developed short screening was used to identify families in psychosocially at-risk situations (c.f. Neuhauser et al., 2015). It included the following dimensions: 1) parental risks (low level of education, early parenthood, alcohol or drug abuse, sickness and disabilities), 2) familial risks (single parenthood and partnership conflicts), 3) social risks (lack of social integration and dissocial environment), 4) material risks (unemployment, financial problems, confined living space), and 5) child-related risks (high-risk pregnancy, health issues, prematurity). Families were included if at least two items from the four core fields were applicable while no protective factors attenuating these risks were present. If inclusion criteria were met, the families were assigned to either the intervention (IG) or the control group (CG) condition using a stratified block randomization regarding location, risk, family structure, and German language skills (for a more detailed description of the recruitment and randomization process see Neuhauser et al., 2015). After randomization, 251 children (IG = 133; CG = 118) participated in the baseline measurement at three months postpartum (t_0). The children and their families were reassessed at 12 (t_1; N = 234), 24 (t_2; N = 232) and 36 (t_3; N = 218) months. Children who dropped out of the study (N = 38) had older mothers, more siblings, and more mothers without post-compulsory education. They did not differ in terms of sex, group condition, German language skills, and SES. If participants showed insufficient German language skills (30.7% of the cases), researchers were assisted by female intercultural interpreters. Moreover, the questionnaires were translated into the languages most represented in the study (e.g. Albanian, Portuguese, Turkish) and linguistically validated by an external translation bureau.

At t_2 and t_3, families were able to participate voluntarily in the additional measurement of methylation levels and nail cortisol concentrations (NCC). If written informed consent was given, fingernail clippings of all ten fingers of the child were cut by the mother, and saliva samples were collected using Oragene kits (OG-575) for Assisted Collection (DNA Genotek, Kanata, Ontario, Canada) by the research assistant. The children were not allowed to eat, drink or brush their teeth 30 minutes before. Participating children received a small present at both time points: a children's book at t_2 and a tub of Play Doh at t_3.

At t_2, 142 children (134 families [8 twins], IG = 54%, 54.9% girls) participated in this sub-project. The mothers (N = 16; 11.3% single mothers) had an average age of 29.99 years (SD = 7.11) at the birth of the participating child. 14.1% (N = 20) had no compulsory education and 21.8% (N = 31) had no post-compulsory education. The mothers were Swiss

(30.3%), Asian (19.9%), from the Balkans (11.9%) or Portuguese (11.3%), while Turkish, African, and American mothers or those from other European countries each accounted for less than 10%. The International Socio-Economic Index of Occupational Status (ISEI), which is based on international data regarding income and education (Ganzeboom, De Graaf, & Treiman, 1992), ranged from 16 to 85 (M = 38.34, SD = 16.21). Participants of the sub-project showed a significantly higher ISEI compared to non-participants (U = -2.76, p = .006). No other differences were found in this regard. At t3, 24 children dropped out of the subproject, and 25 additional children from the ZEPPELIN sample were recruited. As these 25 additionally recruited participants did not differ on any of the aforementioned variables from the 24 children who had dropped out, they were integrated in the analyses.

5.2.2 Intervention

The IG received the early intervention program "Parents as Teachers" (PAT; PATNC, 2011). PAT is an educational home visitation program that aims to 1) help parents to understand child developmental aspects and improve their parenting skills, 2) detect developmental shortcomings, 3) prevent child abuse and neglect, and 4) enhance school readiness (for a more detailed overview see Neuhauser, 2014). Home visits were carried out by experienced and trained parent educators. Additionally, families were invited for group meetings and informed about public child-friendly activities in the surrounding area (Lanfranchi & Neuhauser, 2013). To counteract attrition, the CG received incentives such as birthday greeting cards, small birthday presents, and monetary benefits of 180 CHF (approx. 184$) at t_1 and 130 CHF (approx. 133$) at t_2 and t_3.

5.2.3 Parental sensitivity

At t_0 and t_1, a three-minute free play parent-child interaction was videotaped and rated using the Child-Adult Relationship Experimental Index (CARE-Index) for toddlers (Crittenden, 2004). The CARE-Index assesses parental sensitivity in a dyadic context and is therefore characteristic not of an individual, but rather of a specific relationship. Interactions are rated on a scale from 0-14 and include seven dimensions: facial expression, verbal expression, position and body contact, affection, turn-taking contingencies, control, choice of activity. The CARE-Index is well validated with families from different ethnic backgrounds (Farnfield, Hautamäki, Nørbech, & Sahhar, 2010). Coders were trained by Crittenden and passed the

corresponding reliability test. All coders were blinded to group condition. In a test set of 25 videos, inter-rater reliabilities were good, with intraclass correlations (ICC) of .82 at t_0 and .72 at t_1.

5.2.4 Child behavior problems

Parents rated child behavior problems at t_2 and t_3 using the Child Behavior Checklist for ages 1.5 – 5 (CBCL 1½-5; Achenbach & Rescorla, 2000). The CBCL 1½-5 is a standardized questionnaire with 99 specific problem behaviors rated on a 3-point scale regarding the previous two months: 0 (not true), 1 (somewhat or sometimes true), 2 (very true or often true) and one open-ended item for parents to report any additional problems. It contains seven syndrome scales: emotionally reactive, anxious or depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behavior. The first four syndrome scales are grouped under internalizing behavior problems and the last two scales are grouped under externalizing behavior problems. The total problem score includes the sum of all items. The present study used T-scores for internalizing, externalizing, and total behavior problems. Alpha coefficients were good, ranging from .82 to .88.

5.2.5 FKBP5 methylation

Saliva samples were analyzed in the laboratory of the McGill Group for Suicide Studies at the Douglas Institute, Montréal, Canada. DNA was isolated using prepIT-L2P kit (DNA Genotek, Ontario, Canada) following the manufacturer's instructions before bisulfite treatment (500ng) with EZ 96-DNA methylation-Gold kit #D5007 (Zymo Research, Orange, CA, USA). For subsequent analysis, a targeted bisulfite sequencing method (c.f. Chen et al., n.d.) and Next Generation Sequencing (NGS) were used. Primers described in Paquette et al. (2014) were ordered with a common sequence tag (CS1-forward primer, CS2-reverse primer) at the 5'end. Polymerase chain reaction (PCR; T annealing = 58 °C; cycles = 40) was performed using Kapa HiFi HotStart Uracil + Ready Mix (Kapa Biosystem, MA, USA) and 10 µM primers. Barcoding with Illumina FLD indices (llumina, San Diego, CA, USA) was performed with an additional PCR (T annealing=60°C, cycles=10). The pooled library was added to the MiSeq Reagent Kit v3 (600-cycle) and sequenced on a Miseq platform (llumina, San Diego, CA, USA). Four intron 7 CPGs next to or within GREs were analyzed (Figure 6).

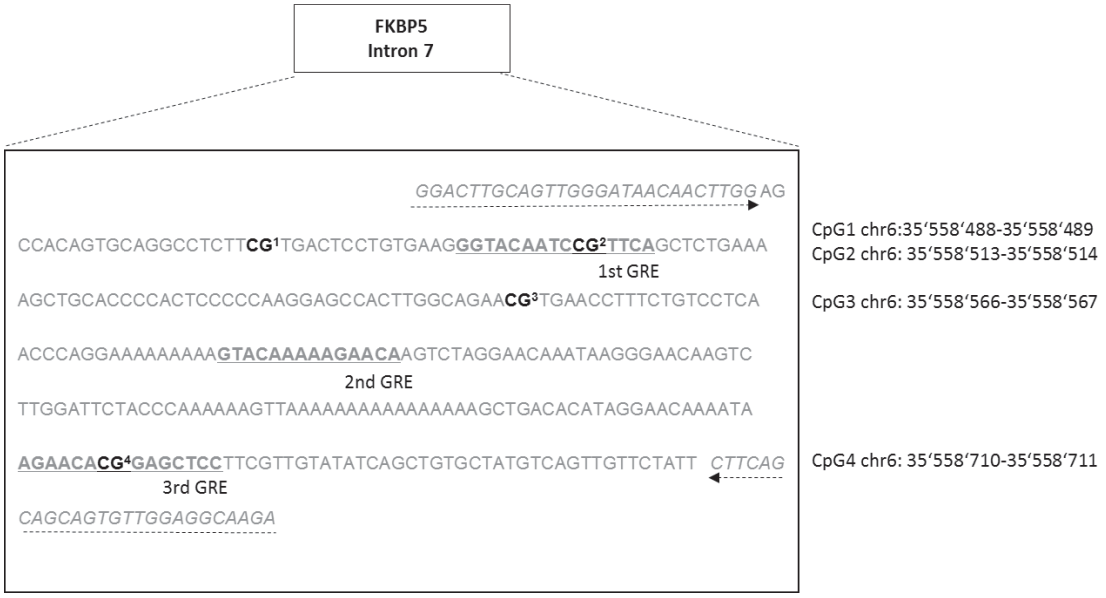

Figure 6. Chromosomal positions in the human FKBP5 locus (intron 7), 5‘-3‘ orientation

Primer sequence italicized. Five cytosine-phosphate-guanine (CpG) sites (in bold/black) analyzed on the proximity to three consensus glucocorticoid response elements (GREs; in bold/underlined). Chromosomal positions (hg19) of the CPGs are indicated on the right.

5.2.6 Nail cortisol concentrations

Cortisol is assumed to enter the nail plate through the nail matrix and through capillaries in the underlying nail bed of the finger pulp. Considering an average fingernail growth rate of three millimeters per month, fingernail clippings should represent a period lasting from approximately five to nine months prior to the present, which can be measured retrospectively (De Berker, André, & Baran, 2007). All nail clippings were stored at -20°C before analysis based on the protocol of Kirschbaum, Tietze, Skoluda, and Dettenborn (2009) used for hair cortisol. The intra- and inter-assay coefficients of variation were below 5%.

5.2.7 Covariates

Baseline psychosocial risk factors were integrated into the analyses as covariates, and were assessed in an interview using the *Heidelberger Belastungsskala* (HBS; Heidelberg Stress Scale). The HBS was developed by Stasch (2007) and consists of the same dimensions as the aforementioned short screening. Notably, familial risks and parental risks were combined, which resulted in four dimensions: 1) parental and familial risks (HBS family), 2) social risks

(HBS social), 3) material risks (HBS material), and 4) child-related risks (HBS child). All four dimensions were rated on a scale from 0 (no risk) – 100 (extremely high risk) by three members of the research team. In a randomly chosen subsample of 30 families, ICCs were good and excellent, ranging from .64 (HBS family) to .84 (HBS material).

5.2.8 Statistical analysis

Statistical analyses were conducted using SPSS, version 22 (IBM, Corporation). Descriptive statistics revealed extreme values for cortisol and methylation. Therefore, values +/-3 SDs from the mean were winsorized for all analyses (Wilcox, 2010). Overall, seven extreme values for nail cortisol at both measurement time points and one extreme value at t_2 for CpG1 and CpG2, respectively, were transformed. Since parametric assumptions were seldom met, all analyses are based on nonparametric statistics or bootstrapped (1'000 samples, bias-corrected) partial correlations and multiple regressions. Sex, group condition, and the HBS scales were used as covariates.

5.3 Results

5.3.1 Descriptive statistics

Descriptive statistics of the study variables are depicted in Table 4. There were no group condition or sex differences in parental sensitivity, childhood behaviors or HBS scales. Boys showed higher levels of methylation at CpG2 t_2 (U = -2.5, p = .012) and NCC t_3 (U = -2.9, p = .003). While Wilcoxon matched-pairs signed-ranks tests revealed significant increases between the measurement time points for parental sensitivity (U = -5.2, p = .000), externalizing problems (U = -2.8, p = .005), and total behavior problems (U = -2.8, p = .006), significant decreases were found for nail cortisol (U = -3.5, p = .001) and methylation at CpG1 (U = -2.6, p = .010). Within measurement time points, methylation in most of the CPGs was positively correlated (exceptions: CpG1 t_2 + CpG4 t_2; CpG1 t_3 + CpG3 t_3). However, except for methylation at CpG3 (r_s = .204, p = .039), no significant associations were found between measurement time points, either for methylation or for NCC. Concerning the HBS scales, positive correlations were found for HBS child and NCC t_2 (r_s = .231, p = .020) and for HBS social and methylation at CpG3 t_3 (r_s = .173, p = .047).

Table 3. Descriptive statistics of study variables

	N	*M*	*SD*	Range
FKBP5 methylation (%)				
CpG1 t_2	134	94.05	5.93	46-100
CpG2 t_2	134	86.59	11.08	47-100
CpG3 t_2	133	64.25	15.46	18-100
CpG4 t_2	131	54.14	15.54	20-94
CpG1 t_3	131	92.25	4.43	79-100
CpG2 t_3	132	87.49	5.82	68-100
CpG3 t_3	132	63.42	11.19	38-100
CpG4 t_3	131	51.50	8.19	35-75
Nail cortisol (pg/mg)				
t_2	123	280.08	265.92	30-1052
t_3	126	161.80	151.81	10-575
Parental sensitivity				
t_0	126	5.60	1.75	1-10
t_1	132	6.70	2.18	0-13
Behavior problems (T- scores)				
Internalizing t_2	115	52.41	10.93	29-74
Externalizing t_2	115	50.95	8.43	28-71
Total t_2	115	53.04	9.71	30-75
Internalizing t_3	109	52.52	11.48	29-77
Externalizing t_3	109	49.83	9.32	28-71
Total t_3	109	50.88	10.85	29-77
Risk factors t_0				
HBS family	142	46.43	21.47	0-91
HBS social	142	34.09	20.62	0-90
HBS material	142	35.92	25.21	0-91
HBS child	142	20.53	20.31	0-80

Note: HBS: Heidelberg Stress Scale.

5.3.2 FKBP5 methylation and NNC

Using partial correlations (bootstrapped), NCC t_2 was found to be negatively associated with methylation at CpG2 t_2 (r = -.309, p = .001). There were no other correlations for NCC t_2. Likewise, NCC t_3 was negatively associated with methylation at CpG2 t_3 (r = -.202, p = .034) and at CpG4 t_3 (r = -.204, p = .003), but positively associated with methylation at CpG1 at t_2 (r = .229, p = .028). Moreover, a decrease in NCC was associated at a trend level with an increase in methylation at CpG2 (r = -.223, p = .056).

5.3.3 Parental sensitivity and FKBP5 methylation

Although most of the interactions consisted of mother-child dyads (98,4%), there were 4 (t_2) and 3 (t_3) father-child dyads, respectively. As results did not differ significantly when excluding fathers, they were included in the analyses.

Baseline parental sensitivity showed no significant associations with FKBP5 methylation. However, a trend was found with methylation at CpG4 t_3 (B = .912, KI 95% [-.02, 1.84], p = .057, R^2 = .08), suggesting a positive relation, which became statistically significant at t_1 (B = 1.015, KI 95% [.11, 1.86], p = .029, R^2 = .11; Figure 7a). Moreover, parental sensitivity at t_1 predicted methylation at CpG2 (B = .786, KI 95% [.27, 1.32], p = .002, R^2 = .10). This relation was moderated by group condition (B = 1.150, KI 95% [.28, 2.32], p = .010, R^2 = .14), with the IG showing a stronger positive relation (Figure 7b). The interaction was strengthened by controlling for baseline parental sensitivity (p = .007, R^2 = .15). In addition, the increase in parental sensitivity in both groups from t_0 to t_1 predicted methylation at CpG2 t_3 (B = .712, KI 95% [.14, 1.28], p = .002, R^2 = .10; Figure 7c). Becoming more sensitive as a parent resulted in higher methylation at CpG2 in the child at 36 months. However, change in sensitivity was unable to predict change in methylation at either CpG site.

5.3.4 Parental sensitivity and NCC

Even though parental sensitivity and NCC were not related significantly, we found three trends: Parental sensitivity at t_0 and t_1 were both negatively associated with NCC t_2 (B = -26.101, KI 95% [-55.44, .04], p = .085, R^2 = .08; B = -17.940, KI 95% [-42.95, 1.86], p = .092, R^2 = .07). Additionally, a change in parental sensitivity showed a negative association with NCC t_3 (B = -12.231, KI 95% [-24.61, -.02], p = .063, R^2 = .11). Therefore, at a trend level, more parental sensitivity was associated with less NCC at t_2, and an increase in parental sensitivity was related to less NCC at t_3. However, change in parental sensitivity was not associated with change in NCC.

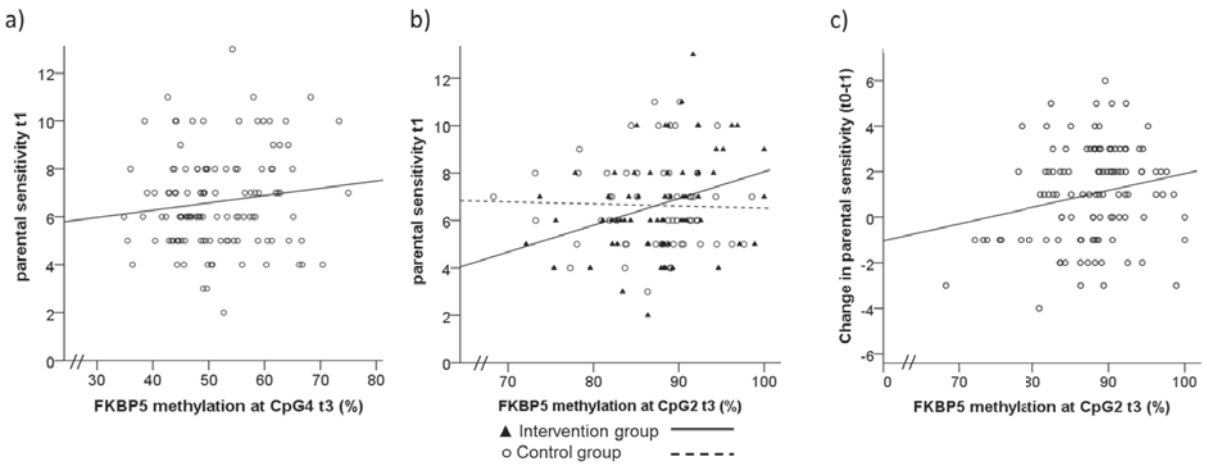

Figure 7. Relations between parental sensitivity and FKBP5 methylation

a) At CpG4 t_3. **b)** The positive association at CpG2 t_3 was moderated by group condition. Children in the intervention group are represented by circles and children in the control group by black triangles. **c)** Relation between change in parental sensitivity and FKBP5 methylation at CpG2 t_3.

5.3.5 FKBP5 methylation and child behavior problems

No associations were found for NCCs or for methylation within measurement time point t_2. Internalizing problems at t_2 were predictive at a trend level for methylation at CpG3 t_3 (B = .171, KI 95% [-.10, .35], p = .089, R^2 = .07). Within t_3, internalizing problems were positively related to methylation at CpG2 (r = .227, p = .029), CpG3 (r = .210, p = .043; Figures 8a, 8b) and at a trend level at CpG1 (r = .174, p = .097). Moreover, methylation at CpG1 t_2 significantly predicted internalizing problems at t_3 (B = .415, KI 95% [.03, .80], p = .046, R^2 = .13; Figure 8c). No associations were found for change scores.

Externalizing problems at t_2 predicted methylation at CpG2 t_3 (B = .142, KI 95% [-.00, .28], p = .037, R^2 = .09; Figure 8d) and were negatively associated at a trend level with methylation at CpG4 (r = -.718, p = .090) at t_3. Regarding the change scores, one trend was found between change in externalizing problems and methylation at CpG4 (B = -.165, KI 95% [-.32, .01], p = .068, R^2 = .10), indicating that an increase in externalizing behavior problems was related to a decrease in methylation at CpG4.

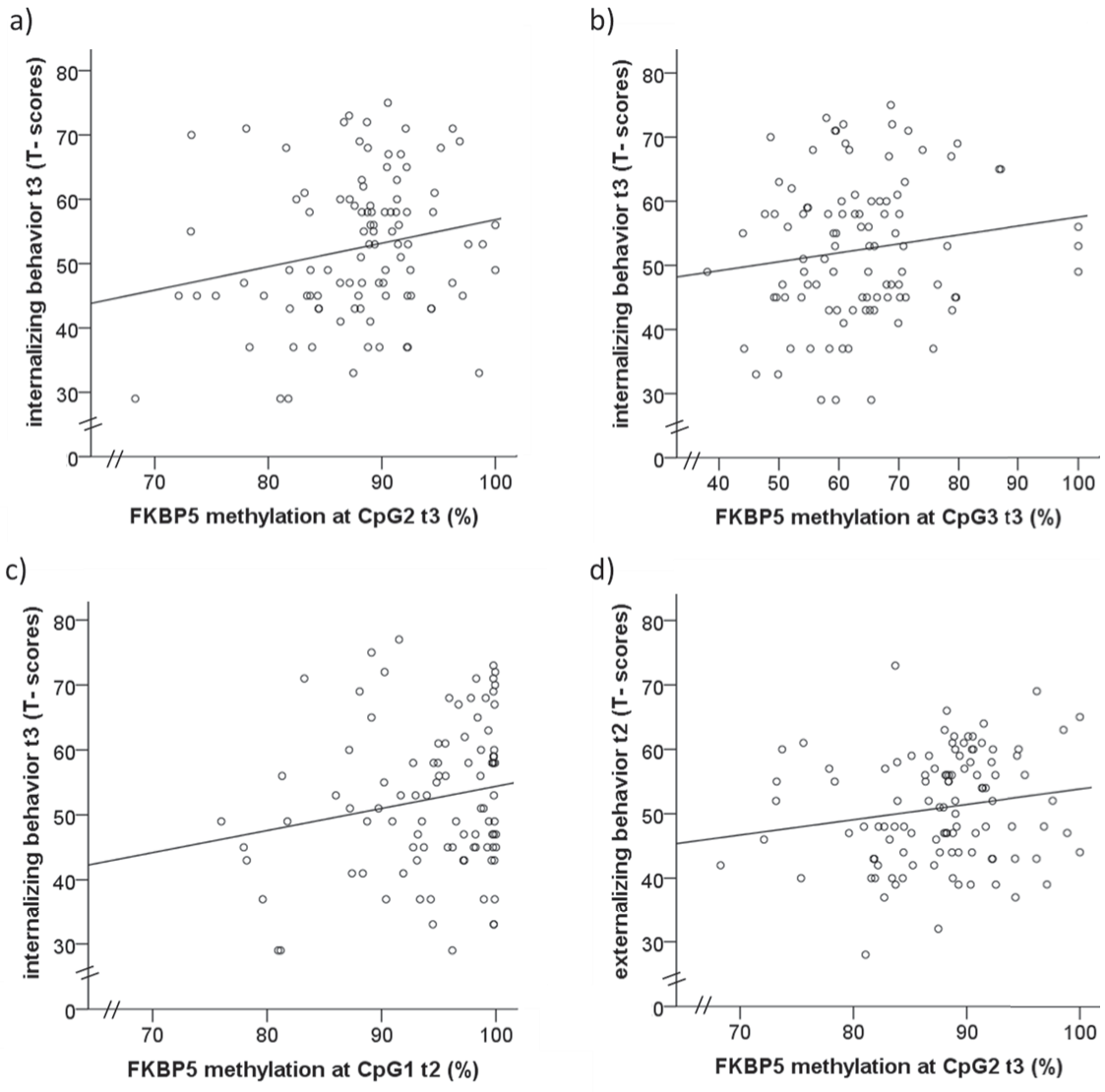

Figure 8. Relations between child behavior and FKBP5 methylation

Child behavior presented in T-scores. Positive associations within measurement time point t_3 between internalizing child behavior and methylation **a)** at CpG2 **b)** and CpG3. **c)** Associations between methylation at CpG1 t_2 and internalizing child behavior at t_3, and **d)** externalizing child behavior and methylation at CpG2 t_3.

5.3.6 Effects of PAT on FKBP5 methylation and NCC

Group differences were tested using bootstrapped multiple linear regressions. While no effects were found for NCC, significant group differences were found for methylation at CpG4 t_2 (B = -6.368, KI 95% [-11.56, -1.09], p = .025, R^2 = .06) and at CpG1 t_3 (B = -2.211, KI 95% [-3.65, -.76], p = .010, R^2 = .08). At both CPGs, methylation was higher in the CG than in the IG (Figure 9a). Next, change scores were examined and revealed significant associations with methylation at the same CPGs (Figure 9b). Compared to the IG, the CG showed a

significant decrease (5.7%) in methylation at CpG4 (B = 7.579, KI 95% [.66, 14.99], p = .040, R^2 = .10). At CpG1, the opposite effect was found (B = -3.136, KI 95% [-5.93, -.44], p = .046, R^2 = .08). Whereas methylation in the CG remained constant, the IG showed a significant decrease (3.0%).

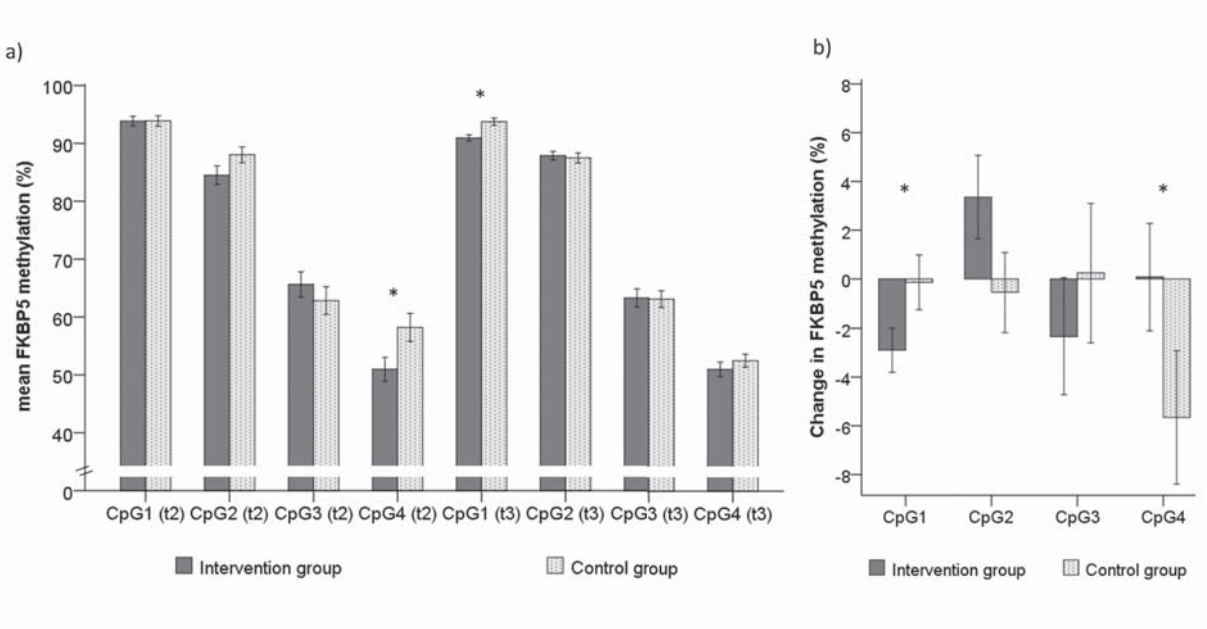

Figure 9. Group differences in FKBP5 methylation

a) Group differences in FKBP5 methylation at intron 7, CpGs 1, 2, 3, 4 at t_2 and t_3. b) Change in FKBP5 methylation from t_2 to t_3. Methylation and change in methylation (mean ± 1 standard error) are represented by dark grey bars for the intervention group (IG) and by light-grey dotted bars for the control group (CG). * p < .05.

5.4 Discussion

This is the first study to investigate FKBP5 methylation in association with NCC, parental sensitivity, and child behavior in healthy children living in psychosocially at-risk families. Moreover, we examined the effects of the early intervention program PAT on FKBP5 methylation. NCC was negatively related to methylation within but not across measurement time points. No significant associations between NCC and parental sensitivity, child behavior or PAT were found. In contrast, changes in parental sensitivity and 12-month postnatal parental sensitivity were positively related to methylation at 36 months. The latter relation was moderated by group condition, with a stronger association in the IG than in the CG. Regarding child behavior, our findings suggest that higher FKBP5 methylation is related to more internalizing problem behavior and, to a lesser extent, to more externalizing problem behavior. Further-

more, FKBP5 methylation was found to be higher in the CG compared to the IG at specific CPGs. Finally, the CG showed a significant decrease in methylation at CpG4 compared to the IG, whereas the IG showed a significant decrease in methylation at CpG1 compared to the CG.

As expected, NCC was negatively related to FKBP5 methylation. This was true only within but not across measurement time points. Moreover, none of the biological parameters, except for CpG3, were related between the measurement time points, which may indicate frequent change in HPA axis activity. As Karsten and Baram (2013) pointed out, neuronal gene expression may be persistently "re-programmed" via epigenetic modifications, especially during early postnatal development. Generally, many more significant associations regarding FKBP5 methylation were found at t_3 than at t_2. Therefore, besides frequent changes in HPA axis activity, different phases of development seem to be accompanied by different gene × environment interactions, indicating different sensitive developmental periods of biological embedding. Presumably, changes in HPA axis activity may be particularly frequent during the first two years of life, allowing for a highly flexible adaptation to the environment. More research examining changes in FKBP5 methylation within shorter timeframes over several phases of development into adulthood is needed to uncover sensitive time windows and underlying influential factors.

Generally, associations differed with regard to individual CpGs. This is in line with previous research and may be due to different effects of HPA axis activity on individual CpGs (Kertes et al., 2016; Yehuda et al., 2015). CpG2, which lies within the first GRE, seems to be especially prone to environmental influences. It was positively associated with parental sensitivity, change in parental sensitivity and both internalizing and externalizing behavior problems. In contrast, CpG3, which is more distal to GREs, was only significantly associated with one psychosocial variable (internalizing problems). Additionally, it was the only site, which was correlated between the two measurement time points, indicating a certain stability.

Regarding NCC, except for negative correlations with methylation and trends regarding parental sensitivity, no associations were found. This is in line with recent findings regarding hair cortisol concentrations (HCC). HCC was found to be associated with poor parenting skills, but was not associated with internalizing or externalizing behavior problems (Ouellette et al., 2015). However, research regarding NCC is scarce. Although moderate associations with HCC and saliva cortisol (area under the curve) levels collected four months previously were found (Izawa et al., 2015), to date, there is only one psychoneuroendocrine study indicating non-significant higher NCCs during a stressful period (Warnock et al., 2010).

Parental sensitivity was positively associated with FKBP5 methylation, which is in accordance with previous results regarding the 11β-HSD2 and the NR3C1 genes (Conradt et al., 2016). Additionally, group condition moderated this association insofar as only children in the intervention program PAT showed the aforementioned positive relation. This finding suggests that PAT was able to increase the relevance of maternal sensitivity and its influence with regard to biological embedding. Underlying mechanisms such as the interplay between risk and protective factors have to be further investigated. Finally, a greater increase in parental sensitivity from birth to the age of one year predicted higher methylation at three years. Our results underline the relevance of parental sensitivity in the first year of life and its role as a protective factor, causing possibly enduring alterations in FKBP5 methylation.

With regard to child behavior, we found positive relations mostly with internalizing but not with externalizing behavior problems. These results are consistent with two recent studies investigating NR3C1 methylation and child behavior (Dadds et al., 2015; Parade et al., 2016). Notably, findings regarding externalizing problems and HPA axis functioning have been inconsistent, with small effect sizes (Alink et al., 2008). However, it has been suggested that internalizing problems are caused by HPA axis hyper-activation, whereas externalizing problems are due to hypo-activation (Hartman et al., 2013). This assumption is supported by the fact that elevated morning cortisol was found to be associated with internalizing problems, whereas low basal cortisol was related to externalizing problems (Laurent et al., 2016). Moreover, some researchers assume that externalizing problems are more likely to be linked to HPA axis reactivity under stress conditions than to HPA axis basal activity (van Goozen et al., 2007), which could explain our non-significant results. In line with this assumption, Fries et al. (2015) found no correlations between FKBP5 methylation and basal mRNA and protein expression. They argued that FKBP5 methylation may only be relevant for GR-mediated but not for basal FKBP5 expression. Interactions between child behavior and HPA axis activity seem to be extremely complex, and more research clarifying interactions between child behavior, basal and reactive FKBP5 methylation, mRNA, protein expression, and cortisol is needed.

Relations between FKBP5 methylation and both parental sensitivity and child behavior were positive, which seems to be contradictory at first glance. However, our results are in line with those of Paquette et al. (2014), who demonstrated higher methylation in relation to higher infant arousal. Previous research in adults indicates that severity of circumstances may play a relevant role insofar as short-time or less severe risk exposure seems to increase FKBP methylation, whereas exposure to severe chronic stressors may lead to a constant reduction of

GR sensitivity indicated by persistently low methylation levels. For example, FKBP5 methylation was negatively associated with war trauma but positively related to chronic stress (Kertes et al., 2016). Moreover, patients with early-stage bipolar disorder (BD) showed increased methylation, whereas the number of previous manic episodes was related to decreased methylation (Fries et al., 2015). Negative relations were also reported for other chronic diseases such as Alzheimer's disease (Blair et al., 2013) and chronic kidney disease (Smyth, McKay, Maxwell, & McKnight, 2014).

This is in line with our results regarding PAT, demonstrating higher methylation in the CG than in the IG. Assuming that PAT aims to reduce risks while strengthening protective factors, the CG is expected to be exposed to more risk and fewer protective factors, causing a short-term increase in methylation. Similarly, although not directly comparable, severity of PTSD symptoms in war veterans was positively related to FKBP5 methylation three months after cognitive behavioral treatment (Yehuda et al., 2013). Finally, the IG showed a significant decrease in methylation at CpG1 compared to the CG, while at CpG4 the roles were inverted, indicating functionally different environmental influences on the HPA axis. Further investigations concerning the effects of PAT, such as changes in the environment, in characteristics of the mothers, children, and in mother-child interactions are needed to identify factors responsible for methylation changes. Moreover, responders and non-responders should be identified and investigated separately, as they were found to show different HPA axis activity. In two intervention studies, treatment responders showed a decrease in FKBP5 methylation while non-responders showed an increase (Roberts et al., 2015; Yehuda et al., 2013). However, in this study, change in child behavior was not associated with change in FKBP5 methylation, although a negative trend was found for change in externalizing problem behavior. An increase in externalizing behavior problems was accompanied by a decrease in methylation.

Several limitations of the current study have to be considered. First, we did not analyze other HPA axis-related and possible interactive parameters such as genotype, gene expression, and methylation patterns in other stress-related genes (e.g. NR3C1). The rs1360780 genotype was found to have a moderating effect between childhood adversities and FKBP5 methylation (Klengel et al., 2013). Inverted relations have been shown depending on genotype. While child abuse was negatively related to methylation in risk allele carriers, it was positively associated in protective genotype carriers (Yehuda et al., 2015). Furthermore, change in methylation was associated with CBT treatment response only in those children carrying the risk allele (Roberts et al., 2015). As Klengel et al. (2014) stated, genotype may not only differ between vulnerable and resilient individuals but also between those who are

more or less reactive to the environment, for better or for worse. Change in FKBP5 methylation could therefore represent vulnerability and flexible adaptation to environmental requirements at the same time.

Second, we used targeted bisulfite NGS, which has not previously been done regarding FKBP5 methylation. Most of the studies used pyrosequencing, as described by Klengel et al. (2013). In general, methodological aspects have to be considered when interpreting results. Different studies used different methods, investigating different CpGs in different tissues. While we, and many other researchers, focused on the same CpGs in intron 7 as did Klengel et al. (2013), others used a 450K methylation array, which does not include intron 7 (e.g. Kertes et al., 2016; Weder et al., 2014), or looked at exon 1 (e.g. Yehuda et al., 2013). Moreover, we collected saliva DNA, which was found to more closely reflect methylation patterns in the brain than DNA from leukocytes (Smith et al., 2015). However, even though broad common impacts are possible across tissues, significant associations may be tissue-specific (Kertes et al., 2016).

Fourth, child behavior was rated only by the parents and may be biased. As it is known that problem perception of parents, children, and therapists differ significantly, a multi-informant approach would be desirable (De Los Reyes & Kazdin, 2005).

Finally, we examined healthy children living in psychosocially at-risk families. Although the study sample showed high external validity, the generalizability of our results is restricted to psychosocially at-risk families living and receiving support in Switzerland.

More research is needed to clarify the relations between genotype, methylation, gene expression, GR sensitivity, and cortisol. Prospective longitudinal studies may help to clarify stability and changes in methylation and identify critical time periods during child development. It would be desirable to investigate prospective changes in risk factors such as critical life events or maternal depression, which may influence methylation levels, and interactions between risk and protective factors, which may prevent deleterious biological embedding.

HPA axis activity seems to be extremely flexible in early child development, adapting to environmental influences. Therefore, it is important to understand the underlying mechanisms of biological embedding during this sensitive time period. Childhood adversities have been related to long-term decreased methylation of FKBP5 in intron 7. This is the first study to emphasize the importance of parental sensitivity in the process of biological embedding. It represents the first protective factor investigated in relation to FKBP5 methylation, possibly buffering the negative effects of risk factors. Moreover, associations with child behavior problems

indicate that possible negative embedding may already manifest at the age of three. However, early intervention programs may help to reduce negative long-term consequences. HPA axis activity represents a very complex system including several influencing factors, which themselves show various interactions. More research is therefore needed to clarify the underlying mechanisms.

PART III: GENERAL DISCUSSION

6 Summary of Findings

Findings of the first study indicate that adaptive child development cannot be represented by a single latent factor integrating social, cognitive, and personal child characteristics. Nevertheless, our results suggest that it is possible to combine both problematic and positive child characteristics simultaneously when examining specific aspects of adaptive child development. First, a latent factor was found, involving the child characteristics prosociality, aggression, inhibitory control, and attentional focusing. Meanwhile, self-efficacy and anxiety did not load on the latent factor. However, they were associated with the other four factors and could be integrated into the model. Second, except for socioeconomic status, all contextual risk factors showed the expected associations. Parental conflicts, strict parental control, and victimization were positively predicted the built latent factor representing an indicator of adaptive child development, whereas harmonious parental relationship and classroom climate represented negative predictors. Moreover, post-hoc analyses revealed gender differences, indicating that associations between self-regulatory competences and anxiety differ between boys and girls. More specifically, boys showed positive relations between anxiety and aggression and between inhibitory control and attentional focusing, whereas in girls these associations were not significant. Instead, girls showed a significantly stronger association between anxiety and attentional focusing.

The second study provides evidence for the importance of FKBP5 methylation regarding child development. This was the first study investigating the relation between FKBP5 methylation and internalizing and externalizing behavior problems. Externalizing behavior problems at the age of two positively predicted FKBP5 methylation at the age of three. In contrast, FKBP5 methylation at two predicted internalizing behavior problems at three. Furthermore, FKBP5 methylation and internalizing behavior problems were positively associated at age three. No relations were found regarding changes in these variables. Subsequently, we demonstrated for the first time that parental sensitivity influences FKBP5 methylation at specific CpG sites. Parental sensitivity at the age of one year positively predicted FKBP5 methylation at the age of three years. This association was moderated by group condition with the children in the IG showing a stronger relation compared to those in the CG. Moreover, an increase in parental sensitivity in the first year of life was able to predict FKBP5 methylation at the age of three years. Furthermore, FKBP5 methylation at specific CpG sites was higher in the CG compared to the IG, indicating an influence of the early intervention program PAT.

Finally, while the CG showed a significant decrease in methylation at CpG4 compared to the IG, the IG showed a significant decrease in methylation at CpG1 compared to the CG. Notably, although FKBP5 methylation was negatively related to NCC at the ages of two and three, no significant relations with the psychosocial variables were found for NCC

In the following chapters, these findings will be discussed and integrated into the existing literature. Furthermore, strengths and limitations of the conducted empirical studies will be discussed, followed by practical implications and considerations for future studies.

7 Discussion and Integration of Findings

The concept of adaptive child development is not clearly defined and conceptualizations differ enormously across studies and research fields. The present research proposes that instead of being defined as either the absence of problematic or the presence of positive child behavior, adaptive child development may be better represented by both of these child characteristics. However, no global factor was found for prosociality, aggression, inhibitory control, attentional focusing, self-efficacy, and anxiety, indicating that there are conceptual differences. While the four characteristics prosociality, aggression, inhibitory control, and attentional focusing highly loaded on one factor, self-efficacy showed only a small loading, and anxiety did not share any common variance with them. It should be noted that the model-fit was poor and loadings should not be interpreted (Byrne, 2009). Nevertheless, prosociality, aggression, inhibitory control, and attentional focusing showed relatively high zero-order correlations, which is in line with previous research (Eisenberg et al., 2001; Pandolfi, Magyar, & Dill, 2009). Both prosociality and aggression can be seen as components of social behavior (problems) that are absent or present in DBD, and inhibitory control and attentional focusing representing both self-regulation skills can be seen on a continuum with ADHD symptoms such as hyperactivity and inattention. Together, they all represent positive and negative externalizing characteristics, which are known to be associated with each other (Achenbach & Rescorla, 2000; Egger & Angold, 2006; Pandolfi et al., 2009; Tan, Dedrick, & Marfo, 2007). In contrast, anxiety and self-efficacy may belong to the spectrum of internalizing characteristics. They were highly correlated, which is in accordance with previous findings (Rudy, Davis, & Matthews, 2012). Notably, most of the research examining child behavior problems used the CBCL (Bayer et al., 2008; Keenan & Wakschlag, 2000; Pandolfi et al., 2009; Pihlakoski et al., 2006; Tan et al., 2007), a validated test with externalizing symptoms represented by aggressive behavior and attention problems, and internalizing symptoms represented by emotional reactivity, anxiousness/depressivity, somatic complaints, and withdrawn behavior (Achenbach & Rescorla, 2000). However, the two-factor model with externalizing and internalizing behavior could not be tested in this study, due to under-identification. More manifest variables would be needed. Next, a MIMIC model was tested with self-efficacy and anxiety predicting the latent factor, and although the regressions got significant, the model showed a poor model-fit and data cannot be interpreted. However, when relating self-efficacy and anxiety directly to the other four ‘externalizing’ variables, the model-fit was excellent. The model

suggests that ‘internalizing’ characteristics are not directly related to the common variance explained by the ‘externalizing’ characteristics, but still are related to the single factors. This finding matches the previously mentioned assumption that associations with long-term consequences for internalizing problems can mostly be explained by comorbid externalizing problems (Evensen et al., 2016; Fergusson et al., 2007).

Notably, inhibitory control and attentional focusing shared variance that could not be explained by the latent factor. This may be due to the fact that they were assessed with the same questionnaire and they both represent aspects of self-regulation, often combined into the concept of effortful control, which may have an additional cognitive component (Stevens et al., 2015). Therefore, instead of dividing adaptive child behavior into internalizing and externalizing aspects, it may also be represented by three conceptually different but overlapping aspects: social competence, cognitive abilities, and personality. More research is needed to test this assumption. However, post-hoc analyses revealed that this covariance was only significant in boys. No prior study examining gender differences regarding the association between inhibitory control and attentional focusing was found. However, research regarding ADHD showed that females have fewer impulsive and more inattentive symptoms compared to males (for a review, see Gershon, 2002). Nevertheless, in this study, girls showed higher self-regulation skills in both inhibitory control and attentional focusing.

Examining the associations between the ‘internalizing’ and the ‘externalizing’ characteristics, self-efficacy was positively related to prosociality, inhibitory control, and attentional focusing, whereas it was negatively correlated with anxiety, which is in accordance with our expectations. However, with regard to aggression, the association was not significant, and even became positive after including the contextual variables. This is in line with research in adolescence (Perry et al., 1986). The authors argue that aggressive adolescents often see aggression as a normal response that results in positive outcomes. Therefore, they feel confident about their capacity to carry out aggressive behavior, and consequently, may show higher aggression-related self-efficacy. Notably, in this study, self-efficacy was assessed as a general concept. Prior research revealed that domain-linked or specific measures of self-efficacy work better in predicting behavior (Bandura, 1989). Nevertheless, research in children suggests that high levels of aggressive behavior are related to an overestimation of several competences (for a review, see Jiang & Johnston, 2014). For example, children who overestimated their level of social acceptance were more likely to be aggressive (Diamantopoulou, Rydell, & Henricsson, 2008; Sandstrom & Herlan, 2007; White & Kistner, 2011). Moreover, aggression

was reported to be positively associated with overestimations of academic competence, athletics, and appearance in elementary school children (Hymel, Bowker, & Woody, 1993).

Similarly, no association was found between aggression and anxiety in the overall sample, but a positive relation was discovered for boys in post-hoc analyses. As before, this may be due to the different mean levels of aggression between boys and girls. Girls showed significantly lower aggression levels than boys, which is in line with prior research (e.g. Nivette, Eisner, Malti, & Ribeaud, 2014). However, while boys generally show more physical, proactive, and reactive aggression, girls are assumed to more likely engage in indirect forms of aggression such as spreading slanderous rumors and excluding others (Marshall et al., 2015). Future studies should integrate different forms of aggressive behavior when examining gender differences.

In contrast to our expectations, anxiety was positively related to prosociality, inhibitory control and attentional focusing. While most prior research indicated that anxious children are less able to ignore distractions and consequently show less effortful control (for a review, see Nigg, 2006), we found only one study showing a positive association with internalizing behavior (Murray & Kochanska, 2002). The authors discuss that inhibited or over-controlled children may be more cautious and vigilant, consequently, feeling more easily distressed by novel stimuli which increases the risk for future anxiety. A similar mechanism may be assumed for the positive association with procociality. Anxious children may want to avoid conflicts and social distress and therefore, more often engage in prosocial behavior. This hypothesis is in line with a recent study examining joint developmental trajectories of prosocialitiy and problem behavior, which found that prosociality can co-occur with both low and high anxiety (Nantel-Vivier et al., 2014).

Our findings regarding the effects of contextual risk and protective factors on child adaptive behavior were mostly in accordance with our expectations. While the suggested risk factors (parental conflicts, strict control, and victimization) showed negative associations, assumed protective factors (harmonious parental relationship and classroom climate) were positively related to the latent factor. However, SES as one of the most studied risk factors that was consistently reported to show negative effects on child development with specifically strong associations regarding externalizing disorders (Reiss, 2013), was unrelated to the latent factor. This lack of association may be explained by the fact that SES was measured with the ISEI of the primary caregiver only. In most of the cases, the primary caregivers were the mothers, who often were working part-time, which is not necessarily representative for the

family SES. Therefore, the SES of the father or the one of both parents may be more representative.

In conclusion, the developed model suggests that externalizing adaptive behavior can be represented by both, the absence of problematic and the presence of positive child characteristics, and that the same may be true for internalizing adaptive behavior. Nevertheless, these two aspects should be treated as conceptually different components of adaptive development, and the nature of their inter-relationship should be further investigated. Moreover, aspects of self-regulation may explain additional variance of adaptive child development, involving an additional cognitive aspect. Importantly, although there were significant gender differences regarding the child characteristics, factor loadings were not statistically different, indicating that the built indicator of adaptive child behavior works simultaneously for girls and for boys. Moreover, contextual risk and protective factors showed the expected effects on the latent factor, possibly indicating its usability as an indicator of adaptive child behavior.

As the second study was the first to analyse FKBP5 methylation and NCC in association with child behavior problems, parental sensitivity, and the early intervention program PAT, the findings are integrated into related research.

First of all, it should be noted that neither NCC nor FKBP5 methylation (except for CpG3) were related across time points, indicating that neuronal gene expression is persistently 're-programmed' via epigenetic modifications during the first years of life (Karsten & Baram, 2013), which results in the marked changes in the HPA axis (Alink et al., 2006; Gunnar & Quevedo, 2007).

In contrast to our expectations, no significant associations were found between NCC and any of the psychosocial variables. This puts the usability of NCC as a chronic biological stress parameter into question. However, HCC was also found to be unrelated to externalizing and internalizing behavior (Ouellette et al., 2015). It has to be noted that the retrospective time frame is assumed to lie between four and five months (Izawa et al., 2015). However, in this study, it was assessed at the same time as child behavior symptoms and much later than parental sensitivity, which may be a reason for the missing associations. Nevertheless, NCC was negatively associated with FKBP5 methylation, which is in line with prior studies (e.g. Yehuda et al., 2015).

Looking at previous research the absence of a relation between NCC and behavior problems is somehow not surprising. Previous research reported inconsistent findings regarding the association between cortisol and externalizing and internalizing behavior problems.

Some studies found positive associations (Hart et al., 2005; van Bokhoven et al., 2005), whereas others found negative (Alink et al., 2006), or no (Hartman et al., 2013) associations. Hypocorticolism, which is related to prolonged stress, is seen as a possible explanation for these inconsistencies. While acute stress is associated with increased cortisol levels, severe and chronic stress results in decreased cortisol levels and a blunted cortisol response in response to stress (Cicchetti & Rogosch, 2001; Heim, Ehlert, & Hellhammer, 2000; Hellhammer & Wade, 1993). A further explanation for the reported inconsistencies is given by the adaptive calibration model of Del Giudice et al. (2011). The model states that highly stressful or chronic negative experiences lead to a repeated or chronic activation of the autonomic and adrenocortical systems in order to enable heightened vigilance and responsiveness to environmental changes. This strategy is referred to as fast life history, indicating an effective short-term adaptation, which probably results in negative long-term consequences. However, extremely supportive contexts may result in minimal activation of the stress response systems, causing a problem to later threat, as the system is not prepared for such circumstances (slow life history). In contrast, moderate stress levels result in stress inoculation (Lyons & Parker, 2007) supporting the development of adaptive coping strategies. Finally, it has to be noted that early childhood represents a hyporesponsive period that starts around six months postpartum and extends over the childhood years (Gunnar & Quevedo, 2007). Moreover, externalizing behavior problems show a peak between the ages of two and three (Keenan & Wakschlag, 2000). Therefore, the relation between externalizing behavior problems and HPA axis activity may change with age, leading to inconsistent results.

In contrast to NCC, positive associations between child behavior problems and FKBP5 methylation were found. FKBP5 methylation at CpG1 (t_2) predicted internalizing behavior problems one year later. Moreover, FKBP5 methylation at CpG2 and CpG3 (t_3) was associated with internalizing behavior problems (t_3). Additionally, externalizing behavior problems at the age of two years positively predicted FKBP5 methylation at CpG2 one year later. Meanwhile, no significant associations were found regarding changes in these variables. These positive associations were contrary to our expectations. As low levels of FKBP5 methylation were reported to be associated with child abuse (Klengel et al., 2013), we expected the associations to be negative. However, our results are in line with those of Paquette et al. (2014), who demonstrated a positive relation between placental FKBP5 methylation and infant arousal. Moreover, research in adults reported positive associations with chronic stress (Kertes et al., 2016) and early-stage bipolar disorder (Fries et al., 2015). In contrast, negative associations were reported for war trauma (Kertes et al., 2016), number of previous manic episodes

(Fries et al., 2015), Alzheimer's disease (Blair et al., 2013), and chronic kidney disease (Smyth et al., 2014). Similar to the findings in cortisol levels, FKBP5 methylation may show differences with regard to the chronicity and severity of stress, but in the opposite directions. While short-time risk exposure may increase FKBP5 methylation, exposure to severe chronic stressors may result in a constant reduction of GR sensitivity indicated by persistently low methylation levels.

Notably, three associations were found with internalizing behavior problems, whereas only one relation was found for externalizing behavior problems. Similarly, two recent studies examining NR3C1 methylation reported significant relations with internalizing behavior problems, but no association with externalizing behavior problems (Dadds et al., 2015; Parade et al., 2016). Notably, findings regarding cortisol and externalizing behavior problems not only have been inconsistent, but also showed small effect sizes (Alink et al., 2008). This may also be the case regarding associations with FKBP5 methylation.

Concerning parental sensitivity, no relation was found for NCC. However, there was a negative trend with parental sensitivity at the age of one. Moreover, parental sensitivity was positively related to FKBP5 methylation. This is in line with findings from a recent study, showing negative associations between maternal responsiveness and methylation in the 11β-HSD2 and the NR3C1 genes, which are known to be inversely related to FKBP5 methylation (Conradt et al., 2016). In addition, and increase in parental sensitivity in the first year of life predicted FKBP5 methylation at the age of three. Interestingly, the association with FKBP5 methylation at CpG2, which lies within a GRE was moderated by group condition, with only the IG showing a positive relation. This finding indicates that PAT was somehow able to increase the influence of maternal sensitivity on FKBP5 methylation. However, it is not clear, which aspects of the intervention caused this effect and further analyses should be conducted to understand underlying mechanisms.

Differences in group conditions were found at CpG4 (t_2) and CpG1 (t_3) with the CG showing higher FKBP5 methylation compared to the IG. Although, contrary to our expectations, these results are in line with those regarding behavior problems. Assuming that PAT aims to reduce risks while strengthening protective factors, the CG is expected to be exposed to more risk and fewer protective factors, causing a short-term increase in FKBP5 methylation. Examining the change in FKBP5 methylation from the age two to three revealed a significant decrease at CpG1 in the IG compared to the CG, which was in accordance to our hypothesis. However, at CpG4, the CG showed a significant decrease compared to the IG, maybe indicating functionally different environmental influences on specific CpG sites. Generally, associa-

tions differed across CpG sites, which is in line with previous research regarding FKBP5 methylation (Kertes et al., 2016; Yehuda et al., 2015) and NR3C1 methylation (Turecki & Meaney, 2016). Notably, most associations were found for CpG2 and CpG4 that lie within GREs, and are suggested to be especially prone to environmental influences (Klengel et al., 2013). Importantly, most associations were found for FKBP5 methylation at the age of three, indicating that this age may represent a sensitive developmental period, in which biological embedding takes place.

8 Strengths and Limitations

The main strength of the two empirical studies presented in this thesis is the fact that they both rely on prospectively assessed data. This reduces the risk of possible recall biases reported in retrospective studies (Blome & Augustin, 2015). Moreover, the results of the first study (COCON) are based on a large sample size (N = 838), which is needed for structural equation modelling using several variables. Moreover, the examined subsample was taken out of a large data pool, representative for the German- and the French-speaking part of Switzerland. In addition, the use of structural equation modelling enabled the simultaneous integration of several risk and protective factors. Many studies used cumulative risk factors, adding up single variables to reduce complexity (for a review, see Browne, Plamondon, Prime, Puente-Duran, & Wade, 2015). This approach has proven useful in that it explains more variance compared to the examination of single variables (Fergusson & Horwood, 2003). However, as these factors are mostly dichotomized, variance is reduced and all risk and protective variables are equalized regarding their effect on the outcome measure. This may not be reflective of real life scenariousy, as for example the death of a parent may explain a different amount of variance compared to low SES, parental mental health problems, or child abuse. As our results suggested, victimization seems to have a stronger impact on child behavior than, for example, parental strict control. Therefore, structural equation modelling enabled us to examine the effects of several separate factors on adaptive child behavior at the same time, while simultaneously controlling for all other variables. Moreover, instead of focusing either on problem behavior or competences, both aspects were integrated into the same model. Another strength of the first study is its multi-informant approach. All child characteristics were rated by the primary caregivers and the teachers. As informants' reports commonly disagree (De Los Reyes & Kazdin, 2005), combined ratings may better represent actual child characteristics.

Despite its many strengths, several limitations have to be considered regarding the first study. First, although using a multi-informant approach, combining primary caregiver and teacher ratings, no child-ratings were used. Second, the combination of the ratings does not take into account that informant discrepancies may provide meaningful information (De Los Reyes et al., 2015). Third, surveys of mental health problems in children may be susceptible to nonresponse bias, as parents and maybe even teachers could be reluctant to report child behavior problems. As there were many missing teacher ratings, bias cannot be excluded.

Fourth, despite many significant associations, effect sizes were small, which may be due to the big sample size that increases the likelihood for the p value to become significant (Sullivan & Feinn, 2012). Fifth, generalizability of our results is limited to preschool children living in Switzerland. Sixth, the number and choice of the problematic and positive child characterisitcs is selective. Although, the selected characteristics are assumed to represent the most central aspects (social, cognitive, personal) of development, many other characteristics such as hyperactivity, depression, and self-worth have not been investigated. Moreover, each child characteristic was assessed with only three to five items that may not be able to fully represent the assumed characteristic. This may explain the small internal consistencies found in primary caregivers (Cronbach's α ranged from .51 to .69). However, similar values for caregiver ratings were reported by Guion, Mrug, and Windle (2009). Many of the child characteristics represented general concepts that did not differentiate between subcomponents, such as general self-efficacy, general anxiety, and general aggression were assessed. Despite, previous research suggesting the use of specific measures of self-efficacy, such as aggression-related self-efficacy, parenting self-efficacy, or sports-related self-efficacy (Bandura, 1989). Moreover, it was shown that specific anxiety disorders had different associations with other child behavior problems (Egger & Angold, 2006) and that boys and girls engaged in different forms of aggression (Marshall et al., 2015). Similarly, the number and choice of risk and protective factors was selective. Although, the selected risk and protective factors were known to play a central role in child development, due to their chronicity, many other possible variables, such as parental mental health problems, or maternal sensitivity (see Table 1) were not examined. Finally, we did not test for non-linear associations.

The second study used a subsample of a longitudinal randomized controlled intervention project from birth to the age of three years. This enabled a longitudinal perspective of the study variables. Moreover, this is the second study examining NCC as a promising marker of chronic biological stress in relation with psychosocial variables. Similarly, FKBP5 methylation was investigated for the first time with regard to parental sensitivity and child behavior problems in toddlers. In addition, this study has many methodological strengths. First, regarding NCC, instead of using nails of single fingers as reported in previous studies (Ben Khelil et al., 2011), the nails of all ten fingers were used. This reduces possible bias of influencing factors such as handedness, and differences in nail growth rates across the digits. Second, regarding FKBP5 methylation, we examined individual CpG sites instead of average methylation. As associations differ across CpG sites, it is assumed that effects of HPA axis activity may be

different across individual CpG sites (Kertes et al., 2016; Yehuda et al., 2015). Moreover, saliva samples were collected to assess methylation. Evidence suggests that saliva more closely reflects methylation patterns in the brain than DNA from leukocytes (Smith et al., 2015). Furthermore, Next Generation Sequencing was used, which shows high accuracy (Chen et al., n.d.). Third, parental sensitivity was assessed using video-typed interactions that reflected authentic, unbiased behavior. Additionally, the trained raters were blinded for group condition. Finally, an early intervention program was used that was reported to be suitable for children at-risk. The intervention program PAT involves home-based individual support by trained professionals. It is manualized and has previously been reported to have positive effects (Neuhauser, 2014).

Several limitations should be mentioned. First, no baseline measurement of the biological parameters was conducted. Consequently, it remains unclear whether differences regarding group conditions can exclusively be attributed to the intervention, as differences may already have been present at three months postpartum. Second, NCC and behavior problems were assessed at the same time. However, initial evidence suggests that NCCs represent a retrospective time period of about four to five months (Izawa et al., 2015). Therefore, it may be better to assess matching these time frames. Third, except for FKBP5 methylation, no other HPA axis-related parameters such as histone modification, microRNA, acetylation, genotype, gene expression, NR3C1 methylation, etc. were assessed, although epigenetic changes do not act in isolation, but interact with each other (Koch et al., 2013). Moreover, genotype has been shown to play a central role regarding FKBP5 methylation. The rs1360780 genotype was found to moderate associations between childhood adversities and FKBP5 methylation (Klengel et al., 2013). While in risk allele carriers, child abuse was negatively related to methylation, it showed a positive association in protective genotype carriers (Yehuda et al., 2015). Similarly, only risk allele carriers showed an association between change in methylation and CBT treatment response (Roberts et al., 2015). Therefore, genotype may not necessarily distinguish between vulnerable and resilient individuals, but rather indicate differences between more or less reactive individuals, may it be for better of for worse (Klengel et al., 2014). Fourth, tissue-specific effects cannot be excluded (Kertes et al., 2016) and fifth, child behavior problems were rated only by the parents and may be biased. Finally, our results can only be generalized to at-risk children.

In conclusion, this thesis provides a novel perspective on adaptive child behavior. It is suggested that adaptive child behavior may better be represented by both the absence of problem-

atic and the presence of positive child characteristics. However, externalizing and internalizing aspects should be kept separately, while allowing for inter-relationships. Moreover, it underlines the importance of the early life environment regarding HPA axis activity, which represents a biological system responsible for maintaining physiological stability. Moreover, our findings contribute to a deeper understanding of gene x environment mechanisms that contribute to adaptive child development. Furthermore, it emphasizes the relevance of early intervention programs in children at risk. However, many questions remain and future studies should further advance research in the area of early childhood, which seems to represent a time period that remains important throughout the whole life.

9 Outlook, Implications, and Conclusions

The first study provided evidence that adaptive child behavior can be represented by both the absence of problematic and the presence of positive child characteristics. These combined effects may more adequately represent adaptive or maladaptive child behavior and therefore, may result in a better understanding of the underlying dynamics. In turn, a better understanding of the various interaction effects may enable more specific prevention and intervention, simultaneously reducing problematic behavior and risk factors, while promoting positive characteristics and protective factors. Future research should not only differentiate between externalizing and internalizing aspects, but also investigate their inter-relationships. Moreover, the role of self-regulatory skills as a conceptually different aspect of adaptive child behavior should be further investigated. Furthermore, the latent factor models should be evaluated, comparing them with other health-related outcome measures such as the recently developed Diagnostic Adaptive Behavior Scale (Tassé et al., 2016). Additionally, group comparisons should be conducted, to identify group specific variations in the factor loadings and regression weights. As found in our study, factor loadings do not seem to differ between boys and girls, indicating a similar underlying mechanism in both genders. However, differences could be found comparing other groups such as specific disorders (e.g. major depressive disorder versus bipolar disorder), abused and non-abused children, or even risk-allele carriers and protective-allele carriers. Therefore, such models may be useful in integrative research. Moreover, latent indicators of adaptive child behavior should be longitudinally examined, investigating latent change and trajectories, and how they are influenced by contextual factors. Finally, such latent factor models could be flexibly adapted to specific needs, for example, by integrating different forms of aggression into the externalizing aspect when comparing gender differences.

The second study underlines the importance of early intervention programs in at-risk children. It indicates that intervention in the first years of life can change HPA axis activity and therefore may be able to influence biological embedding, possibly buffering long-term effects of early adversities. Specifically, intervention programs should aim helping the parents to increase their parental sensitivity in the first year of life. However, more prospective studies are needed to see if our findings can be replicated. Future studies should investigate the influence of contextual variables as well as changes in these variables on FKBP5 methylation, to identi-

fy possible risk and protective factors. Longitudinal studies may further clarify stability and changes in methylation and cortisol levels from birth to adulthood, which may provide central information about sensitive developmental periods. Ideally, this would be complemented by parameters representing the functioning of the immune and autonomic systems, which would allow for a deeper understanding of the process of biological embedding. Moreover, cortisol and FKBP5 methylation should be simultaneously measured in different tissues, thereby taking into account the retrospective time frame. Future studies should investigate the associations between FKBP5 methylation and child behavior problems more closely, examining the subscales and using multiple informants. Importantly, genotype and other HPA axis-related parameters should be assessed and controlled for. The interaction effect of genotype and DNA methylation may offer some explanation for the inconsistent findings regarding FKBP5 methylation and cortisol in behavior problems or disorders. Furthermore, responders and non-responders should be identified, to shed light on the complex relation between genotype, methylation, treatment response, and behavior problems. With the three-hit concept of vulnerability and resilience, a theoretical framework for this complex relations has been offered (Daskalakis, Bagot, Parker, Vinkers, & Kloet, 2013). The model suggests that genetic predispositions (HIT-1) interact with epigenetic modifications that are altered by early-life environmental factors (HIT-2). Together, they program gene expression patterns during brain development, which are relevant for an evolving phenotype. The fit between this certain programmed phenotype and later-life environments (HIT-3), to which the phenotype is exposed to, may increase or decrease the probability of developing psychiatric symptoms or stay healthy. However, this model still remains to be tested.

10 References

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