Family Interactions and Cortisol Expression in Children with Attention-Deficit/Hyperactivity Disorder

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is highly prevalent in children and adolescents worldwide. Typical symptoms include inattention, impulsivity and hyperactivity. Comorbidity with other disorders, such as Oppositional-Defiant Disorder (ODD) or Conduct Disorder (CD) are very common. Due to child symptoms, families of children with ADHD are prone to impaired family functioning. This includes strained parent-child relationships, higher conflict, more negative emotional experiences and less positive family interactions (Johnston & Mash, 2001; Whalen et al., 2011). Based on the conjecture of physiological under-arousal in children with ADHD (Barkley, 1997), the physiology of individuals with ADHD became a biopsychological research interest. The most frequently investigated biomarker is cortisol, an end product of the Hypothalamus-Pituitary-Adrenal (HPA)-axis, and a principal actor in the bodily stress response. Results regarding diurnal HPA-axis functioning in children with ADHD are largely inconsistent. While some found an effect of ADHD on diurnal cortisol, an equally large body of research did not replicate the claimed difference to non-affected individuals. Again others suggest that differences in HPA-axis functioning are solely related to disruptive comorbid symptoms. HPA-axis functioning is health-relevant and calibrated throughout childhood and adolescence (Boyce & Ellis, 2005; Del Giudice et al., 2011). The axis reacts to everyday experiences (Belsky & Pluess, 2009) and the present thesis aims to inquire, how child symptoms as well as family interactions are connected to cortisol expression.

This thesis contributes to understanding two - potentially interacting - determinants of child development and later physical and mental health: The parent-child relationship and the physiological stress regulation in children with ADHD. This was realized through three empirical contributions, based on an intensive saliva and diary sampling design with *N*= 145 children (*n*= 65 with ADHD) between 7 and 16 years of age and their parents. Five diurnal saliva samples were collected over seven days. Using a smartphone application, children and one of their parents answered momentary

assessment questions three times a day. This allowed capturing family interactions, displayed behavior and positive and negative affect as well as child symptoms.

Study 1 set out to determine whether children with symptoms of ADHD or rather, disruptive behavior such as ODD/CD showed a distinct output of diurnal salivary cortisol compared to non-affected peers. Therefore, the cortisol awakening response (CAR) as well as total output across the day via area under the curve (AUC) were derived for children with ADHD, children with symptoms of ODD/CD and a comparison group. Neither ADHD nor ODD/CD symptoms were associated with diurnal cortisol expression. Cortisol was significantly related to child age and stage of puberty, corroborating the importance of developmental-specific covariates in salivary bioscience with children and adolescents.

Study 2 focused on everyday interactions between children and their parents to examine the relationship between child symptoms, positive and negative parent behavior and positive and negative affect of children and parents. Child symptoms significantly predicted more negative as well as less positive parent behavior towards the child in all models. Negative parent behavior also predicted higher parent negative affect, emphasizing the impact of children's behavioral symptoms on healthy family relationships.

Study 3 was designed to test whether everyday experiences in the parent-child relationship would be associated with HPA-axis responses. This assessment of natural interactions in everyday family environments as well as child symptoms and diurnal cortisol found some of children's ADHD and comorbidity symptoms to predict cortisol.

In summary, the results suggest that children and adolescents with ADHD or comorbid disruptive symptoms do not differ from comparison children in regards to diurnal cortisol. However, the investigation of cortisol sampled concurrently to the assessment of psychosocial events, showed that children's symptoms were related to their HPA-axis output. Child symptoms' impact on family dynamics became especially apparent in the association with more negative and less positive parent behavior towards the child.

Family interactions and parent behavior are an important target for prevention, intervention and therapy. Enabling positive and affectionate family relationships is crucial to healthy child development, particularly in the presence of ADHD and comorbid impairments. As parents of children with ADHD and comorbidities face more challenges, families should be provided with the necessary skills to evade vicious cycles where children and parents reinforce one another's dysfunctional behavior. Interactions of everyday family life are key to our understanding of HPA-axis adaptation to the environment and stress-health links in children and later adults.

1 Introduction

"*In physics, laws are derived that apply to every unit in a group, based on the simple assumption that all of the units are identical. All electrons are the same.*

In developmental psychopathology, laws are derived that apply to no one individual unit in the group.
People are all different."

(Sameroff & Mackenzie, 2003, p. 613)

Children become different people because, throughout their development, they make different life experiences. The family environment and the quality of shared experiences between children and their parents lay the foundation for a healthy child development (Essex et al., 2002; Evans & Kim, 2007; Lucas et al., 2018). Family environments have the power to positively influence determinants of future resilience. Depending on the quality of the relationships, they can however pose a risk for adverse experiences and later vulnerability (Repetti et al., 2002). Parents and primary caregivers contribute to the calibration of the Hypothalamus-Pituitary-Adrenal (HPA)-axis, a major regulator of the physiological stress response, of a developing child. Therefore the family has an effect on lifelong characteristics of children's stress physiology (Bauer et al., 2002; Gunnar & Donzella, 2002; Miller et al., 2011; Slopen et al., 2014; Repetti et al., 2002). The bodily stress system thus, too, has a high variability from person to person (Kudielka & Rohleder, 2011).

The quote also applies to the special population studied in this thesis: Children with behavioral difficulties, specifically Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD). The diagnosis of ADHD subsumes different forms of behavior and symptoms which vary from one child to another (Thapar & Cooper, 2016).

The purpose of this doctoral thesis is to contribute to the understanding of underlying stress mechanisms occurring in children with ADHD. Specifically, whether children with ADHD show different stress response patterns than comparison children. A further aim is to clarify the potential role of comorbid symptoms of oppositional and conduct behavior problems. The cortisol expression of

children with ADHD, requires a more comprehensive investigation, since prior research efforts have produced inconsistent findings (Study I). Further knowledge about symptom-related differences in stress response patterns is particularly relevant because it offers a potential link to understanding the differential stress physiology children may show in response to experiences in their environment.

High levels of impulsive and hyperactive, and especially aggressive and antisocial behaviors may be particularly challenging in interpersonal contexts and lead to more distressed interactions in the family. The second goal of this study is therefore to examine, whether potential interactions in the family (with e.g. negative parental behavior, child symptoms) explain variance in children's and parent's momentary affect (Study II).

Finally, psychoneuroendocrine measures as introduced in Study I will be considered in combination with family interactions as investigated in Study II. Investigating daily family interactions at the same time as cortisol samples allows testing how family interactions are associated with children's cortisol levels (Study III). The approach is characterized by combining momentary assessment of children's and parents' daily lives (three times/day) with children's salivary cortisol (five times/day), the major end product of the HPA-axis.

The present thesis will first describe the characteristics and diagnostic features of externalizing behavioral difficulties (ADHD, ODD and CD), introduce the functioning of the human physiological stress response system and illustrate the processes of family interactions. An overview of the current state of research is presented in terms of how the topics of this thesis are interrelated, followed by a summary of the conducted research project and its methodology. The research questions and the project's methods will be briefly summarized prior to the full articles, followed by a general discussion and conclusions for future research.

2 Child Psychopathology

The present thesis investigates family interactions and HPA-axis functioning in children with psychopathology. The focus is hereby set on the externalizing behavior spectrum, specifically ADHD as well as ODD and CD.

ADHD is among the most common childhood disorders, affecting up to 9.4% of children (Danielson, 2018). Individuals with ADHD frequently show one (≥ 50%) or more (≥ 25%) comorbid psychiatric disorders (Efron et al., 2016; Jensen & Steinhausen, 2015; Larson et al., 2011). Comorbidity between ADHD and ODD or CD is substantial. For ODD and ADHD, 50% children meet diagnostic criteria of both clinical pictures (Bendiksen et al., 2017; Nock et al., 2007; Harvey, 2016; Waschbusch, 2002). For CD and ADHD, 30-50% of children qualify for both diagnoses (APA, 2013; Bendiksen et al., 2017; Biederman et al., 1991; Larson et al., 2011). It is still not well understood, why such high overlap exists (Harvey et al., 2016). While the DSM-5 refers to possibly shared temperamental risk factors (APA, 2013), others more specifically postulate a genetic cause or shared gene-environment interaction factors (Rutter et al., 2002).

The development precursor model (Atherton et al., 2020; Biederman et al., 1996) suggests that one disorder precedes the other: ADHD symptoms are thought to disrupt family functioning and lead to heightened parenting stress. This results in a higher frequency of negative parenting practices and higher occurrence of parent psychopathology (Johnston & Mash, 2001). ODD is theorized to develop out of this strain on family functioning and dysfunctional family interactions caused by ADHD (Beauchaine et al., 2010; Deault, 2010; Harvey et al., 2016; Johnston & Jassy, 2007). Symptoms of ODD may in turn contribute to the development of later conduct problems (Miller-Johnson et al., 2002), with ODD often preceding CD (APA, 2013).

At present, research can often not uniquely disentangle influences of the single disorders, as they appear so comorbid, and for some effects (e.g. HPA-axis functioning) the contributing role

remains unclear (e.g. Freitag et al., 2009; Fairchild et al., 2018 for a review). Therefore, testing hypotheses concerning child ADHD should always take relevant comorbidities into account (Burke et al., 2008; Freitag et al., 2009).

It is a contribution of this thesis to investigate the expression of symptoms of all three disorders. The examined age range of the present research project, children and adolescents from 7 to 16 years, covers typical age spans for the presence of ADHD, ODD and CD symptoms (APA, 2013).

2.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD is a neurodevelopmental disorder, defined by an impairing degree of inattention, disorganization and/or hyperactivity-impulsivity. Inattention and disorganization hereby speak for difficulties of staying on task, (seemingly) not listening when spoken to, or loosing and forgetting material to a degree, that does not match the age or developmental stage of a child. Hyperactivity and Impulsivity imply excessive motor activity, fidgetiness, the disturbance of others and the inability to stay seated or wait. These symptoms likewise are more pronounced than can be expected of children at the respective age and developmental stage. ADHD regularly persists throughout adulthood and entails impairment in the scholarly, professional, social and familial level of functioning (APA, 2015). Children with ADHD are more likely to be rejected by peers (e.g., Hoza et al., 2005).

The DSM-5 classifies three subtypes of ADHD, with either inattentiveness (ADHD-IN) or hyperactivity and/or impulsivity (ADHD-HI) being the predominant symptomatic features, and a combined type, where symptoms from both subtypes are equally present. Diagnostic criteria of ADHD-IN comprise difficulties holding attention without distraction, organizing tasks, and being forgetful. In contrast, ADHD-HI is diagnosed based on excessive motor activity, difficulty waiting one's turn or interrupting others.

Reduced school performance is quite typical for children with ADHD (Frazier et al., 2007), although most children with ADHD present a normal-range or above-average IQ (APA, 2013). Especially relevant for the present thesis is the elevated risk for interpersonal conflict and family relationships

characterized by discord and negative interactions (APA, 2013). Child ADHD often results in impaired family functioning (Breaux et al., 2019; DuPaul et al., 2001; Harpin, 2005). Especially getting ready in the morning and weekends pose a challenge for children with ADHD, and consequently, their families (Whalen et al., 2006a; Lovell et al., 2013).

Prevalence

The prevalence among children and adolescents has been indicated from 3 to nearly 10% (Danielson, 2018; Polanczyk et al., 2015; Sayal et al., 2018). A comprehensive meta-analysis concluded the worldwide, pooled prevalence to be at 5.3% (Polanczyk et al., 2007). It has to be noted, that the basis for this systematic review and meta-regression were DSM-III or DSM-IV and ICD-9 or ICD-10 criteria and diagnostic criteria of the current DSM-5 and ICD-11 do slightly vary.

Prevalence rates for ADHD should not be interpreted independent of the country and culture of the population studied. The tendency of varying prevalence rates indicates a potential bias in symptom ratings depending on cultural background (Mann et al., 1992; Miller et al., 2009) and access to resources and diagnosing practitioners. As a first example, the DSM-5 (APA, 2013) points out that in the United states, the ADHD prevalence seems to be lower in African American as well as Latino populations compared to Caucasians (Froehlich et al., 2007; Kessler et al., 2006; Miller et al., 2009).

As a second example, in Switzerland, the prevalence of diagnoses appears to be different across the different language (and cultural) regions. The percent of children diagnosed in the Italian-speaking part of Switzerland is less than in the German-speaking region (Ellner, 2013), which is explained due to manifold cultural and structural differences across the regions (Thuerkauf, 2016).

ADHD is typically recognized and diagnosed when children enter the first grade of school. However, the peak of diagnosis has been predicted to shift to preschool-age (Dupaul et al., 2001). DSM-5 criteria foresee that the full set of symptoms has to be present before age 12 for diagnosis (APA, 2013).

In children, boys are twice as likely to be affected as girls are. Seemingly, girls more often present the ADHD-IN subtype while boys more often fulfill ADHD-HI subtype criteria (APA, 2013). Longitudinal studies point out that ADHD can persist throughout adulthood and children do not grow out of it. Although hyperactivity and impulsivity often decrease with age and brain maturation, mostly the dimension of inattention will persist (Faraone et al., 2006). Consistently, the prevalence in adults is stated to be around 2.5% (Simon et al., 2009).

Etiology and Risk Factors

To date, there is no comprehensive etiological model for the emergence and maintenance of the disorder. The cause of ADHD can be described as multifactorial, mostly discussed as a mixture of genetic dispositions and environmental conditions (Campbell, 2014). Some etiological models of ADHD have placed a large emphasis on heritable factors (Biederman & Faraone, 2002), and a strong genetic inheritance is indeed the case (APA, 2015). However, the elevated ADHD transmission in first-degree biological relatives (Stawicki et al., 2006) and correlation with specific genes (Gizer et al., 2009) are neither sufficient nor causal contributors (APA, 2013).

Specific early-life risk factors in association with ADHD such as small birth weight, intrauterine nicotine or alcohol exposure, infections (e.g. encephalitis) or contact with environmental toxins (e.g. lead) were found in correlational studies, but the causality of associations remains to be confirmed while controlling for confounding factors. Studies have however associated prenatal maternal stress (McIntosh et al., 1995; Huizink et al., 2007) or anxiety and depression (Barker, 2013; O'Connor et al., 2003) with later child ADHD or externalizing behavior, presumably through intrauterine cortisol exposure, especially in the last trimester (Handschin, 2015). In an attempt to explain varying prevalence rates across different countries, efforts were made to explain associations with geological features, e.g. sunlight exposure, or the lack thereof, as a risk factor for ADHD (Arns et al., 2013). Family characteristics cannot serve as a sufficient cause for ADHD; however, they can contribute to symptom expression and progression of ADHD (APA, 2013). To conclude, one factor alone unlikely elicits the

onset of ADHD on its own and the etiological influences are probably highly variant from child to child (Johnston & Mash, 2001; Thapar et al., 2013).

2.2 Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD)

Oppositional Defiant Disorder and conduct disorder are classified as disruptive, impulse-control and conduct disorders, comprising difficulties with self-regulation of emotions and behaviors. Symptoms appear to an extent that is not appropriate for the social and age-specific context and which can be differentially diagnosed from ADHD symptoms (APA, 2013).

The reason the two clinical diagnoses have been summarized as one variable, is the high overlap of characteristics and the fact, that children with ODD are at high risk to develop CD later in adolescence. Although not all children with ODD will develop CD later in life, most cases with CD have previously fulfilled ODD criteria (APA, 2013; Burke et al. 2010; Ullsperger et al., 2016). Especially a childhood-onset (before age 10), leads to the prognosis of heightened risk for later criminal behavior.

Problematic behaviors of ODD or CD are in discord with age-specific social norms or rules and violate the rights of others. Individuals with ODD/CD struggle with acknowledging authority. Symptoms of ODD are high irritability and anger, arguing and defiance, vindictiveness, as well as refusal to comply with authority figures and rules. Symptom overlap between ADHD and ODD is possible, because ADHD children might as well develop oppositional attitudes towards school related and social tasks, which is challenging for differential diagnosis. Core symptoms of ODD are a pattern of problematic interactions with others. Child ODD symptoms affect the whole family, for example by higher conflict and weaker family bonds in families with a child with ODD, compared to families with children without ODD (Greene et al., 2002). Problems go beyond the family context and can occur at school or with other children, with common peer rejection (Hamilton & Armando, 2008).

CD includes attributes of violence. Individuals diagnosed with CD display aggression against objects, persons, or animals and harm them physically or psychologically. Assaults can be verbal or physical

and can include the use of weapons. Common behaviors include trespassing, alongside destruction of property and theft. Symptoms of CD also negatively affect family functioning and relations to primary caregivers (APA, 2013). Frequent conflict with family members, teachers and romantic partners results in impairment of social life and emotional adjustment. Later in life academic and occupational performance are often affected.

Prevalence

For ODD, the DSM-5 reports prevalence rates between 1 and 11%, with a strong dependence on age and gender. The average is estimated around 3.3% (Canino et al., 2010). ODD appears 1.5 times more frequently in boys than girls (Demmer et al., 2017), though this ratio is only applicable before adolescence (Boylan et al., 2007; Nock et al., 2007). Similar to ADHD, ODD manifests around preschool-age with frequent diagnoses in middle childhood (APA, 2013).

The prevalence rate of CD is also indicated with a range of 2 to 10%, and a median at 4% (for a one-year population prevalence). Prevalence rates are typically higher in males than females and rise from childhood to adolescence; the disorder rarely finds an onset after age 16 (APA, 2013). The two main subtypes of CD are based on the age of onset: childhood (before age 10) or adolescence (no symptoms prior to age 10). Compared to ADHD, prevalences of ODD and CD are quite stable across different countries and cultures (APA, 2013).

Etiology and Risk Factors

Etiology models concerning ODD and CD are mostly based on dysfunctional family interactions, including child-rearing methods that are harsh or neglectful, inconsistent parenting practices or disturbed child supervision, due to a frequent change of caregivers. For CD specifically, child maltreatment and neglect, such as physical abuse or the exposure to early institutional living, parent criminality or delinquent peer groups were noted (APA, 2013).

For CD, a higher influence of genetic and environmental risk factors is acknowledged (Moffitt, 2005; Rhee & Waldmann 2002) than for ODD. Some reports conclude that prenatal stress, caused by

maternal stress, is related to a heightened risk for behavioral and emotional difficulties (Barker et al., 2009; Huizink et al., 2007; McIntosh et al., 1995; O'Connor et al., 2003). The genetic contribution is visible through an increase in CD diagnoses for children with biological parents with CD, or siblings with CD. However, the risk is equally increased in the case of adoptive parents with CD, which hints at the importance of environmental factors. Some biomarker patterns have been associated CD. Examples include a lower heart rate and lower skin conductance (Lorber, 2004; Ortiz & Raine, 2004). The recommended treatment for CD is family therapy (Jacob, 2006; Searight et al., 2001).

Concerning ODD, the DSM-5 (APA, 2013) does not state a possible genetic influence in etiologic models. This view is challenged by others (Harvey et al., 2016; Rutter et al., 2002).

In addition to a strong focus on dysfunctional parenting and child-rearing practices, the DSM-5 recognizes the existence of biological markers in association with ODD. These describe abnormalities in the prefrontal cortex or the amygdala, and a relation between ODD diagnosis and diminished cortisol output. The editors however note, that most studies were not able to separate children with ODD from children with CD, hence it remains unclear whether the finding of lower cortisol is specific to ODD (APA, 2015).

This is consistent with the literature review for the present thesis, where published studies form a contradictory picture, whether ODD and CD are both related to HPA-axis functioning, or if ODD or CD contribute or even drive an effect on their own. In line with the description chosen for the DSM-5, the two clinical disorders and their symptoms are thus a combined variable for this thesis.

3 Physiological Stress Response

This chapter introduces the role and functioning of the physiological stress system in humans. In the body's resting state, but particularly under stress, two systems play a major part in bodily functioning: the autonomous nervous system (ANS) and the Hypothalamic-Pituitary-Adrenal (HPA)-axis. Although both steer important components of the whole metabolism, the present thesis focuses on the HPA-

axis and the expression of one of its main endproducts: the steroid hormone cortisol. In order to explain the HPA-axis system, which is pertinent for this thesis, the concept of stress will be introduced.

3.1 The Concept of Stress

Depending on the domain of application, the term or concept of stress has many definitions. Psychologically and cognitively, stress can be understood as the result of the subjective evaluation, to not being able to meet the demands of a specific situation with own resources and capabilities. The most prominent theoretical ground explaining the evaluations upon a perceived stressor is the transactional stress model (Lazarus & Folkman, 1984; 1987). An occurring situational stimulus will be assessed for its relevance and possibility of threat in a primary evaluation. The stimulus will be classified as either positive, irrelevant or potentially threatening. A stressor is the challenge to which the body would react with an unspecific reaction (Selye, 1973). If the stressor is deemed threatening, a second evaluation will serve to estimate the capabilities to meet the demands with resources (e.g. options of action, coping skills). At this stage, a strategy may be conceptualized how to tackle a potentially threatening stimulus. Upon anticipated success, the person will again reappraise the situation. If the demands are not anticipated to be capably met, feelings of stress are the consequence. The interpretation of the stimuli is hereby central to the evaluations and appraisal. Thus, it is the subjective cognitive processes, rather than the objective threat itself that determine the resulting stress reaction (Lazarus und Folkman, 1984). Since the evaluation process is subjective, the same situational demands can elicit a stress response in one person, but not in another (Cohen et al., 1997). Stressors can be positive or negative and internal or external (Lazarus, 1984), thus including small everyday occurrences like parent-child encounters to profound life events, such as a worldwide pandemic. Stressors cause physical and mental adaptive responses, which are especially effective in the short-term. In the long-term, the adaptive responses can lead to maladaptive changes (Koss & Gunnar, 2018) depending on the different reactions to perceived stress (Koss & Gunnar, 2018; Miller et al., 2011; Oh et al., 2018). According to Lazarus and colleagues (Lazarus & Folkman, 1984; 1987;

Smith & Lazarus, 1990) the way of coping with stress is a process that every person learns based on experiences early in life, which is why the childhood years are so relevant for this topic. Already during childhood, the cognitions about resources and skills define the appraisal of a situation. Thus, stress reactions can cause cognitive changes with enduring consequences (Rice, 2012).

On a physiological level, stress can be described as a deviation from homeostasis. In constant energetic exchanges with the environment, the organism strives to keep its target values in equilibrium through processes of adaption. Therefore, through endocrine mechanisms, a change in physiological target values can mostly be rebalanced by the body most of the time. However, in the case of strong, sudden and new disturbances or threats, the routine system adaptations will not be enough to meet the momentary demands (Kaluza, 2015). An unspecific emergency reaction - the stress reaction - will be initiated (Cannon, 1929). All stimuli, which move the body away from homeostasis, qualify as stressors. The stress reaction summarizes all physiological, behavioral or cognitive-emotional processes a person will engage in upon facing a stressor (Kaluza, 2015).

The adaptive performances to reach a relative state of stability after an abnormal state are physiologically exhausting and therefore have costs for the body. These costs have been termed ‘allostatic load’ by McEwen (1998) as they refer to the bodies shift from homeostasis to allostasis (Ehlert, 2011). The HPA-axis and allostatic load are thought as an explanatory link of how individual differences in the biology of stress reactions can be explained by early childhood experiences (Berry et al., 2014; Boyce & Ellis, 2005; Del Giudice et al., 2011; Miller et al., 2011)

The hormones and their metabolites released during a stress reaction have a protective effect, as long as the stress-causing stimulus is acute and short-lived. In the long run however, the system can become dysfunctional, which is why chronic stress can be harmful (McEwen, 2000).

Heightened allostatic load occurs if the stress response becomes maladaptive, e.g. through frequent stressors or insufficient recovery after stress reactions. It can be of physiological or psychological

nature and has been associated with serious health consequences (Bøe et al., 2018; DeMorrow, 2018; Hall et al., 2012; Lasikiewicz, 2008; McEwen, 1998).

The fluid transition from acute to chronic stress is difficult to disentangle, as characteristics of acute and chronic stress often occur at the same time (Lundberg, 2011). Especially the HPA-axis has been associated with the reaction to chronic stress (Reece et al., 2011) and the maintenance of health and the onset of disease (DeMorrow, 2018; Hall et al., 2012; Lasikiewicz, 2008; McEwen, 1998). The functioning of the HPA-axis will be further explained in the following chapter, along with an introduction to cortisol, the hormone activated through the HPA-axis, which was measured in the present study.

3.2 Hypothalamus-Pituitary-Adrenal (HPA) - Axis Functioning

The HPA-axis drives and controls all systems that are involved directly or indirectly, during and after facing a stressor. It can mobilize bodily resources but also suppress physiological functions, like the immune system or the reproductive system (Joseph & Whirledge, 2017). The axis is involved in preparing and mobilizing the body for a fight or flight reaction (Bear et al., 2009).

Confronted with a physiological, psychological or emotional stressor, parvocellular neurosecretory cells in the nucleus paraventricularis of the hypothalamus stimulate the production of corticotropin-releasing hormones (CRH). Through the bloodstream, CRH reaches the pituitary gland, where adrenocorticotropic hormones (ACTH) will be released. When ACTH reaches the kidneys, cortisol will be discharged from the adrenal cortex. The HPA-axis system possesses an important feedback loop, initiated when free cortisol binds with cortisol-affine receptors at the pituitary gland and the hypothalamus, signaling a throttling of new CRH messenger production. This ensures that the level of cortisol does not become too high (Bear et al., 2009). Through the feedback system, a short-term activation of this system can easily be rebalanced by the body. Nevertheless, the allocation of resources is intense for the endocrine and metabolite systems. A longer-term activation (e.g. chronic stress) can lead to maladaptive HPA-axis consequences. Intensive and extensive overuse of the system

can disable the effectiveness of the feedback system, resulting in higher cortisol release (Gunnar & Cheatham, 2003; Koss & Gunnar, 2018).

Dysregulation of HPA-axis functioning can be expressed through hypo- or hyper-reactivity, with a medium level of activation being the healthiest stress response pattern (McEwen, 1998; Boyce & Ellis, 2005). Studies and reviews conclude that if a stressor is met by hypo- or hyperactivity of the axis, it likely leads to negative consequences (Adam & Kumari, 2009; Koss & Gunnar, 2018; Kuras et al., 2017; Oh et al., 2018), because inadequate HPA-axis responses will enhance allostatic load (McEwen, 1998). Hyperreactivity can, in the long-term, lead to a chronic downregulation of the HPA-axis response, resulting in subsequent hyporesponsivity (Oh et al., 2018). HPA-axis dysregulation has been associated with psychopathology; it plays an important role in a wide range of several psychiatric disorders like depression, anorexia nervosa, obsessive-compulsive disorder and panic disorder (Buitelaar, 2013; Tsigos & Chrousos, 2002).

The stress response systems and their context-dependent effects are adaptively evolved psychobiological mechanisms that react to specific features of childhood environments (Bauer et al., 2002; Berry et al., 2014; Essex et al., 2002; Granger, 1998; Miller et al., 2011; Repetti et al., 2002). On this basis, the stress response systems are calibrated to adaptively match the setting (Boyce & Ellis, 2005; Del Giudice et al., 2011), referred to as biological sensitivity to context. The HPA-system is active from birth and therefore reacts to early-life stressors. Very young children have been observed to typically show a hyporesponsivity of the axis, theorized to protect the developing brain from toxic effects of a strong stress reaction (Gunnar & Cheatham, 2003; Lupien et al., 2009; Lupien et al., 2018). Another form of protection for the stress system of a developing child can be social support. Especially primary caregivers of young children can buffer the stress response and negative effects of a stress response. If the social relationships of a child's environment are of good quality and children are securely attached, they show a weaker stress response to a stressor, compared to their insecurely attached peers (Gunnar et al., 1996; Nachmias et al., 1996). The HPA-axis is calibrated individually and

early, and children are dependent on external regulation through primary care givers throughout the developmental course. Their stress reaction orients itself at the external regulation before their own self-regulating capacities are fully developed (Gunnar & Cheatham, 2003; Hostinar et al., 2015). Investigations about the effects of the social environment on the stress systems have focused for example on maternal sensitivity and responsiveness (Bornstein and Manian, 2013; Berry et al., 2016), two characteristics that are thought to promote beneficial HPA-axis calibration.

Further environmental conditions, such as SES also play an important part in HPA-axis calibration and particularly low SES has been connected to HPA-axis dysregulation, through greater exposure to stressful life events (Chen et al., 2010; Desantis et al., 2015; Gustafsson et al., 2010; Lupien et al., 2001, see Dowd et al., 2009 for a review).

In turn, the negative effects of low SES have also been found to be successfully buffered through social support and secure attachment. A study comparing securely and non-securely attached children of low SES households, found children with secure attachments to show lower cortisol output compared to the high cortisol levels of their low SES but non-securely attached peers (Johnson et al., 2018).

The HPA-axis, and especially cortisol, are hypothesized to be a missing link to describe how early life experiences can get ‘under the skin’ and explain lifelong consequences for mental and physical health (Kudielka & Rohleder, 2011; McEwen, 1998; Miller et al., 2011; DeMorrow, 2018). The present thesis was therefore interested in the connection between child psychopathology, social environment or family interactions and cortisol.

3.3 Cortisol and Behavioral Symptoms

The steroid hormone cortisol is responsible for important bodily functions, such as immune system suppression, body growth, blood pressure, as well as how carbohydrates, fat and protein are metabolized (Ehlert & von Känel, 2010; Lundberg et al., 2011). Cortisol can be determined in hair and fingernails, urine, blood or saliva. Determining cortisol levels in saliva is a popular choice, due to being

a reliable, fast and non-invasive measure of cortisol (Granger et al., 2012; Trilck et al., 2005), qualities very suited for research with children.

In mammals, cortisol follows a specific diurnal rhythm. With awakening, cortisol rises rapidly. Approximately 30 minutes after awakening in the morning, cortisol is observed to show its daily peak with circa 50% of increase in values compared to values at awakening, known as the cortisol awakening response (CAR; Stalder et al., 2016; Wuest et al., 2000). After its peak, cortisol slowly decreases throughout the day, reaching a nadir in the first half of the night (Kudielka & Rohleder, 2011).

Several points of the cortisol diurnal curve, or calculations derived from the diurnal curve, are associated with variables of behavior or psychopathology (Buitelaar, 2013; Tsigos &Crousos, 2002). Especially the CAR has been related to several forms of psychopathology (Fries et al., 2009; Dietrich et al., 2013). The CAR reflects state rather than trait characteristics of HPA-axis functioning and is very susceptible to anticipated events, like the demands of the upcoming day (Elder et al., 2018; Fries et al., 2009; Wetherell et al., 2015). Results relating the CAR to variables of family environment are not always consistent (Fries et al., 2009). Regarding developmental programming of the CAR, it is thus difficult to formulate clear hypotheses (Del Giudice et al., 2011; Dockray et al., 2010). The CAR was calculated differently in previous literature, by either focusing on the proportion or percent increase from baseline to morning peak (Stalder et al., 2016) or by deriving the area under the curve (AUC) out of at least three morning measurements (typically assessing waketime, 30 minutes after waketime and 60 minutes after waketime). The AUC can be defined by two different reference points: If calculated with respect to zero, or ground (AUCg), the whole area under the curve is taken into account and it is used as an index of the total cortisol output. Alternatively, it can be referenced to the first point of cortisol measurement, deriving an AUC with respect to cortisol increase (AUCi) (Pruessner et al., 2003). Besides the CAR, there is interest to quantify a total cortisol output (e.g. of the whole day). For this cause, the trapezoid formula has been used to calculate the AUC, e.g. from wake to a

bedtime sample. In addition, some research has focused on the afternoon slope (e.g. from morning or noon to evening measurements) (Koss & Gunnar, 2018; Lupien et al., 2009).

In addition to basal cortisol activity, it is also common to measure cortisol reactivity. Usually experimental designs expose participants to a stressor like a social evaluation scenario or the provocation of pain and then investigate the relationship between baseline cortisol and the values during and after the stress reaction (Koss & Gunnar, 2018). In contrast to a planned stress exposure in an experimental setting, this thesis examines cortisol reactivity to everyday experiences in children's family environment in study III.

Cortisol patterns are thought to be quite stable in individuals, signaling an almost trait-like attribute (Hellhammer et al., 2007) when comparing it between individuals. However, it still yields significant state-like variation if measured across several days; within-person the state variance is higher than the trait variance (Shirtcliff et al., 2005). Consistently, within- and between-persons, cortisol values sampled at weekdays are different from cortisol values sampled at weekend days (Thorn et al., 2006). It is therefore advised to measure as many days as possible (however reasonable in terms of participant burden) and to be sensible about whether cortisol shall be sampled on weekdays or weekends. In line with Stewart and Seeman (2000) as well as Rotenberg et al. (2012), who advocate at least three weekdays of cortisol sampling for a stable estimate of CAR, this study incorporated 7 days of measurement. Cortisol output is dependent on age and concordantly pubertal stage of children and adolescents (Adam, 2006; Netherton et al., 2004; Oskis et al., 2009), as the HPA-axis is developing in parallel with biological maturity and the close interaction with the Hypothalamic-Pituitary-Gonadal-axis (Joseph & Whirledge, 2017; Kudielka et al., 2009).

The HPA-axis and its cortisol output is said to be the link in how basic body functions interact with the environment, and more specifically with behavioral aspects of life (Kudielka et al., 2012; Miller et al., 2011). Studies have captured the effects between the quality of caregiving and later HPA-axis and emotion regulation, especially in regards to early life experiences, such as maltreatment (Berry et al.,

2016; Gunnar & Cheatham, 2003; Ouellet-Morin et al., 2011). Since cortisol plays a major part for allostasis, periods of acute stress can lead to allostatic load and therefore a dysregulation of the HPA-axis activity (McEwen, 1998).

Researchers have linked child ADHD to abnormal cortisol patterns (Kaneko et al., 1993). This was followed by Blomqvist et al. (2007) who reported lower cortisol values at waketime + 30min in 13-year-olds with ADHD, compared to controls in regards to a dentist visit. Isaksson et al. (2012) confirmed that cortisol values of ADHD children were significantly lower in the morning (wake, wake + 30min) and at bedtime, across subtypes and controlling for comorbidities. Okabe et al. (2017) found a lower CAR in children with ADHD versus controls. Lately, children with ADHD were found to display lower CAR and diurnal cortisol values, regardless of subtype, compared to controls (Angeli et al., 2018).

In parallel, it was proposed that endocrine HPA-axis changes are related to the occurrence of externalizing behavior: ODD or CD symptoms have been associated with abnormal diurnal cortisol expression in girls (Pajer et al., 2001) and boys (Schoorl et al., 2016). Other studies did however not find a relationship between basal cortisol and CD (e.g. Fairchild et al., 2008). Freitag et al. (2009) observed an attenuated CAR only in ADHD children with comorbid ODD, not in children with ADHD without ODD comorbidity. Sondeijker et al. (2007) found an association between various disruptive behavior disorders and cortisol, but not with ADHD. The authors thus questioned, whether the effects found for children with ADHD, were rather driven by comorbid ODD. Since diagnoses of ODD and CD are frequently comorbid with ADHD (see Chapter 2), it is difficult to disentangle contributions of ADHD and oppositional/conduct disorder behavior to variation in CAR. For adolescent males with ADHD and partly comorbid CD, it was described that ADHD severity predicted reduced levels of cortisol while CD severity predicted heightened cortisol (Northover et al., 2016).

Finally, other studies report no differences at all: When examining afternoon samples, no difference in cortisol was observed between control children, children with ADHD, ODD or ADHD+ODD combined (Snoek et al., 2004). Imeraj et al. (2011) report differences in diurnal slope but found no

change in CAR between children with ADHD, ADHD+ODD or controls. Vogel et al. (2017) reported an association between ADHD symptoms in adults and cortisol at first, but after controlling for the comorbidities of anxiety and depression, the effect disappeared. Pesonen and colleagues (2011) investigated diurnal cortisol as well as cortisol reactivity to a stressor. They found symptoms of ADHD only to be associated with the reactivity to a stressor, not diurnal cortisol. Finally, Wang and colleagues (2011) measured cortisol and dehydroepiandrosterone (DHEA). Only DHEA levels, but not cortisol, differed significantly in children with ADHD and controls.

Concerning diurnal variations, the connection of ADHD and comorbidities with cortisol remains unclear in many aspects. Differences in measures and methods render previous investigations difficult to compare. Furthermore, results are partly limited in their generalizability. Blomqvist et al. (2007) demonstrated that only the subsample of ADHD-HI showed lower cortisol morning values than controls, emphasizing that subtype distinction is favorable in ADHD research. Additionally, the age span in previous samples varies widely. In one case, while examining a sample aged 7 to 16 years, different cortisol patterns for participants with ADHD were only true for a subgroup above 10 years of age (Isaksson at al., 2012).

The cited studies differ in the number of sampling occasions per day as well as the number of study days. In addition to a limited number of samples or study days, some studies only consider weekend days. There is also high variance in the characteristics of samples studied and most importantly, the reports refer to diverse cortisol indices, making previously published results difficult to compare. The inconsistency, whether children or adolescents with ADHD, ODD or CD significantly differ from control children and the methodological room for improvement form a research gap, which is being addressed with the present thesis.

4 Family Interactions

Parents do not uni-directionally influence their children and the relationship, children also have an important influence on their parents and parental behavior (Burke et al., 2008; Frick et al. 2003;

Hutchison et al., 2016; Lansford et al. 2011; te Brinke et al., 2017). Bell (1968; 1979; Bell & Harper, 2020) acknowledged this mutual influence between parents and their children. This mutual influence was further defined as bidirectional or transactional influences between children and parents by Sameroff (1975; 2009) as the transactional model of development. Children and parents are sensitive to the behavior of one another. Bidirectionality is reached through reciprocity and cumulating influences: children's behavior causes parental responses, which subsequently influence children. This process continues throughout parent-child interchanges and therefore shapes child development (Sameroff, 1975; 2009).

The bidirectionality in parent-child relations is particularly important for the context of child internalizing and externalizing behavior (Pardini, 2008; Paschall & Mastergeorge, 2016) and the development of delinquency and conduct disorder (e.g., Anderson et al., 1986; Jaffee et al., 2004).

Patterson's (1982; 2002) coercion model conceptualizes bidirectional influences in the context of child aggressive behavior. Based on operant conditioning (negative reinforcement), it theorizes a mutual reinforcement of aggressive behavior, explaining how clinical child disruptive behavior can emerge out of the parent–child relationship (Paschall & Mastergeorge, 2016). According to Patterson (Patterson, 1982; 2002), aggressive child actions, which can be light in the beginning, provoke aversive responses from their parents, for instance negative discipline. The effort to force the child to obey could also embrace ineffective punitive strategies like empty threats (Stoolmiller et al., 1997). Parental control attempts however lead to child resistance and an increase of problem behavior intensity, resulting in the parent declaring more threats than are ever enforced or the parent giving in (Snyder 1991). The same mechanism has been reported in relation to too timid discipline, contributing to worsening ODD behavior (Burke et al., 2008). When parents back down in their attempt to stop the child's aggressive conduct, the child's aversive behavior will be negatively reinforced (elimination of undesired stimuli), with the child learning, that this type of behavior will likely lead to the same parental reaction in similar future situations. Conflict-laden parent-child relationships will develop over time, forming a vicious circle out of aggressive child behavior and parent negative reinforcement.

Longitudinal designs show, that the association between parent behavior and child antisocial behavior is best explained by considering both parent- and child-driven effects (Larsson et al 2008; te Brinke et al., 2017; Burke et al., 2008). The influence can go both ways, with worsening effects for of aggressive or oppositional child conduct in the case of negative parenting practices (i.e. ineffective discipline; Snyder et al., 2005) as well as improvements through positive parenting practices (warmth and sensitivity; Boeldt et al., 2012; Christiansen et al., 2010).

Studies consistently demonstrated how the theoretical models can be implemented in real-life settings (Coley & Medeiros, 2007; Del Vecchio & O'Leary, 2006; Eddy et al., 2001; Pearl et al., 2014; Verhoeven et al., 2010) and emphasize the importance of transactional frameworks (Hutchison et al., 2016). Advances in data analyses contributed to explaining the etiology of dysfunctional socialization courses and the development of psychopathology (Hinshaw & Beauchaine, 2015; Pearl et al., 2014).

The Family Environment

The family environment is very important for children's physical and mental development as well as early learning experiences, with lifelong consequences (Bailey et al., 2009; Belsky & Pluess, 2009; Evans & Kim, 2007; Gunnar & Cheatham, 2003; Keller et al., 2005; Marsman et al., 2012; Repetti et al., 2002). Parents and other family members serve as role models and references for model learning (Bandura, 1971, Deater-Deckard, 2014). Witnessed behavior and coping mechanisms of family members therefore greatly shape future child behavior and their neuroendocrinology (Gunnar & Cheatham, 2003). Family members regulate a child's emotions and directly contribute to shape their reaction to stress with a long-term calibration of the HPA-axis (Gunnar & Donzella, 2002) and child behavior (Lee et al., 2018; Loman & Gunnar, 2010).

While the family can possess qualities to support children and be a nurturing place, the family can - under certain circumstances - be an environment of high stress. Unfavorable environments like poverty and low SES (Repetti et al., 2002), aggressive family interactions or maltreatment (Berry et al., 2016; Bruce et al., 2009), the lack of maternal sensitivity and responsivity (Bornstein and Manian,

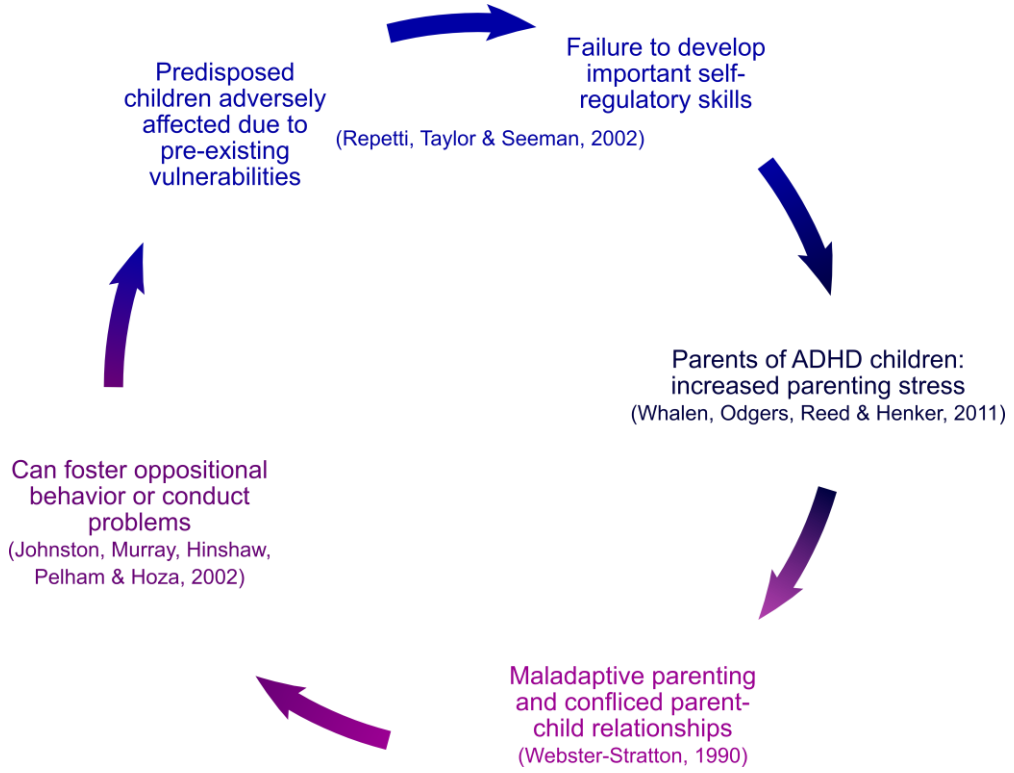
2013; Gunnar & Cheatham, 2003) can harm child development and contribute to the risk of psychopathology (Berry et al., 2016; Evans & Kim, 2007; Repetti et al., 2002; 2011).

Johnston and colleagues (2002) note that unresponsive parenting could be linked to increased self-regulation deficits of the child, which could then foster oppositional behavior or conduct problems (Bernier et al., 2012; Johnston et al., 2002). Family situations characterized by negative affectivity or high conflict may thwart responsive parental behavior. Heightened parental stress can lead to lower tolerance and an increased focus on problematic child behavior (Morgan et al., 2005), furthering mechanisms of a coercive cycle (Figure 1).

Harvey and colleagues (2016) acknowledge that parenting holds its challenges, even in the best of circumstances. Raising children naturally leads to the experience of stress for most parents. However, this stress is known to decrease with time and is accompanied by positive feelings, among others self-efficacy. These improvements are less apparent in parents of children with disabilities (Deater-Deckard 2004; Hutchison 2016 et al., 2016; Lovell et al., 2013). Child psychopathology in general, such as child internalizing or externalizing problems, can lead to heightened stress and less satisfaction among parents (Lange et al., 2005; Lovel et al., 2013). Families, where behavioral problems of the child extend the usual challenges of child rearing are especially at risk for negative parenting behavior and high conflict (Johnston & Mash, 2001; Repetti et al., 2002). This could lead to a coercive cycle (see Figure 1) where child and parent both reinforce unwanted behavior. Children with predisposed risks (e.g. developmental delays, insufficient self-regulation skills) are particularly likely to find themselves in interactions that can lead to further dysregulation of affect and maternal psychopathology (Paschall & Mastergeorge, 2016).

Figure 1

Coercive Cycle of Child and Parent Behavior (with Example References)



Child Externalizing Symptoms and Family Functioning

While a reduced quality of life was concluded for parents of children with many forms of psychopathology (see Dey et al., 2019, for a review), externalizing child symptoms can be especially challenging. ADHD symptoms affect the child itself, but also its siblings, its parents' marital functioning, and even the whole community (DuPaul et al., 2001; Harpin, 2005; Mikami & Pfiffner, 2008). Indeed, strained family relationships, heightened parental stress and psychopathology are amongst the most frequently reported difficulties, leading to a variety of consequences, like negative parental behavior, further provoking symptomatic behavior (Johnston & Mash, 2001). Especially children with ADHD-HI pose a challenge to parents, as they tend to be more chaotic and display less self-control compared to children with ADHD-IN. Parents of children with ADHD-HI consequently display more negative behavior towards their child (Weinberger et al., 2018). Consistently, studies

report heightened parent-child disagreement, parental stress, maternal negative moods, and anger as well as perceptions of lower parenting effectiveness and quality of life (Whalen et al., 2006a; 2006b, 2011; Primack et al., 2012; Wiener et al., 2016; see Johnston & Mash, 2001 for a review). Symptoms of ODD/CD in children do likewise affect the family, due to the high visibility and troubling quality of direct aggression (De Haan et al., 2013).

Especially child ODD/CD symptoms predict impaired family functioning. ADHD symptoms alone are often less related to family functioning or quality of parent-child interactions (Burke et al., 2008; Kashdan et al., 2004). In a longitudinal study, Burke and colleagues (2008) additionally found child ODD to predict less involved parents and poorer communication, while ADHD symptoms alone were not associated with parental behavior. However, many reviews conclude that ADHD alone confronts families with severe challenges (Deault, 2010; Johnston & Mash, 2001; McCleary, 2002; Morgan et al., 2005) and an improvement in ADHD symptomatology has been shown to improve parents' stress as well as feelings of competence (Heath et al., 2015).

The general consent is that a combination of ADHD and ODD/CD diagnoses has a cumulative negative effect (Garbani, 2019; Sollie et al., 2016). The conclusion is, that ADHD, ODD or CD alone will likely lead to disturbed family, school or social functioning. A combination of disorders additionally worsens prognosis (Harvey et al., 2016; Waschbusch, 2002), compared to single-diagnoses.

To summarize, the nature of family interactions is important for child development. Therefore, the present thesis investigates daily exchanges between family members, in regards to their characteristics and positive or negative valence. Based on the presented models, this thesis considers the child's and parent's perspective, the child's and parent's behavior and the child's and parent's outcomes and feelings in a continuous assessment.

Many studies investigate parenting as a trait concept, assuming that positive and negative experiences children might have with their parents are highly stable. In everyday family reality however, children's interactions with their parents are event-specific and naturally fluctuate from day-

to-day and within-day. Some interactions might contain more conflict and discord or parental discipline, while other experiences comprise praise, favorite activities, interest and warmth (Almeida, 2005; Lippold, 2014). The presence of negative experience does not imply an absence of positive experience and vice versa, speaking for a separate examination of occurrences (Dallaire et al., 2006; Lippold et al., 2014). In order to capture this variance, positive as well as negative experiences between children and parents have been correspondingly assessed as distinct constructs in this project.

To conclude the previous three chapters, biosocial models investigating the interplay of physiological functioning, individual characteristics (e.g. child development, psychopathology) and social environments (e.g. parent-child relationships) are important for our understanding of the underlying mechanisms that protect or harm child development and health. The following chapters of this thesis will introduce to conducted research project (chapter 5), designed to answer this project's research questions (chapter 6), and their addressment with three research articles (chapters 7, 8 & 9). The findings will then be summarized and discussed for their strengths and limitations before a final conclusion (chapter 10).

5 The LAMA Project

The present thesis presents hypotheses and results from the Life with ADHD in Momentary Assessment (LAMA)-Project. Funding for this project was acquired specifically for the preparation of the present doctoral thesis, made possible through a fellowship from the Swiss National Science Foundation (Doc.CH, P0FRP1_172013). All three studies included in this thesis are based on the data of the LAMA project. The aims and methods of the project will therefore be summarized before the presentation of the conducted studies.

5.1 Overview

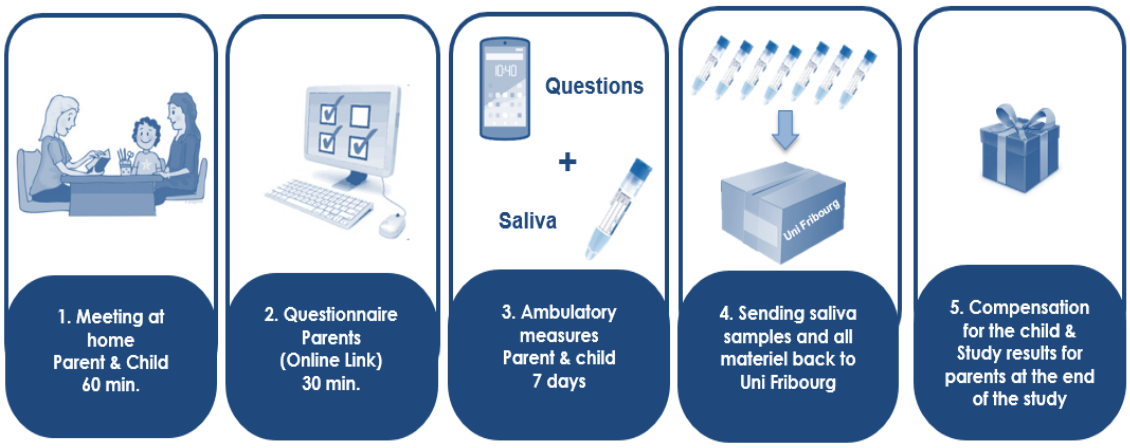
The proposed project was designed to investigate behavioral symptoms of children with and without ADHD, as well as comorbid externalizing symptoms, and their potential linkage with the HPA-axis and family interactions. Since previous findings are inconclusive about aspects of externalizing psychopathology which are related to HPA-axis dysregulation (Imeraj et al., 2012; Issakson et al., 2012; Pesonen et al., 2011; Vogel et al., 2017; Wang et al., 2011), a primary aim was to measure whether the presence of behavioral symptoms would predict diurnal cortisol output. A second aim was then to examine the link between ADHD or ODD/CD symptoms and distressed family interactions. Due to the distressing nature of externalizing symptoms (De Haan et al., 2013; Lang et al., 1989), children, who display more symptoms might experience more distressed interactions prone to high discord, negative parental behavior and negative affect within their families. An environment burdened with negative family interactions, negative parent behavior and children's symptoms is in turn hypothesized to predict the functioning of the physiological stress response. An identification of particular symptoms associated with differences in endocrine functioning and the investigation of associations of these symptoms with negative parent behavior and distressed family interactions as key features of risky families, are important steps for the understanding of children's psychological and physical health (DeMorrow, 2018; Lasikiewicz, 2008; Marsman et al., 2012; Slopen et al., 2014).

5.2 Study Design and Methods

The course of the study consisted of recruitment, telephone screening, a visit to the families' homes, a baseline online questionnaire for parents, the study week with momentary assessment as well as saliva samples and the closing procedure, where the families would return all material and saliva samples and children received a voucher for their participation (see Figure 2).

Figure 2

Stages of Study Participation



Recruitment took place via flyers that were distributed at schools, ADHD specialists and ADHD parenting organizations as well as articles in parent magazines and newspapers. The flyer and media announcements provided contact information. Interested parents contacted the principal investigator.

Upon contact by interested families, a phone call with the parent was scheduled, where the detailed study design was explained and individual collection times of saliva in the morning were calculated for each child or family. For children in the ADHD group, details about the diagnosis were assessed (subtype, year of diagnosis, specialist who confirmed diagnosis); for children in the comparison group, the absence of an ADHD diagnosis was inquired. Parents (and boarding school personnel) were asked for any (other) clinical diagnoses or problems. Parents interested in participation were asked to explain the study design and duties to their child(ren) and confirm willingness to participate. After this conformation, a home visit was scheduled.

During the home visit (ca. 90 minutes), all participants (children and parents) had to be present. The study information was repeated and the participating child and parent received smartphones and saliva sampling material as well as a training on how to handle the material. We

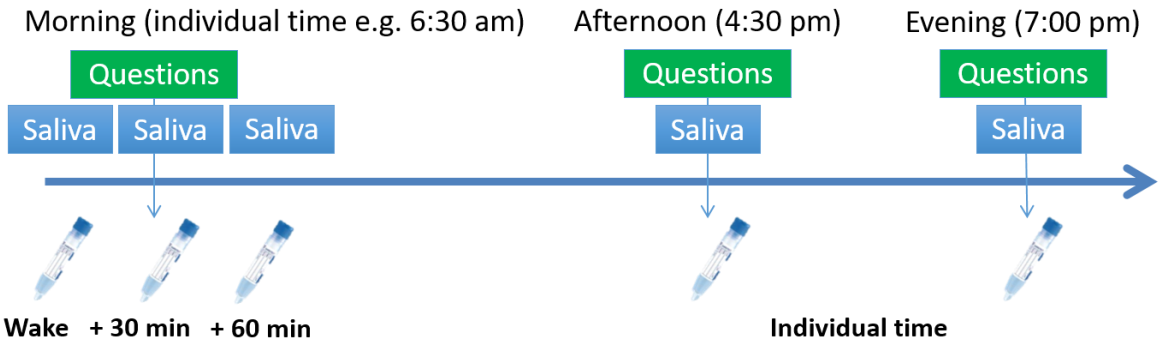
demonstrated the smartphones and their questionnaire application using a test version. Child and parent were both asked to try out test questions and answering formats.

To train saliva sampling, salivettes and their labels and handling were shown with experimenter's test tubes. After the demonstration, the child was given a Salivette to exercise handling and try out the taste und duration of having the salivette in the mouth. Only after this procedure, final Informed Consent from the child was obtained. At the end of the home visit, children and adolescents filled in a self-report puberty questionnaire. They were invited to fill it in by themselves and leave the questionnaire in a sealed envelope. They could always ask the parent or experimenter if they had questions. Some children were too young to understand the questions so the questionnaire was filled in with full assistance by the parent. Following the home visit, parents responded to a background questionnaire online (duration: 40 minutes) in the next days.

Data collection took place at home for 7 days in the following week after the home visit, always starting Monday (see Figure 3). All test-weeks were scheduled during school-weeks, not vacation. This study was approved by the Swiss cantonal ethics committees; Rules of ethical standards and safety were followed. All parents and children above the age of 14 gave written and oral consent; children below the age of 14 gave oral consent to participation. All children gave consent independent from their parents. Children received 50 Swiss Francs for their participation at the end of the study (voucher from a local department or bookstore).

Figure 3

Daily Schedule of Momentary Assessment and Saliva Sampling. Repeated Monday through Sunday.



Momentary Assessment

Each child and parent answered smartphone questions three times a day: In the morning before school or work (time programmed for each family individually, to accommodate different morning routines and ensure sufficient time for saliva sampling), in the afternoon (4:30 pm) and the evening (7:00 pm). Participants had a 90-minute window to respond to questions after the alarm. Answering questions took on average 3 minutes per time point; children had less questions than parents. Momentary assessment is a means of real-time capture of momentary processes over the course of daily life, while evading recall bias, to investigate everyday situations in participant's home and natural setting (Shiffman, Stone, & Hufford, 2008; Trull & Ebner-Priemer, 2014).

Saliva Sampling

Salivettes for saliva sampling were sorted into seven bottles (one bottle for each day), five Salivettes per bottle, with numbers on the top in addition to a label to mark the order of salivettes. Saliva sampling took place five times a day: At waking up, 30 minutes after waking and 60 minutes after waking as well as in the afternoon (around 4 pm) and the evening (around 7 pm). Children were not allowed to eat or drink (water was allowed up to 10 minutes before sampling), brush their teeth or chew gum for 30 minutes before sampling saliva. In the morning, children only had breakfast after the third sample. For part of the families, children had to be waken up earlier than usual to participate

in the study and reach school in time. The time of waking and the two subsequent saliva samples were thus calculated and instructed for each family individually. In the afternoon and evening, families were advised to take saliva samples around the time of momentary assessment. However, in order to reduce participant burden of this intensive sampling study, families were allowed to sample saliva earlier or later than momentary assessment, as long as they could assure to note the exact timing of sampling.

We had two procedures to register exact timing of saliva sampling: A self-reported protocol booklet and objective digital timestamps. The objective method to register time of sampling was the use of either MEMS caps or participants taking time-stamped pictures of the empty salivette tube (because salivette was in the child's mouth at this point) figuring the tube label, so sample could be identified surely. MEMS caps are lids for bottles that record the time and date of opening and closure.

The protocol booklet served participants to note exact time of saliva sampling (hours: minutes) and answer a set of questions about sleep duration and quality, a saliva sample being likely contaminated, consummation of caffeine or similar, sports and activities or any special circumstances that participants would like to let the experimenters know. The protocol booklet also asked for intake of medication and - for girls - the date of their last period (if already menstruating) and oral contraception.

After saliva sampling, Salivettes were kept in the families' refrigerators until the end of the study week. Then, participants express shipped all material back and salivettes were stored at minus 30 degrees Celsius before being shipped to a biochemical laboratory for assay.

6 Summary of the addressed research questions and included studies

The research plan for the present project aimed to answer four research questions through three empirical contributions. Firstly, the psychobiological basis was approached in order to identify possible underlying physiological mechanisms who might accompany symptomatic behavior of children. The hypothesis, that children with ADHD would show a distinct HPA-axis regulation was tested before, but

yielded inconsistent results (Angeli et al., 2018; Imeraj et al., 2012; Issakson et al., 2012; Okabe et al., 2017; Pesonen et al., 2011; Vogel et al., 2017; Wang et al., 2011). Evidence emerged, that not necessarily symptoms of ADHD but rather comorbid symptoms of ODD/CD drive a potential effect between behavioral symptoms and dysregulated cortisol output (Freitag et al., 2009; VanGoozen et al., 2000). Therefore, the first research question aimed to test a general confirmation of an association between ADHD symptoms and HPA-axis output. Whether the effect was attributable to ADHD symptoms alone, or rather to symptoms of ODD/CD, generated the subsequent second research question.

1) Do children with ADHD symptoms in general show different cortisol patterns than non-ADHD children?
2) Are differences in HPA-axis output due to comorbid ODD/CD symptoms?

To address these two questions, the first study compared three indices of cortisol output (CARi and CARg in the morning, and AUCg of total diurnal output) across children with different degrees of ADHD or ODD/CD symptoms.

Secondly, the family level was targeted. The objective was to test if, in the current sample, the children's display of symptoms was directly related to more negative family interactions. It was assumed that children with behavioral difficulties might cause and experience more negativity in the parent-child dyad:

3) Are child symptoms of ADHD or ODD/CD related to more negative family interactions, dysfunctional parental behavior and negative affect in parents and children?

This research question was addressed with Study II, by conducting a model where child symptoms would be associated with child and parent negative affect, mediated by family interactions, specifically parent behavior towards the child.

While the first study was designed to investigate behavioral symptoms and diurnal, basal cortisol and the second study was designed to establish the nature of behavioral symptoms in family interactions, the last study aimed towards cortisol reactivity in dependence of family interactions.

Thirdly, the psychobiological and psychosocial level were thought to be combined with the following research question:

4) Are negative family interactions due to child symptoms predictive of HPA-axis dysregulation?

Following this chapter, the manuscripts of the three sub-studies designed to answer the described research questions, will be presented.

7 Study I: Diurnal Profiles of Salivary Cortisol in Children with and without ADHD and Comorbidities

Background. Studies examining whether children with Attention-Deficit/Hyperactivity Disorder (ADHD) and comorbidities of oppositional or conduct behavior show a distinct diurnal cortisol output, have yielded inconsistent results. Inconsistencies may be rooted in differences of study design, sample characteristics and the specific indices of cortisol under investigation. This study evaluates postulated relationships through an intensive study design. It provides improvement in regards to number of saliva samples, repeated measures of salivary cortisol and number of participants, while assessing important confounding covariates, i.e. child age, pubertal stage, sex, BMI, often ignored in prior research.

Methods. *N*= 145 children (*n*= 65 with ADHD) between 7 and 16 years of age participated in home sampling of salivary cortisol. Five diurnal samples over seven days were collected to investigate the cortisol awakening response (CAR) as well as diurnal cortisol (total output across the day via area under the curve; AUC). Three two-level structural equation models were tested, with ADHD and comorbidities hypothesized to predict: 1) a smaller CAR with respect to ground (CAR_g) 2) a smaller CAR with respect to increase (CAR_i), and 3) a lower diurnal cortisol AUC from first (wake) to last (evening).

Results. Previously reported physiological differences of children and adolescents with ADHD, and symptoms of oppositional or conduct behavior, in regards to HPA-axis activity did not emerge in this sample. Significant predictors for cortisol were limited to child age and pubertal state. Neither ADHD nor Symptoms of oppositional or conduct behavior explained significant variance of CAR_g, CAR_i nor diurnal AUC. Intrapersonal variation of cortisol was high across days, with 59 to 76 % of variance attributable within-child.

Conclusion. To our knowledge, this is the first study across a full week of intensive cortisol sampling. Incorporating covariates specific to development, such as age and stage of puberty, is crucial for our understanding of cortisol functioning in children and adolescents. Findings highlight the importance of developmentally specific aspects for research with youth in salivary bioscience and all investigations of endocrine systems, susceptible to developmental changes throughout the life span.

Diurnal Profiles of Salivary Cortisol in Children with and without ADHD and Comorbidities

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in youth, affecting around 5% of children and adolescents (Polanczyk et al., 2014; Sayal et al., 2018). Symptoms are categorized into three subtypes: 1. Predominant inattention (ADHD-IN). 2. Predominant hyperactivity/impulsivity (ADHD-HI). 3. Combined presentation. For ADHD-IN, diagnostic criteria comprise difficulties holding attention without distraction, organizing tasks, and being forgetful. In contrast, ADHD-HI is diagnosed based on excessive motor activity, difficulty waiting one's turn or interrupting others (American Psychiatric Association APA, 2013). ADHD is frequently diagnosed with at least one comorbid disorder (Efron et al., 2016). Most commonly Oppositional Defiant Disorder (ODD), with a prevalence of 30-50% among youth with ADHD, as well as Conduct Disorder (CD) in about 25% of youth with ADHD (APA, 2013; Bendiksen et al., 2017). Typical behaviors for ODD are arguing and refusal to comply with rules, while CD includes attributes of violence and aggression (APA, 2013).

Hypothalamic-pituitary-adrenal (HPA)-axis dysregulation has been linked to psychopathology (Tsigos & Chrousos, 2002). Clarification of HPA-axis functioning in individuals with symptoms of ADHD or ODD and CD is important, as dysregulation poses a risk of physical and mental health consequences (DeMorrow, 2018; Lasikiewicz, 2008; Miller et al., 2011; Zhang et al., 2016). ADHD has been associated with physiological under-arousal, attention-seeking and behavioral inhibition deficiencies (Barkley, 1997), characteristics that could be related to blunted patterns of cortisol expression.

Various studies portrayed a difference in diurnal cortisol, as a sign of HPA-axis dysfunction, in children and adolescents with ADHD compared to non-affected peers (Angeli et al., 2018; Blomqvist et al., 2007; Isaksson at al., 2012; Okabe et al., 2017). However,

findings are not conclusive as this was not always replicated and many found that ADHD symptoms were not associated with basal, diurnal cortisol levels (Freitag et al., 2009; Imeraj et al., 2012; Pesonen et al., 2011; Sondeijker et al., 2007; Vogel et al., 2017; Wang et al., 2011). Some previous studies have limited generalizability, due to differences in methodological approaches or samples studied:

1) Number of sampling occasions (number of sampling days and samples per day). Multiple day measurement would account for changes in cortisol expression due to daily events or stress (Elder et al., 2018; Wetherell et al., 2015) in contrast to sampling cortisol on two (weekend) days and using the mean. Cortisol values collected on the weekend tend to differ from values on weekdays (Thorn et al., 2006).

2) Dissimilar cortisol indices. Certain authors refer to cortisol raw or mean values (e.g. upon wakening) (Blomqvist et al., 2007; Isaksson et al., 2012), others refer to diurnal slope (Okabe et al., 2017) or investigate the total diurnal release of the day (Angeli et al., 2018), while others focus on the cortisol awakening response (CAR). The CAR was investigated either through mean or percent increase from baseline awakening cortisol to the next measurement (Angeli et al., 2018; Okabe et al., 2017) or by calculating the area under the curve (AUC) out of three or more morning measurements (Imeraj et al., 2012; Freitag et al., 2009, Sondeijker et al., 2007; Vogel et al., 2017). Depending on how the CAR was quantified, results cannot be directly compared.

3) Sample characteristics. Studies have been conducted with children and adolescents of various age spans with findings depending on participant age. In one case, while examining a sample aged 7 to 16 years, lower mean values of cortisol for participants with ADHD compared to controls were only true for a subgroup older than 10 years (Isaksson at

al., 2012). Angeli et al. (2018) found children with ADHD to differ from controls regarding CAR and diurnal cortisol output, focusing on pre-pubertal children.

Diagnoses or symptoms of ADHD have been assessed in different manners (e.g. diagnostic interview vs. parent report) and subtype distinction has not always been considered. Blomqvist et al. (2007) demonstrated that only the subsample of ADHD-HI showed lower cortisol morning values than controls, emphasizing that subtype distinction is favorable in ADHD research. Comorbidities of ADHD have only sometimes been considered and controlled. Vogel et al. (2017) reported an association between ADHD symptoms in adults and cortisol at first, but after controlling for the comorbidities of anxiety and depression, the effect disappeared. Additionally, previous studies suggest that endocrine HPA-axis differences correlate with the occurrence of ODD or CD rather than ADHD: Externalizing behavior, as seen in ODD or CD has been associated with decreased cortisol expression (Pajer et al., 2001; Schoorl et al., 2016). Freitag et al. (2009) found an attenuated CAR only for children with ADHD if they had comorbid ODD symptoms. Kariyawasam and colleagues (2002) also found lower afternoon cortisol values for children who had ADHD and ODD (based on one single saliva sample per child). Finally, Sondeijker et al. (2011) found diurnal cortisol to be associated to other forms of disruptive behavior disorders in children, but not ADHD symptom scales, measured in a population study with more than 1700 child participants. Since comorbidity is highly prevalent, the contribution of ODD/CD should be considered when examining cortisol expression in the context of ADHD (Bendiksen et al., 2017; Freitag et al., 2009).

The Present Research

The present study seeks to combine many of individual aspects previously studied and begins to address some of these gaps in our understanding of ADHD and its link to HPA-axis

regulation. We present data from multiple measures (5 samples/day), repeated across 7 days. To attend to the role of participant age and enable to link previous findings, limited to certain age groups, participants from seven to 16 years, spanning from pre-puberty to post-puberty participated. We investigate differences in cortisol among children and adolescents with and without symptoms of ADHD, as well as comorbid symptoms of ODD or CD. ADHD is being assessed by two means: Presence of clinical diagnosis coupled with (parent-reported) symptoms in daily life. We examine three indices of diurnal cortisol in relation to HPA-axis function, namely the CAR, calculated using morning AUC with respect to ground and increase (CAR_g and CAR_i, respectively), as well as total diurnal HPA-axis output (AUC_g).

We hypothesize, that children with ADHD symptoms will exhibit lower levels of cortisol, than children in the comparison group. Severity of symptoms is hereby thought to predict lower CAR diurnal AUC values. In addition, we assume differences in HPA axis functioning between ADHD subtypes. We expect children with ADHD-HI to show an attenuated CAR and a smaller diurnal AUC, compared to children with ADHD-IN and comparison children. Further, we anticipate children with oppositional or conduct disorder behavior to also show lower cortisol expression, as hypothesized for children with ADHD. We expect externalizing behaviors to have a larger effect on the explanation of variance compared to ADHD.

2 Method

2.1 Participants

Participants were 145 children (38% girls) between 7 and 16 years of age (*M*= 11.50, *SD*= 2.00) recruited via public schools, through ADHD specialists (psychologists, psychiatrists, and physicians), parenting organizations and media (parent magazines and newspapers) from 2018-2019. The study accepted siblings to participate (*n* = 83 families enrolled more than one child). Inclusion criteria were as follows: child age between 7-16 years, attending school in Switzerland, absence of clinical diagnoses except for ADHD, ODD or CD. Diagnosis of ODD or CD was an inclusion criterion for the ADHD group as well as the comparison group. We considered ADHD in two different ways: parent-reported symptoms and presence of clinical diagnosis. Official diagnosis from a physician or clinician was applicable for *n*= 65 children (17 girls, 48 boys; Table 1). Children without ADHD diagnosis, were included in the comparison group (*n*= 80; 37 girls, 43 boys). For each child participant, one parent joined the study (94% mothers), except in the case of children who were attending a boarding school for children with difficulties (*n*= 12)[1].

Nearly 75% of families stated a monthly net (after taxes) household income above the country's average (FSO, 2017). The category "low income" is only applicable to five families in the sample, in contrast to 22 families in the highest range of roughly 'above 12'000 USD' per month, after taxes. All participating parents graduated from high school, and more than 50% completed higher education training, 40% are in possession of a college or university degree.

[1] For *n*= 12 children, the study protocol had to be adapted due to attendance of a boarding school (for behavioral difficulties or because of custody withdrawal from the state). For this subgroup, parents consented to their child's participation but did not participate themselves. While presence of ADHD diagnosis was known for this group from the authorities due to previous medical and psychological check-ups, no parent-reported ADHD or ODD/CD symptoms could be obtained. For testing the main effect with ADHD and ODD/CD symptoms, they were thus excluded, but were included for testing ADHD as dichotomous predictor. Saliva sampling was only scheduled for weekdays, as boarding school infrastructure did not enable weekend sampling.

2.2 Procedure

Participating families were visited in their homes by research staff. The home visit (approx. 90 minutes) required attendance by the participating children and parents. Study information and saliva sampling materials and trainings were provided during this visit. Salivettes were sorted and labeled for each day and time point. Following experimenter demonstration, each child exercised handling, and practiced saliva sampling. Before the sampling period, parents competed an online background questionnaire (approx. 40 minutes) including demographic info, symptom ratings and various screenings (see 2.3 Measures). Children received a gift card for the equivalent of about 50 US Dollars for their participation at the end of the study. This study was approved by the cantonal ethics review board. All rules of ethical standards and safety were followed. All parents and children above the age of 14 gave written and oral consent; children below the age of 14 gave oral consent to participation. All children gave consent independent from their parents.

Data collection took place within the home for seven days following the home visit, always starting on a Monday. All sampling weeks were scheduled while the children were attending school (not during vacations or school breaks). Child participants were asked to collect saliva samples five times across the day: upon waking up, 30 minutes after waking, and 60 minutes after waking, as well as in the afternoon (around 4:30 pm), and the evening (around 7:00 pm). Saliva collection times for morning samples were planned with the research staff before the sampling period for each child individually, to accommodate every family's morning routine to promote compliance with sampling protocols. Breakfast consumption was possible only after collection of the third sample, since children were not allowed to eat or drink, brush their teeth, or chew gum 30 minutes before each sample.

The time of sampling was assessed through: a) parent or adolescent self-report (SR) as well as b) a digital time-stamp collected via either Medication Event Monitoring Systems (MEMS) caps or time-stamped photographs taken by participants. Due to the high costs of caps, not all families were provided with MEMS caps. Approximately half of families were instructed to provide a photograph of the tube label on the empty salivette tube (because salivette was in the child's mouth at this point) for each sample collected as a means of verifying sample collection times.

2.3 Measures

2.3.1 HPA-axis functioning (salivary cortisol)

Saliva collection took place within the home for seven days following the home visit, always starting on a Monday. All sampling weeks were scheduled while the children were attending school (not during vacations or school breaks). Child participants were asked to collect saliva samples five times across the day: upon waking up, 30 minutes after waking, and 60 minutes after waking, as well as in the afternoon (around 4:30 pm), and the evening (around 7:00 pm). Saliva collection times for morning samples were planned with the research staff before the sampling period for each child individually, to accommodate every family's morning routine to promote compliance with sampling protocols. Breakfast consumption was possible only after collection of the third sample, since children were not allowed to eat or drink, brush their teeth, or chew gum 30 minutes before each sample. The time of sampling was assessed through: a) parent or adolescent self-report (SR) as well as b) a digital time-stamp collected via either Medication Event Monitoring Systems (MEMS) caps or time-stamped photographs taken by participants. Due to the high costs of caps, not all families were provided with MEMS caps. Approximately half of families were instructed to provide a photograph of the tube label on the empty salivette tube (because salivette was in

the child's mouth at this point) for each sample collected as a means of verifying sample collection times.

Saliva was obtained using Sarstedt cortisol Salivettes with instructions to move the swab around the mouth for 1-2 minutes until completely wet. Saliva samples were refrigerated in the participants' home refrigerators until the end of sampling week, then transported back to the University and stored at -30°C until assay. Samples were assayed for salivary cortisol at the Technical University of Dresden, Germany, with immunoassay kits (CLIA, IBL-international, Germany). The intra-assay CV and inter-assay CV were calculated with 4.5% and 5.2%, respectively.

Less than 5% of cortisol data were missing due to participants not taking the sample. AUC indices for morning and diurnal cortisol were computed (trapezoid formula) using cortisol raw concentrations. We considered three different AUC applications for cortisol: 1. CAR with respect to ground (CAR_g), in order to consider baseline morning HPA-axis function, 2. CAR with respect to increase (CAR_i) to emphasize the change in morning cortisol and 3. The total diurnal cortisol concentrations across the day (AUCg, all five samples). Adhering to Expert Consensus guidelines (Stalder et al., 2016), CAR values were set to missing if waketime sample was missing or deviated > 15 minutes from reported awakening. Diurnal AUC was defined as missing if first or last sample of the day was missing.

Regarding sample time assessment, less than 10% of self-reported times (SR) were missing, but objective time-stamp methods were applied less conscientiously reported (18% data missing). For cases with missing SR times, but present objective time-stamp data, the objective time was used. Sensitivity analyses revealed no change in results for analyses with or without using the objective time. A major concern in salivary bioscience studies conducted in the home, compared to a controlled laboratory setting, is sampling schedule adherence.

For CAR, in about 3% of sampling occasions, the three saliva samples in the morning were not taken within the planned timespan of 60 minutes. We considered cases with CAR sampling durations under 45 minutes or over 75 minutes, as violations of the sampling protocol and thus omitted them, to improve the validity of our awakening indices (Imeraj et al., 2012; Rotenberg et al., 2012).

2.3.2 ADHD

We considered two different variables for ADHD: 1) diagnosis and 2) symptom rating.

ADHD Diagnosis. Dichotomous grouping variable based on clinician or physician performed assessment with official report confirming diagnosis, used as a covariate.

ADHD Symptoms. Continuous variable based on parent-report of Conners 3 Scales (Conners et al., 2011) with four-point response scale from 1 "*not at all (never/rarely)*" to 4 "*fully applicable (very frequently)"* (recommended cutoff ≥ 2). All parents completed the 10-item short screening for ADHD ($\alpha = .93$) to compute a composite score. For ADHD subtype differentiation, parents of children diagnosed with ADHD additionally completed the Conners subscales for Hyperactivity/Impulsivity ($\alpha = .73$) and Inattentiveness ($\alpha = .62$).

2.3.3 ODD/CD

ODD/CD diagnosis. None of the children presented official clinical diagnoses of ODD or CD. However, the parent-reported symptom rating clearly indicated symptoms above the recommended Conners cut-off value of 2. A dichotomized variable was created based on the symptom cut-off. However, the preference was to capture ODD and CD symptoms as/on a continuum.

ODD/CD symptoms. All parents completed the Conners subscales for oppositional behavior, aggression/spitefulness and conduct problems ($\alpha = .90$) (Conners et al., 2011) with

four-point response scale from 1 "*not at all (never/rarely)*" to 4 "*fully applicable (very frequently)"* to compute a composite score.

2.3.4 Puberty

Physical Development Scale (PDS) was assessed with a self-report adaption used by Earls et al. (2002) of the Pubertal Development Scale (PDS) (Petersen et al., 1988). Child participants completed the self-report questionnaire independently, if possible, and placed it in a sealed envelope. Younger children completed this questionnaire with assistance from either their parent or the experimenter (according to the child's choice). Items included questions for all sexes (growth spurt, skin changes, body hair), as well as two questions, either for girls (menstruation, breast growth) or boys (deeper voice, beard) for the computation of a puberty sum score. Answers were given on a 4-point scale from 0 *"not yet started"* to 3 *"seems completed"*, with a high internal consistency (α_{girls}= .89, α_{boys}= .92). This scale has been evaluated previously (e.g. Bond et al., 2006; Earls et al., 2002).

2.3.5 Other measures

BMI. Body mass index (calculated as weight in kg/[height in meters]^2) using parent-reported height and weight of children.

Time of Peak. It has been assessed whether all participants show a daily cortisol peak at sample 2 (wake+30 minutes in this study) as would be expected theoretically (Stalder et al., 2016). Around 30% of participants did not peak at sample 2. Sensitivity analyses were conducted to test if exclusion of time points with peak ≠ 2 would lead to different results but the findings of the present article remain the same. Since it is believed to be biologically plausible that not everybody peaks 30 minutes after wakening (Law et al., 2013), all time points were considered for analyses.

Time Duration. While the study protocol in the morning had strict instructions regarding the timing of the saliva samples (wake, wake+30min, wake+60min), the afternoon and evening samples could be scheduled freely by families to enhance compliance. As a result, time durations between first and last sample varied by day and across children. When comparing diurnal AUCs between and within children, these different time durations may pose a problem, as the trapezoid formula will yield higher AUC values for longer time durations between first and last sample. We therefore added time duration in minutes as a covariate (CAR: time between samples 1 and 3; diurnal AUC: time between samples 1 and 5).

2.4 Data analyses

Two children (from the same family) ended participation in the study after completing the first day of saliva sampling, data from this day were included in the analyses. One child had to be excluded from the analytic sample, due to implausibly high cortisol values (> 300 µmol/liter); the child had a fever and was on medication during the sample collection period. Three parents did not complete the baseline questionnaire. The final sample for analyses with ADHD as a dichotomous variable based on diagnosis therefore included all participants. Analyses with ADHD and ODD/CD symptoms (based on parental questionnaire) consisted of *N*= 129 children. A priori power analysis indicated sufficient power (> .80 at α= .05) with *N*= 100 participants for an estimated medium effect size (f^2 =.15).

Regarding ADHD subtypes, parent reported symptoms only identified *n*=5 children with ADHD-HI and *n*=24 children to only show symptoms of ADHD-IN, the vast majority of children qualified for the "combined" subtype due to meeting the clinical characteristics of both, inattention and related problems, as well as hyperactivity/impulsivity. Due to the imbalance of children of either subtype, ADHD subtypes were not analyzed separately.

Exploratory analyses however showed no association of ADHD-HI or ADHD-IN with cortisol outcome variables.

In addition to the main predictors ADHD and ODD/CD symptoms, the following covariates were considered: Child age, pubertal state, child sex, BMI, time of peak and time duration. Among these considered covariates, only child age, pubertal state and the time duration of saliva sampling were associated with the dependent variables (CAR_i, CAR_g, diurnal AUC) in this sample. We therefore only included these covariates in the final models (in this order, following the main predictors ADHD and ODD/CD). To answer our research questions, we conducted a structural equation model (SEM), including a path model as well as a measurement model for all days of cortisol assessment, with cortisol indices conceptualized as a latent factor (see Figure 1). Since many families enrolled more than one child into the study, data are nested within family. To account for the dependence of sibling data, a Multilevel Modeling (MLM) framework, with family as Level 2, was applied. The measurement part was integrated in the final model (see Figure 1) and conducted for each of the three dependent variables (CAR_g, CAR_i, diurnal AUC_g) separately. All analyses were conducted in MPlus 6 (Muthèn & Muthèn, 2010). To accommodate the positively skewed distribution of cortisol data, the Robust Maximum Likelihood (MLR) estimator was used.

Measurement Model Evaluation

The measurement models for the latent cortisol factors (CAR_i, CAR_g, diurnal AUC), a confirmatory factor analysis, yielded an acceptable model fit (see Table 4).

A differentiation of models by week vs. weekday was indicated by indices of model fit (see Table 4). The CAR was more susceptible to weekday-weekend differences than diurnal AUC; especially CAR_g seemed to be sensitive in this aspect. Therefore, the results including the measurement and structural parts will only be reported for the 5-day model (data collected on weekdays Monday through Friday).

3 Results

The overall Model fit for the measurement model and the path model combined were acceptable to good (see Table 2). As displayed in Table 3, ADHD symptoms were not associated with any measure of HPA-axis functioning (no significant relations with CAR_i, CAR_g, nor diurnal cortisol output via AUC_g). Regression coefficients, point towards a negative association, which is in the hypothesized direction. Likewise, for ODD/CD symptoms, there was no significant association with any cortisol index examined. Here, regression coefficients are positive, implying an increase in symptoms was related to an increase in cortisol. ADHD (based on diagnosis) and ODD/CD were also tested as dichotomous predictors in an alternative model and equally yielded no significant associations with any of the dependent variables.

For overall diurnal cortisol output (AUC) and the CAR_g, child age was the only statistically significant predictor of HPA-axis function (β= .331, p= .023, [95% CI: 0.047, 0.615], resp. β = .261, p= .046, [95% CI: 0.005, 0.518]), generally, older children exhibited higher cortisol output. Pubertal stage predicted the CAR_i (β = .304, p= .044, [95% CI: 0.009, 0.599]) which higher pubertal stage being associated with increased cortisol.

Cortisol Variability

Intraclass coefficient (ICC) calculations show a large part of cortisol variance attributable to within-child (across days) variability. For diurnal AUC, 61% of the total variance accounts for within-child variance. In the case of CAR we see a clear distinction of CAR_g and CAR_i: For CAR_g, the total variance is portioned into 58,6% of within-child vs. 41.4% between-child variation of cortisol. For CAR_i, we observe a within-child portion of variance as high as 76.3% and only 23.7% of variance explained by between-children effects.

4 Discussion

The present study examined a relation between ADHD and ODD/CD symptoms (and diagnosis) and HPA-axis functioning among children and adolescents. We assessed clinician-diagnosed ADHD and additionally had parents rate actual symptoms, to ensure our sample included participants with a wide range of symptoms and to avoid sampling bias regarding health care utilization. Our study approach was complex and designed to address many of the gaps in our understanding of ADHD and HPA-axis functioning among children; specifically, we collected cortisol assessments in the home, with multiple sampling occasions per day and on multiple days, and we calculated three commonly examined measures of diurnal HPA-axis function (comparing CAR and diurnal curves, calculated via AUC).

With these robust methods, we found no significant relations between neither ADHD nor ODD/CD and CAR_g, CAR_i or diurnal cortisol AUC. For this study and sample, we therefore see no differences in HPA-axis regulation, measured through cortisol, across children and adolescents with ADHD symptoms nor symptoms of comorbid ODD/CD, compared to non-ADHD or non- ODD/CD comparison children of the same age.

Our results are partly in contrast to previous findings (Angeli et al., 2018; Isaksson et al., 2012; Okabe et al., 2017), who show distinct cortisol patterns in children and adolescents

with ADHD compared to non-ADHD controls. However, the used methodologic approach and targeted indices of cortisol as well as sample characteristics vary widely by study. Previous results are only applicable to pre-pubertal children (Angeli et al., 2018) but also not applicable to children below age 10 (Isaksson et al., 2012). Therefore, previous conclusions are not universal and do not necessarily support each other (Imeraj et al., 2012; Isaksson et al., 2012; Okabe et al., 2017; Pesonen et al., 2011; Sondeijker et al., 2007; Vogel et al., 2017; Wang et al., 2011). We assessed cortisol the CAR via AUC_g and AUC_i (Pruessner, 2015) and our results are consistent with previous investigations of CAR measured through AUC (Imeraj et al., 2012; Sondeijker et al., 2007; Vogel et al., 2017). Regarding morning samples (but not CAR-AUC), our findings are consistent with Wang and colleagues (2011) who did not find cortisol to differ between children with ADHD and controls and the study of Pesonen et al. (2011) where ADHD symptoms were related to cortisol reactivity in a stress test, but not with diurnal cortisol. Besides morning cortisol measurements, the total daily release of cortisol has been a topic of interest. Varying in time span, total cortisol output from waking to bedtime cortisol has been reported to be smaller among children with ADHD compared to children without ADHD (Angeli et al., 2018). Our results are inconsistent with these findings and instead show no significant relations between ADHD symptoms and cortisol output across the day. Our results also show no association between ODD and CD symptoms and cortisol measurements. This is in contrast to certain previous findings (Freitag et al., 2009; Northover et al., 2016; Pajer et al., 2001; Schoorl et al., 2016) but in line with others (Fairchild et al., 2008; Imeraj et al., 2012). Similar to ADHD, ODD/CD symptom assessment differs from parent-report, to structural clinical interviews to assessment of pre-existing clinical diagnosis, adding another argument to the complexity and difficulty to compare or generalize findings.

The presented results do not support an association of ADHD and ODD/CD with diurnal HPA functioning cortisol for children or adolescents between 7 and 16 years of age, over and on top of the variance explained by age and puberty. Cortisol research in children and adolescents often comprises wide age spans and therefore participants in different states regarding puberty. HPA-axis changes in this stage are pronounced, due to the axis' close interaction with the Hypothalamic–pituitary–gonadal (HPG) -axis, especially active before and during pubertal maturation. In our models, age and pubertal state as sole predictors of cortisol outcome variables might provide an important hint for the relevance of biological maturation processes in the developing HPA-axis.

Age and cortisol expression are linked, due to developmental hormonal changes in relation to the HPA-axis throughout the life span (Kudielka & Rohleder, 2011). In youth, participant age has been shown to predict cortisol output in various settings (Allwood et al., 2011; Shirtcliff et al., 2005; Stroud et al., 2009).

Puberty marks a critical period of human development, with an advancing HPG-axis maturation to enable reproduction and related processes. Child age and pubertal state are thus important covariates for a sample of developing children and adolescents, as previously reported (Gunnar & Vazquez, 2006; Netherton et al., 2004; Oskis et al., 2009). Our data point towards a linear relationship of increasing cortisol output with increasing child age and pubertal stage. This is consistent with a study from Zhang and colleagues (2016), which found adolescents in late/post-pubertal status showed higher cortisol AUC values compared to pre/early-pubertal participants.

Other covariates recommended for integration in salivary bioscience studies include BMI (Dockray et al., 2009; Marceau et al., 2019) and sex (Oskis et al., 2009). For our sample, these variables were not predictive of cortisol. Regarding sex, our findings are

consistent with Kudielka and Rohleder (2011) who state that, sex differences are typically observed when investigating stress reactivity, while basal cortisol activity is usually not affected by participant sex. This is coherent with findings of studies with children, similar to ours (Imeraj et al., 2012). The present sample did not show any association between cortisol and BMI. Although BMI and cortisol are often associated, they do not always emerge and might be in interaction with a specific BMI range (Ruttle et al., 2013).

According to Stewart and Seeman (2000) and Rotenberg et al. (2012), who advocate at least three weekdays of cortisol sampling for a stable estimate of CAR, this study sampled a full week including week- as well as weekend days. Altered cortisol expression on weekends compared to weekdays has been stated previously (e.g. Thorn et al., 2006) and is mirrored by the lower cortisol values of weekend vs. weekdays for this sample. Similar to previous observations (Segerstrom et al., 2014), our data show large inter- and intra-individual variances and day-to-day fluctuations of cortisol. ICC for CAR and diurnal AUC show that 59 to 76% of cortisol variability is attributable within-child and only 41 to 24% of variance is rooted in between-child differences. Inter- and intra-individual variances in cortisol are biologically plausible, with the understanding of being a consequence of genetic disposition. With cortisol's stable trait-like component to some extent (pointing to inter-individual differences), measuring cortisol also captures a fluctuating state-like component in interaction with the environment and daily events, explaining the high intra-individual differences of cortisol concentrations within children. After all, cortisol is not limited to a trait-like marker, as expression is prone to change with anticipated stress and daily hassles (Elder et al., 2018; Wetherell et al., 2015). This shows, that multiple days of sampling are favorable and provide an advantage in validity over findings that rely on single (and weekend) day measurements. Possibly, high cortisol variance between children and within child render it more difficult to find smaller between-child effects as hypothesized for ADHD on cortisol. We would consider

the amplitude of variances as one imaginable cause of a decreased chance to detect a relation of ADHD or ODD/CD on cortisol, which is subject to further evaluation. Reductions in model fit can equally be rooted in the observable high intra- and interindividual variances across the different days of measurement. Latent state trait modeling could be advantageous for future studies to parse out state and trait variance of cortisol in samples, especially within a longitudinal study design.

Strengths and Limitations

Cortisol expression is naturally dependent on numerous confounding variables, many of them beyond researcher's control. Sampling in children and adolescents in general, and especially at home in their family environment, renders it difficult to control how and when saliva is sampled. To address this challenge, we designed individualized sampling schedules and used dual reporting of subjective and objective sampling times to promote adherence. We also employed an intensive sampling schedule over multiple days, to help reduce measurement error and enhance the validity of our cortisol measures by decreasing the influence of short-term HPA-axis susceptibility.

One of our objectives was to compare different manifestations of child symptoms in their relations to HPA-axis function, particularly in regards to subtypes of ADHD. We lacked sufficient participants in the ADHD-HI subtype group to appropriately examine differences of ADHD symptom expression separately by subtype. Analyses of parent-reported symptoms (versus previous diagnostic report) revealed only few children with HI Subtype in this sample. While not rare in ADHD diagnosis, the aspect of hyperactivity/ impulsivity decreases with age and brain maturation (APA, 2013). Other results on ADHD and cortisol rely on samples with more, or even exclusively, children with symptoms of ADHD-HI (Angeli et al., 2018; Blomqvist et al., 2007; Imeraj et al., 2012; Isaksson et al., 2012; Okabe et al., 2017;

Vogel et al., 2017). Whether all children with ADHD show similar patterns of cortisol expression, or whether subtypes of ADHD –as a proxy for their symptom expression- are psychoneuroendocrinologically distinct, requires further clarification.

The a priori power analysis we conducted before the study for an estimated medium effect size (f^2 =.15) indicated sufficient power with N= 100 participants. Post hoc power analyses revealed a statistical power of .99 for medium effects (f^2 =.15) and .61 for smaller effects (f^2 =.04). Therefore, for small effects, the presented analyses have partly been underpowered. The number of children taking part in this study can be seen as representative, especially in light of the intensive study design, but are typically not quite sufficient to recommend MLM-SEM. In addition to power issues, small sample sizes increase the risk for bias and impair solution propriety (Wolf et al., 2013). Some of these challenges have been met by the repeated measures and the use of dependent latent variables. The statistical approach of MLM-SEM is necessary given the data structure and future research should aim to achieve a larger sample size, e.g. N > 200 (Kline, 2015).

More participants in general and especially more participants with specific symptoms would have increased external validity. In light of generalizability, we would like to highlight some sample characteristics, to enable a better interpretation of results. By recruiting in public schools and via practitioners seeing children with ADHD, a good representation of the general population was targeted. Nevertheless, a high proportion of our participants were of high SES. It remains open for further clarification, if the present results would be mirrored in a sample with low SES or early life adversities. High SES could serve as a protective mechanism, as an unfavorable environment and early adversities pose a risk for HPA-axis dysregulation (Bauer et al., 2002; Essex et al., 2002; Repetti et al., 2002) and low SES may have a direct effect on HPA-axis dysregulation (Clearfield et al., 2014; Zalewski et al., 2012). High SES in turn, often linked to higher family income, a safer neighborhood, favorable

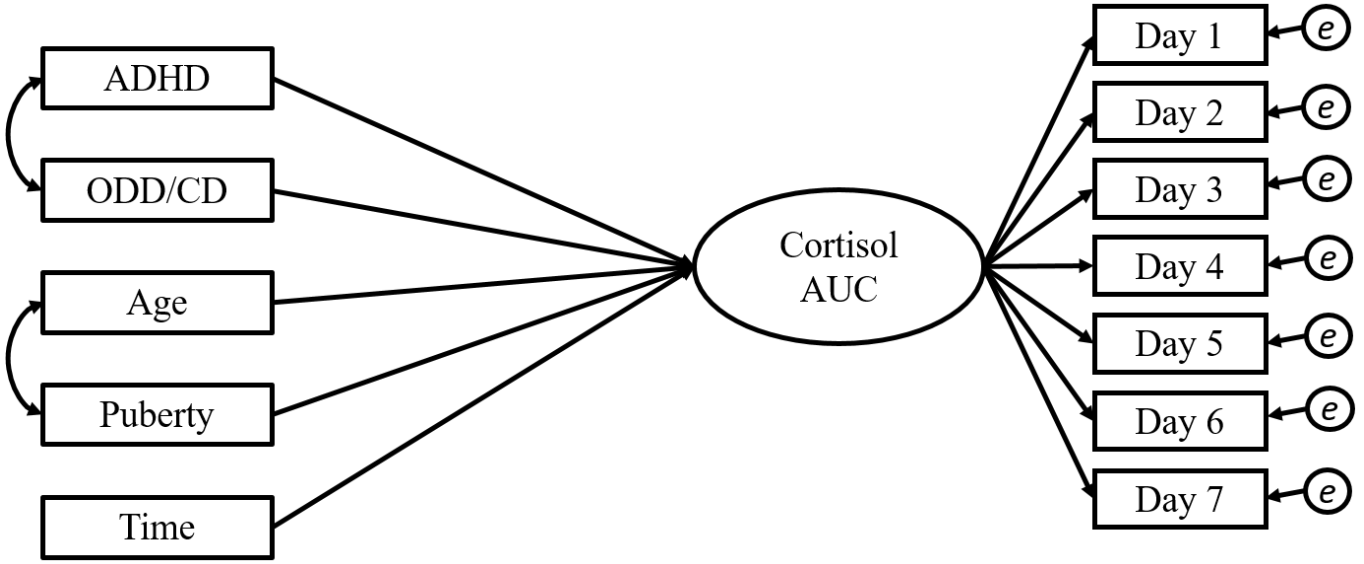
school system, and higher education of parents', often rendering preferable educational styles more likely, might be an underestimated part in the puzzle of healthy HPA-axis regulation due to environment interaction, maybe enabling resilience. The intensive study design in comparison to the low study compensation (round USD 50 for the whole week), might have attracted families with highly involved parents as well as families' handling their daily lives well, despite the child's ADHD or ODD/CD symptoms. Very strained parents, encountering stressful daily lives, might have been less likely agree to participate in an intensive saliva sampling study, due to limited capacity. Future studies putting emphasis on sample environment and comparison of cortisol in high vs. low SES in relation to child psychopathology could advance clarification of ongoing mechanisms.

Despite limitations, our study proposes methodological improvements for future research on this topic in terms of number of cortisol samples per day, multiple days of sampling, weekday and weekend assessment, incorporating comorbidities of ADHD, considering ADHD subtypes, and controlling for confounding variables. The study design provides high ecologic validity, through sampling in children's natural environment during school weeks. With respect to diurnal, circadian cortisol, we suggest to evaluate the previously reported associations of ADHD or ODD/CD with HPA-axis dysregulation with caution, until the research question can be re-assessed in a similar study design, including covariates known to play an important role, and improved methodological aspects of the present and previous findings.

Tables and Figures

Figure 1

Conceptualized Model with Main Predictors (ADHD, ODD/CD) and Covariates (Child Age, Pubertal Stage, Time Duration) Hypothesized to Predict Cortisol AUCs.



Note. Predictors AHDH and ODD/CD: r = .54; Age and Puberty: r = .71; Cortisol AUC represents the three different latent variables of Cortisol indices: Diurnal AUC, CARg, CARi.

Table 1

Sample characteristics of participating children

	ADHD *n*= 65				Comparison *n*= 80			
			Range				Range	
Variable	*n*	*M* (*SD*)	Potential	Actual	*n*	*M* (*SD*)	Potential	Actual
Age	65	11.77 (2.08)		8 - 15	80	11.27 (1.94)		7 - 16
Pubertal state	60	1.72 (.83)	1 - 4	1 - 3.6	78	1.74 (.82)	1 - 4	1 - 3.8
ADHD	57	3.10 (.54)	1 - 4	1.90 - 4.00	73	1.77 (.49)	1 - 4	1 - 3.1
ADHD-IN	24		1 - 4	Cutoff > 2				
ADHD-HI	5			Cutoff > 2				
Combined Type	28		1 - 4	Cutoff > 2				
ODD/CD	26	1.92 (.47)	1 - 4	1.00 - 3.11	73	1.38 (.35)	1 - 4	1 -2.52

Note. ADHD: Attention-Deficit/Hyperactivity Disorder; ODD/CD: Oppositional Defiant Disorder/Conduct Disorder.

Table 2

Summary of Model Fit (final SEM Model). Predictors: ADHD, ODD/CD*, Child Age, Pubertal State and Time Duration of First to Last Sample*

	Model Fit Indices			
Dependent variable	χ^2 (*p*-value)	CFI/TLI	RMSEA	SRMR
Diurnal AUC				
Model a (7 days)	65.877 (*p*= .026)	.917/ .894	.062	.076
Model b (weekdays only)	43.340 (*p*= .012)	.917/ .884	.079	.054
CAR ground				
Model a (7 days)	98.158 (*p*= .004)	.874/.851	.065	.105
Model b (weekdays only)	27.536 (*p*= .3297)	.987/ .982	.029	.047
CAR increase				
Model a (7 days)	64.111 (*p*= .025)	.834/.789	.062	.084
Model b (weekdays only)	29.520 (*p*= .242)	.928 /.899	.039	.064

Note. AUC: Area Under the Curve; CAR: Cortisol awakening response; Model fit indices (and recommended acceptance criteria): CFI: Comparative Fit Index (> .90); TLI: Tucker Lewis Index (> .90); RMSEA: Root Mean Square Error of Approximation (< .08); SRMR: Standardized Root Mean Square Residual (< .10); Used Estimator: Robust Maximum Likelihood (MLR).

Table 3

Summary of Model Results for all Cortisol Indices

	Cortisol Indices					
	Diurnal AUC		CAR_g		CAR_i	
Predictors	*β* (SE)	95% CI	*β* (SE)	95% CI	*β* (SE)	95% CI
Child age	.331 (.145)*****	[0.047, 0.615]	.261 (.131)*****	[0.005, 0.518]	.101 (.181)	[-0.253, 0.455]
Pubertal stage	.268 (.147)	[-0.020, 0.556]	.118 (.149)	[-0.175, 0.410]	.304 (.151)*****	[0.009, 0.599]
Duration (time first to last sample)	.044 (.103)	[-0.158, 0.246]	.033 (.086)	[-0.135, 0.201]	.031 (.107)	[-0.179, 0.241]
ODD/CD	.223 (.138)	[-0.049, 0.494]	.063 (.172)	[-0.274, 0.401]	.275 (.171)	[-0.060, 0.610]
ADHD	– .132 (.127)	[-0.380, 0.116]	– .216 (.135)	[-0.480, 0.048]	– .069 (.146)	[-0.355, 0.216]

Note. ADHD: Attention-Deficit/Hyperactivity Disorder (mean scores); ODD/CD: Oppositional Defiant Disorder/Conduct Disorder (mean scores); *β*: Standardized regression coefficient; SE: Standard error; CI: Confidence Interval.

**p* < .05 ***p* < .01

Table 4

Summary of Measurement Model Fit. Confirmatory Factor Analysis of the Latent Variable Representing Days of Cortisol Measurement.

	Measurement Model Fit Indices			
Dependent variable	χ^2 (*p*-value)	CFI/TLI	RMSEA	SRMR
Diurnal AUC				
Model a (7 days)	34.856 (*p*= .002)	.931/ .896	.104	.070
Model b (weekdays only)	8.841 (*p*= .116)	.984/ .968	.075	.032
CAR ground				
Model a (7 days)	48.721 (*p*= .000)	.870/.806	.134	.083
Model b (weekdays only)	1.704 (*p*= .888)	1.00/ 1.033	.000	.014
CAR increase				
Model a (7 days)	39.763 (*p*= .000)	.793/.689	.115	.076
Model b (weekdays only)	8.869 (*p*= .114)	.936 /.872	.075	.051

Note. AUC: Area Under the Curve; CAR: Cortisol awakening response; Model fit indices (and recommended acceptance criteria): CFI: Comparative Fit Index (> .90); TLI: Tucker Lewis Index (> .90); RMSEA: Root Mean Square Error of Approximation (< .08); SRMR: Standardized Root Mean Square Residual (< .10); Used Estimator: Robust Maximum Likelihood (MLR).

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8 Study II: Daily Family Interactions and Well-Being in Families of Children with ADHD

Background: Parents of children with attention-deficit/hyperactivity disorder (ADHD) often suffer from elevated levels of family challenges (Harpin, 2005; Johnston & Mash, 2001; Whalen et al., 2011). This can undermine positive family interactions and lead to negative behavior towards the child and negative emotional experiences. Due to symptomatic behavioral problems, such as impulsivity and hyperactivity, and common comorbidity of oppositional and aggressive behavior, parents of children diagnosed with ADHD may have difficulties to maintain positive and affectionate relationships with their children. The aim of this study was to investigate how child symptoms as well as negative or positive parent behavior are related to child and parent well-being.

Method: *N*=130 children between 8 and 16 years (37% girls) and their parents, comprising an ADHD group (*n*= 55 parent-child dyads) and comparison group (*n*=75 parent-child dyads), reported on the child's symptoms, positive and negative behavior towards the child as well as positive and negative affect (3 times per day, across 7 days) using a smartphone application. Multilevel within-subject mediation analyses were conducted to test, whether positive and negative parent behavior would mediate an association between child symptoms and positive and negative affect, for children and parents, respectively.

Results: As hypothesized, child symptoms significantly predicted more negative as well as less positive parental behavior towards the child in all models. Negative parent behavior also predicted higher parent negative affect and indicated a trend for a decrease in parent positive affect.

Conclusion: The current data emphasize the impact of children's behavioral symptoms for healthy family relationships. Although children with symptoms of neurodevelopmental disorders profit from positive and favorable parenting, child symptoms are related to unfavorable parental behavior. Targeting parental behavior in clinical practice and fostering positive experiences is important for child and parent mental health in the context of child ADHD.

Daily Family Interactions and Well-Being in Families of Children with ADHD

Family relationships matter, as they – ideally – provide children the healthy environment to develop important skills. Continuous negativity and strain can have a lasting impact and result in dysfunctional relationships that are neither beneficial for children (Hinshaw & Beauchaine, 2015; Johnston & Jassy, 2007), nor parents (Hutchison et al., 2016; Lovell et al., 2012). In face of child symptoms of attention-deficit/hyperactivity disorder (ADHD) and frequently comorbid symptoms of oppositional defiant disorder (ODD) the maintenance of positive, functional parent-child relationships is more difficult. ADHD symptoms of inattention, hyperactivity and impulsivity can be challenging for parents. The deficits in self-regulation require parents to manage child behavior to a greater extent than it is the case for non-affected children. This additional effort has been associated with parenting stress and dysfunctional parent behavior (Deater-Deckard, 2004; Hutchison et al., 2016). Especially ADHD symptoms have been related to more distressed parent-child interactions (e.g. Cussen et al., 2012; Deault, 2010 for a review). Families of children with ADHD are at risk for higher degrees of family conflict, dysfunctional interactions and maladaptive parenting practices and behavior towards the child (Deater-Deckard, 2004; Hutchison et al., 2016; Morgan et al., 2005; Theule et al., 2013). Although ADHD is a chronic disorder (e.g. Kendall, 1998), symptoms can fluctuate between days or within a single day, according to the child's environment and experiences (Whalen et al., 2006a).

The present study investigates daily experiences and family relationships with a momentary assessment approach, where participants answered questionnaires using a smartphone application, three times per day, across seven consecutive days. Considering child as well as parent report and perspectives, we assessed momentary child symptoms, positive and negative behavior towards the child and momentary positive and negative affect in parents and their children with ADHD as well as comparison families. Disentangling mechanisms by assessing

naturally occurring exchanges in the families' home environment enables exploring potential mediating factors of the relationship between child symptoms, child and parent well-being and the nature of family interactions.

Family Interactions and Child Symptoms

Family interactions are likely impaired through a child with externalizing symptoms, such as ADHD, ODD or CD (De Haan et al., 2013; Johnston & Mash, 2001). Bi-directional, transactional frameworks where children and parents influence each other (Hutchison et al., 2016; Sameroff & MacKenzie 2003), highlight the dynamic influences between family members and especially, between children and their family environment (Campbell et al., 2014). In the presence of child pathology there is a higher risk for dysfunctional interactions due to child, as well as parent factors (e.g. Dey et al., 2012; Heath et al., 2014). Previous research established this transactional connection between child symptoms and parental reactions, further worsening child symptoms and increasing relationship strain.

Although conflict and difficulties in child raising are not uncommon, mothers of children with ADHD consistently report poorer family functioning, compared to mothers of children without diagnosis (Deault et al., 2010; Gerdes & Hoza, 2006). The described family disruption mostly concerns problematic behaviors and delayed development, characterized through academic underachievement and learning problems, but also social challenges through episodes of aggression, problems with peers, and isolation from extended family as well as family conflict (Kendall, 1998), putting additional strain on the challenge to raise a child (Theule et al., 2013).

Due to typical symptoms of ADHD, such as hyperactivity/impulsivity or inattention, affected children often experience conflict with parents, siblings or peers, show difficulties to regulate their emotions or cause unwanted interruptions in the daily family routine.

Frequently, items are forgotten, tasks are not being finished, or the child does not seem to listen (e.g. Harpin, 2005). A deficit in executive functioning (maintaining attention, lack of organization and planning ahead, changing from one task to another) easily poses an interruption to basic processes - like getting ready in the morning or being on time-, which is challenging the patience of family members. Frequent comorbidity of oppositional defiant disorder (ODD) and conduct disorder (CD) symptoms, creates an additional difficulty for maintaining positive parenting. Family interactions for children with ADHD have been found to be characterized by more frequent disagreement and discord with their mothers (Whalen et al., 2006a), with child symptoms leading to a higher risk of inadequate parenting (e.g. Wirth et al., 2019). Compared to non-affected peers, children with ADHD are more often non-compliant and have difficulties adapting to change. This has been found to be stressful for parents, increasing the likelihood for negative parenting practices (De Wolfe et al., 2000; Whalen et al., 2011), high conflict, negativity and more control (Wiener et al. 2016). Mothers of children with ADHD report higher feelings of incompetence and frustration when facing difficulties and special needs because of the children's inattention and oppositional–conduct behaviors (McLaughlin & Harrison, 2006; Podolski & Nigg, 2001). An experimental study found that interacting with children displaying symptoms of ADHD and CD, compared to children without symptom behavior, was related to heightened alcohol consummation directly after the interaction for stress relief (Lang et al., 1989; Pelham & Lang, 1993).

Engaging in compromised or even adverse parenting practices and behaviors are more common in parents of children with ADHD (Whalen 2006b; Wymbs et al., 2015). Children's symptoms of ADHD and especially comorbid ODD and CD, can render it difficult for parents to react with sensitivity and responsiveness towards the child (Johnston & Mash, 2001). Parental responsiveness predicts better negative affect regulation in children (Davidov & Grusec, 2006) and self-regulation in general (Deater-Deckard, 2014), a crucial skill in the

context of ADHD. The lack of sensitive and responsive parenting is consecutively related to unfavorable consequences, like behavioral difficulties in later childhood (Berry et al., 2016; Bornstein and Manian, 2013; Johnston et al., 2002) and can contribute to the persistence and amplification of ADHD symptoms (Campbell et al., 2014). Nicholson and colleagues (2005) found parents of children with behavioral problems to use more punishment and harsher parenting techniques than parents of children without behavioral difficulties. Authoritarian parenting, or in the other extreme- too permissive parenting have both been shown to be disadvantageous for children's development compared to authoritative parenting (Baumrind et al., 2010). Especially hostile parenting (due to early disruptive child behavior) was associated with later child ADHD (Harold et al., 2013). Studies show that parents of children with ADHD adopt less positive parenting practices, like laughing or playing (Wymbs et al., 2015) and heightened use of commands and critical feedback (Johnston & Lee-Flynn, 2011). Children with the diagnosis experience less parental warmth and engagement (Tripp et al., 2007) as well as less positive reinforcement for appropriate behavior. Children profit from warm, responsive and sensitive parenting as well as a positive regard, leading to decreased ADHD symptomology as well as less social problems or peer rejection (Hurt et al., 2007; Keown, 2012). So maladaptive parenting practices ultimately lead to further behavior problems and deficits (e.g. executive functioning) in children (Deater-Deckard, 2004; Hutchison et al., 2016; Morgan et al., 2005). Compromised parent-child interactions, can not only adversely affect children, but also parents themselves, furthering the image of a potential vicious cycle: daily conflict between meeting the child's needs and the environmental demands manifests in decreased mental health, through sleep disorders, anxiety, stress, or social withdrawal (Avrech Bar et al., 2018; Johnston & Mash, 2001). Alongside parenting stress, parents of children with ADHD show higher rates of depression, divorce, disrupted parent-child relationships, feelings of parental incompetence, parent psychopathology, and

life stress than parents of children without ADHD (DuPaul et al., 2001; Harpin, 2005; Johnson & Reader, 2002; Margari et al., 2013).

In conclusion, child ADHD symptoms have been identified as a factor that can alter the affective tone and behavioral content in family interactions (Whalen et al., 2006a). Whether everyday exchanges are of positive, loving nature, or conflict-laden and prone to dysfunctional matters for a healthy parent-child relationship and subsequently, the well-being of children and their parents.

Momentary Affect

The relationship between child symptoms and subsequent parenting stress, leading to maladaptive parenting practices and in turn, more child symptoms, has been addressed by previous research (Deater-Deckard, 2004; Hutchison et al., 2016; Morgan et al., 2005; Theule et al., 2013). This study examines the emotional and mood components in family interactions. In order to understand the well-being of children and parents in families with child ADHD or ODD/CD, the nature of interactions and consequent feelings in parent-child relationships, we shift the focus on positive and negative affect and whether affect is directly related to child symptoms or mediated through parental behavior. Well-being is commonly measured through positive and negative affect, or more precisely, the definition of subjective well-being has been stated as the ratio of positive to negative affect over time (Diener, 2009; Larsen, 2009). Positive and negative affect are important for mental and physical health (e.g. Diehl et al., 2011; Pressman & Cohen, 2005). The important role extends to a contribution to e.g. recovery from surgery and coping with pain (Seebach et al., 2012), the buffering effect of social support on stress (Civitci, 2015), resilience and mindfulness (Montero-Marin et al., 2015), psychiatric symptoms (Bekh Bradley et al., 2015), feelings of self-efficacy (Schutte, 2013), life satisfaction (Singh & Jha, 2008), as well as social interactions and cooperation

(Kuhbandner et al., 2010). Positive and negative affect are independent and distinct dimensions (e.g. Diener & Emmons, 1984; Dowd et al., 2009).

Family interactions that cause positive or negative affect are an important target of investigations between child pathology and family well-being. The only previous momentary assessment study targeting affect found that children with ADHD, even if on medication, reported more negative affect than their peers without ADHD (Whalen et al., 2006a).

The Present Study

This study directly connects to previous research (e.g. Rosen et al., 2015; Whalen et al., 2006a; 2011) who concluded the need for a further investigation of parents' daily perceptions of symptoms and reactions towards their children in the home setting. We propose a model that includes the child's and parent's view regarding daily interactions and experiences, reported across seven days. Momentary assessment allows measuring family interactions in the ecologically valid environment of families, capturing naturally occurring exchanges of family members several times a day (Shiffman et al., 2008; Trull & Ebner-Priemer, 2014).

We expected that higher ratings of child symptoms are associated with an increase in negative affect and a decrease in positive affect in parents and children. In addition to this direct effect between symptoms and momentary affect, we hypothesized that the relationship between child symptoms and momentary affect will be mediated through parental behavior. Higher (parent) ratings of child symptoms are thought to predict more negative parent behavior and less positive parent behavior towards the child (path *a*). Negative parental behavior is expected to predict higher negative affect and lower positive affect. For positive parent behavior, we expected a relation with more positive affect and less negative affect in children and parents (path *b*).

Method

Participants

The sample consisted of *N*= 130 children (38% girls) between 8 and 16 years of age (*M*= 11.5, *SD*=1.9) and one of their parents (90% mothers) who participated in the LAMA-Study ("Life with ADHD in Momentary Assessment") in Switzerland.

Children either participated in the ADHD-group (*n*=55) or in the comparison group (*n*=75). All parents are biological parents. The majority of the participating parents were married (70%), the rest were either single, divorced, separated or widowed, round 1% stated to be remarried.

Recruitment and inclusion/exclusion criteria

Children had to be 7 to 16 years of age and attending school in Switzerland. For the ADHD group an official ADHD diagnosis (by a physician or psychologist) had to be present. Children without an official ADHD diagnosis were assigned to the comparison group. Other clinical diagnoses had to be reported.

Procedures

Recruitment took place via flyers that were distributed at schools, ADHD specialists and ADHD parenting organizations as well as articles in parent magazines and newspapers. Telephone screening was used to ensure that prospective participants met the inclusionary and exclusionary criteria. For children in the ADHD group, details about the diagnosis were noted and assessed (subtype, year of diagnosis, specialist who confirmed diagnosis); for children in the comparison group, the absence of an ADHD diagnosis was inquired. Symptoms or Diagnosis of ODD or CD were not an exclusion criterion for neither of the groups. All test-weeks were scheduled during school-weeks, not vacation.

During a home visit (90 minutes) the study information was repeated and the participating child and parent received smartphones. Child and parent were both asked to try out test questions and answering formats. Only after this procedure, final Informed Consent from the child was obtained. Data collection took place at home for 7 days in the following week, always starting Monday between November 2017 and July 2018. Each child and parent answered smartphone questions three times a day: In the morning before school or work (time programmed for each family individually, to accommodate different morning routines), in the afternoon (4:30 pm) and the evening (7:00 pm). Participants had a 90-minute window to respond to questions after the alarm. Answering questions took on average 3 minutes per time point; children had less questions than parents. Children received 50 US Dollars for their participation at the end of the study (voucher from a local department or bookstore).
This study was approved by Swiss cantonal ethics review board; Rules of ethical standards and safety were followed. All parents and children above the age of 14 gave written and oral consent; children below the age of 14 gave oral consent to participation. All children gave consent independent from their parents.

Measures

Child Symptoms

Parents rated the following child symptoms, "My child…": (1) had difficulties to start with a task, (2) had difficulties to finish (3) had difficulties to remember everything, (4) had difficulties coping with new and difficult things, (5) had difficulties to control his/her words and feelings, (6) had difficulties waiting his/her turn, (7) had difficulties listening attentively (8) had difficulties to make an effort for something, (9) had an outburst of rage or threw a tantrum, (10) cried a lot, (11) screamed out loudly (12) was aggressive. The response options consisted of a scale ranging from 0 (*not at all*) to 7 (*very much*). Cronbachs α = .91.

Momentary Affect

Negative affect was measured with the following items: "At this moment, I feel…" (1) ashamed, (2) agitated or restless, (3) angry or irritable, (4) anxious or worried, and (5) stressed (6) frustrated. Negative affect items were the same for parents and children, except for (6) frustrated, which was removed from children's scale after a pre-evaluation revealed concerns of comprehension. Positive affect was measured with the following items: "At this moment, I feel…" (1) happy, and (2) satisfied. Each affect item was presented to the participant on a unique screen. The chosen items were adapted from the children's version of the Positive and Negative Affect Schedules (PANAS-C; Laurent et al., 1999). Items were rated on a 7-point scale from *not at all* to *very much* and were combined to create negative and positive affect summary scores, respectively. Parent negative affect Cronbachs α = .85, Child negative affect Cronbach α = .81. Parent as well as child positive affect Cronbachs α = .80.

Parent Behavior towards the Child

Parents self-reported on the following items describing their behavior towards the child: (1) anger (2) disappointment, (3) impatience, (4) irritability, (5) roughness, summarized into a scale of negative parent behavior (Cronbachs α = .82), and (1) lovingness (2) closeness (3) being caring, summarized into a scale of positive parent behavior (Cronbachs α = .87). All items rated on a 7-point scale (*not at all* to *very much*).

Data Analyses

As shown in Figure 1, we tested whether child symptoms (X) predicted positive and negative child and parent affect (Y), mediated by positive and negative parent behavior (M). We specified multilevel within-subject mediation analyses (Level 1 = repeated measures; Level 2 = parent-child dyad) for parent momentary affect and child momentary affect respectively. The analyses were modelled with MPlus 8.4 (Muthèn & Muthèn, 2019) using the Robust Maximum Likelihood (MLR) estimator, fitting the naturally skewed data.

We followed the approach by Bolger & Laurenceau (2013). This includes group-mean centered versions of predictor, outcome and mediator variables to strip variables of all between-subject variance (Raudenbush & Bryk, 2002) to model the within-subject process - or in this case - within-*dyad* process for the participating families. All paths *a*, *b*, and *c'* were specified to have fixed and random effects. Fixed effects (intercepts) represent the results for the average participant. Random effects are expressed through the variability in participants' slopes.

The total effect (TE) was defined as follows: $c = c' + ab + \sigma_{ajbj}$. This average total effect *c* comprises three parts: *c'* equals the average direct effect, *ab* is the product of the average effects of path *a* and path *b* and σ_{ajbj} signifies the covariance of paths *a* and *b*. The mediation effect was defined as the product of average paths *a* and *b*, plus their covariance σ_{ajbj} (Kenny et al., 2003).

Initially the dataset consisted of *N*= 130 parent-child dyads. However, as commonly observed in momentary assessment studies, few participants were able to complete all 7 (days) * 3 (Questionnaires/day) = 21 assessments for this study, resulting in a final data set of *N*= 108 parent-child dyads for the present analyses (*n*= 49 with ADHD diagnosis). An a priori power analysis for a simple mediation model with three predictors (child symptoms, positive parent behavior, negative parent behavior) signaled appropriate power (> .90) to detect medium effects (f^2=. 15), α = .05, with *N*= 100 parent-child dyads. ADHD diagnoses was added as a dichotomous covariate (0 = No ADHD diagnosis, 1= ADHD diagnosis) for all slopes of the respective associations (path a, path b, path c') and did not show to significantly influence the results.

Results

In sum, the key hypothesis to be tested was whether child symptoms would predict positive and negative parental behavior, which in turn would predict positive and negative

affect in children and parents. Positive and negative parent behavior are not understood to be the absence of the respective other concept, but represent separate concepts that were measured with distinct items. The same applies, for positive and negative affect. Therefore, the research question was modelled through four different model tests, investigating the relationships between: 1) More Negative Parent Behavior and more Negative Affect 2) More Negative Parent Behavior and less Positive Affect 3) More Positive Parent Behavior and less Negative Affect 4) More Positive Parent Behavior and more Positive Affect. All four associations were analyzed together, however separate for children and parent's affect.

Multilevel Model of Child Symptoms Predicting Positive and Negative Affect, Mediated by Parent Behavior

We accounted for the covariation of outcome variables (Child Negative Affect with Child Positive Affect: r =-.251, p = .000; Parent Positive Affect with Parent Negative Affect: r =-.262, p = .000) as well as mediators (Positive Parent Behavior with Negative Parent Behavior: r =-.181, p = .000). In order to account for multiple hypotheses testing in this study we applied a Bonferroni-Holm correction (Holm, 1979) and recommend to reject any reported results of p > .017, due to the multitude of hypotheses to be tested when performing mediation analyses. Results of the conducted model for parents and children are visible in Table 1 and Table 2, respectively.

Results regarding Children

Child symptoms predicting Parent Behavior (path a). On average, higher symptom ratings (X) predicted elevated negative parent behavior (M). Each additional increase on the symptom scale predicted parents' negative behavior to be .650 units higher (*SE* = 0.08, z = 7.64, p = .000). Heterogeneity is large, with a *SD* of .14 for the average effect. For this association, 95% of children have slopes of in the predicted range of .38 to .92. On average, higher symptom ratings (X) also predicted less positive parent behavior (M). Each additional

increase on the symptom scale predicts parents' positive behavior towards the child to be -0.451 units lower (*SE* = 0.11, *z* = -4.26, *p* = .000). With an *SD* of .34 for the average effect, 95% of children have predicted slopes of in the range of -1.12 to .22 for this association.

Parent Behavior predicting Child Affect (path b). Neither positive, nor negative Parent Behavior (M) significantly predicted child negative or positive affect (Y). Subsequently, mediation was not observed in the child models.

Child Symptoms predicting Child Affect (path *c*'). There is an indication for a direct effect (*path c'*) of child symptoms on child affect, however, given the Bonferroni-Holm corrected cut-off of *p* > .017, the reported direct effects should be interpreted with caution. With adjustment for Negative Parent Behavior (M), symptoms were associated with an increase in children's own negative affect (*B* = .172, *SE* = .09, *z* = 1.99, *p* = .046), with a predicted slope range of -.10 to .44 for 95% of children. After adjustment for this mediator, symptoms marginally significantly predicted a decrease in children's own positive affect (*B* = -.290, *SE* = .17, *z* = -1.74, *p* = .082). For this relation, slopes were predicted to range from -.63 to .05 for 95% of children. The following child model total effects (TE) emerged for child symptoms (X) and the respective mediator (M) and dependent variables (Y): TE Negative Parent Behavior (M) and Child Negative Affect (Y): *B* = .141, *SE* = .08, *z* = 1.76, *p* = .078; TE Negative Parent Behavior (M) and Child Positive Affect (Y): *B* = -.234, *SE* = .14, *z* = -1.64, *p* = .099; TE Positive Parent Behavior (M) and Child Negative Affect (Y): *B* = .206, *SE* = .08, *z* = 2.30, *p* = .021; TE Positive Parent Behavior (M) and Child Positive Affect (Y): *B* = -.309, *SE* = .22, *z* = -1.43, *p* = ns.

Results regarding Parents

Child symptoms predicting Parent Behavior (path a). Similar to the observed significant association in the child model, the association between child symptoms and parent behavior shows similar results in parent models. For the average parent participant, child

symptoms significantly predicted an increase in negative parent behavior (*B* = .640, *SE* =.10, *z* = 6.70, *p* = .000) and a decrease in positive parent behavior (*B* = -.448, *SE* = .10, *z* = -.4.37, *p* = .000) with almost the same slope range as observed in the child models.

Parent Behavior predicting Parent Affect (path b). Parent behavior (M) was associated with parent momentary affect (Y) in two cases: Negative parent behavior predicted heightened parent negative affect (*B* = .421, *SE* = .13, *z* = 3.37, *p* = .001) and marginally significantly predicted parent lowered positive affect (*B* = -.537, *SE* = .31, *z* = -1.73, *p* = .084). The predicted slope range for 95% of parents was 0.05 to .79 for negative affect and -0.83 to -0.06 for positive affect.

Positive parent behavior did not show an association with parent affect.

The relationship between child symptoms, negative parental behavior and negative parent affect signaled a significant mediation effect (*B* = .281, *SE* = .12, *z* = 2.40, *p* = .017), however, given the Bonferroni-Holm correction, we have to reject this result as non-significant. There was no indication, that the relationship between child symptoms and parent positive affect would be mediated by negative parental behavior in this study.

Child Symptoms predicting Parent Affect (path *c*'). No direct effect (path *c*') was observed in the parent models, indicating that child symptoms were not directly associated with parent affect, after controlling for parental behavior. None of the parent models showed a significant TE for child symptoms (X) and the respective mediator (M) and dependent variables (Y): TE Negative Parent Behavior (M) and Parent Positive Affect (Y): *B* = -.108, *SE* = .15, *z* = -.72, *p* = ns; TE Positive Parent Behavior (M) and Parent Negative Affect (Y): *B* = -.119, *SE* = .13, *z* = -.95, *p* = ns; TE Positive Parent Behavior (M) and Parent Positive Affect (Y): *B* = .431, *SE* = .39, *z* = 1.11, *p* = ns, except for a trend concerning the mediation model

of child symptoms, negative parental behavior (M) and Parent negative affect (Y): $B = .141$, $SE = .08$, $z = 1.76$, $p = .079$), which does not withstand the recommended Bonferroni-Holm correction.

Discussion

The aim of this study was to investigate whether parent-reported child symptoms would be related to a decreased positive and increased negative parent behavior, as well as decreased positive and increased negative affect in parents, but also children themselves. In addition to a direct effect for child symptoms on momentary affect, we hypothesized that this relationship would be mediated by parent behavior. We found significant associations between child symptoms and parent behavior. As hypothesized, parents who rated higher child symptoms significantly reported more negative parental behavior as well as less positive parental behavior towards their child in all models. The hypothesized indirect effect between child symptoms and positive and negative affect via parental behavior only emerged for parents' negative behavior predicting own negative affect. No direct effects between child symptoms and parent affect have been observed in the presented analyses. For children, neither a direct effect between child symptoms and own positive and negative affect, nor an indirect effect via parental behavior emerged. Our research connects to other research groups that report an association between child symptoms and parent behavior (Cussen et al., 2012; Deault, 2010; Hutchison et al., 2016; Johnston & Mash, 2001; te Brinke et al., 2017; Whalen et al., 2006a; 2006b; 2011).

The observed significant effect between momentary child symptoms and an increase in negative parent behavior and a decrease in positive parental behavior, across all analyses is in line with previous findings (Wymbs et al., 2015). The present results suggest that the effect of child symptoms on parent affect could be mediated by parent negative behavior. Other studies have observed a direct effect of child symptoms on parents' emotional state, however

assessing negative maternal mood and not in a home-assessed diary design investigating family interactions, but with mood inducing techniques like video clips and vignettes (Gerdes & Hoza, 2006).

Progress to investigate daily experiences and interactions in the special population of children with ADHD and their families, has especially been made by Whalen and colleagues: Children with ADHD as well as their parents showed elevated negative affect compared to controls. Mothers of ADHD children more frequently display anger towards children with symptoms and report more frequent conflict (Wahlen et al., 2006a; 2006b). The bidirectional character of parent-child exchanges is particularly manifest in the finding that mothers of children with ADHD are more often angry when with the child. At the same time, children with ADHD respond more sensitively to maternal anger with high stress and longer recovery (Whalen et al., 2009). Furthermore, child ADHD symptoms are related to maternal distress (Whalen et al., 2011). The present study directly continues researching the relation between child ADHD, parent behavior and momentary affect. Whalen and colleagues observed that children with ADHD (symptoms) showed more negative affect. This did not emerge in our sample. However, we tested if negative affect was predicted by momentary occurring symptoms, what was not the case in their study. Interestingly, when parents reported negative behavior towards the child, the also rated an increase in parent negative affect, but not a decrease in positive affect. Positive and negative affect are distinct dimensions and as previous literature defined, one is not merely the absence of the other (Diener & Emmons, 1984). We would judge it plausible, that the chosen items for positive affect (being happy, being satisfied) have not been rated to a lesser extent only because parents rated higher negative affect dimensions at the same point. Being happy in general, whilst e.g. being momentarily angry at the child, do not necessarily exclude one another.

Strengths & Limitations

The present sample is characterized by a socio-economic status (SES) that is considered medium- to very high. The results therefore need re-evaluation in contexts with additional life stress, such as low-income and low SES. Families in these settings face further risk factors which have been associated with higher stress (Noel et al., 2008) and dysfunctional family relationships (Qi & Kaiser 2003) or limited resources for children with special needs (Pinderhughes et al., 2000).

The interpretations of parent-child interactions are correlational, and causality cannot be inferred. We suggest a theoretical model, with child symptoms predicting affect and parent behavior in order to try to shed light on the nature of family interactions occurring in families of children with externalizing behavior. Although momentary assessment designs come with many advantages, such as real-time capture of momentary processes and evading recall bias (Shiffman et al., 2008; Trull & Ebner-Priemer, 2014), we have to note that everyday interactions and psychosocial mechanisms between children and their parents are too complex to be captured in their entirety. Our study encompassed seven days, with questioning three times a day, which enabled investigating family interactions by using repeated measures, within-subject analyses. In line with Elgar and colleagues (2004), we agree that parent-child relationships are likely mediated by many genetic and environmental factors and longitudinal designs with intensive repeated measures over years and decades would allow to infer causal pathways that this study cannot provide.

To our knowledge, this is the first study to investigate child symptoms of ADHD and frequent comorbid externalizing behavior in the combination with parent positive and negative behavior to examine the effects on children's as well as parent's positive and negative affect in everyday family interactions using a momentary assessment approach. Overall, our analyses had appropriate power to detect medium effects (f^2 =.15). However, for

small effects (f^2 =.02) many more participants would have been needed. Since the presented mediation analyses modelled the within-subject process with repeated measures, a higher power, less bias and better solution propriety can be assumed, even for smaller sample sizes (Wolf et al., 2013). For mediation analyses in general, a weaker indirect effect compared to the effects of the component parts (paths *a* and *b*) is to be expected (Wolf et al., 2013). Power analyses, need to be adapted to this difference in strengths of effects within models. Future studies should therefore aim to achieve increased sample sizes to re-test the hypothesized mediation effect.

ADHD often occurs comorbid with symptoms in the spectrum of oppositional defiant disorder or conduct disorder (Beauchaine et al., 2010; Harvey et al., 2016). We therefore complemented the list of momentary ADHD symptoms by typical symptoms of ODD and disruptive behavior disorders. Aggressive, oppositional or antisocial behavior adds even more strain on the family relationships (De Haan et al., 2013), we thus recommend the inclusion of frequently comorbid symptoms in studies of child ADHD symptoms.

Conclusions

Family relationships and daily experiences are important for the development of every child. This study shows that child ADHD symptoms can have an impact on parental well-being. Parent's ratings of child symptoms predicted their own parental behavior and this, in turn, was related to parental negative affect. The effect of child ADHD on the increase of negative parent behavior towards the child and a decrease in negative positive parent behavior provides an insight why parents' of children with ADHD experiences more negative family relationships. The findings emphasize parent behavior as an important mediator of the relation between child symptoms and family well-being. The recommended treatment for children with ADHD is behavior therapy (American Academy of Pediatrics, 2011). Furthering our understanding of family functioning and reciprocal interactions between children with

behavioral difficulties and parents can help to successfully design and implement behavior therapy programs. Momentary Assessment allows us to examine micro-processes that occur during the day and has the potential to further explore and disentangle mechanisms positive as well as negative family mechanisms. Our study shows that families face a higher risk for dysfunctional relationships and negative emotional experiences in the presence of child externalizing symptoms. ADHD symptoms will induce a parental reaction in many situations, but there are better and worse strategies of how to deal with symptoms. High strain and stress through a child's psychopathology will lead to parents admitting to more negative conduct. The behavior that is displayed towards the child can be harmful for the parent-child relationship. The present results therefore emphasize the importance of training and modifying parent behavior towards the child in families of children with externalizing symptoms and to provide resources for parents of children with psychopathology in addition to treating child symptoms.

Tables and Figures

Table 1

Parent Model Results of Within-Subject Mediation Analyses

Level 1 Predictors	Dependent Variable	*B* (Intercepts)	*SE*	*p*	95% CI LL	95% CI UL
Child Symptoms						
	Negative Parent Behavior	.640	.096	.000*****	.453	.827
	Positive Parent Behavior	-.448	.103	.000*****	-.649	-.247
	Parent Negative Affect	-.140	.142	ns	-.418	.137
	Parent Positive Affect	.226	.337	ns	-.435	.886
Positive Parent Behavior						
	Parent Negative Affect	-.036	.061	ns	-.154	.083
	Parent Positive Affect	.143	.145	ns	-.141	.426
Negative Parent Behavior						
	Parent Negative Affect	.421	.125	.001*****	. 176	.665
	Parent Positive Affect	-.537	.310	.084	-1.145	.072

Note. CI= confidence interval; LL = lower limit; UL = upper limit. N = 108 parent-child dyads.

* $p \leq$ .001 after Bonferroni-Correction for multiple hypotheses testing.

Table 2

Child Model Results of Within-Subject Mediation Analyses

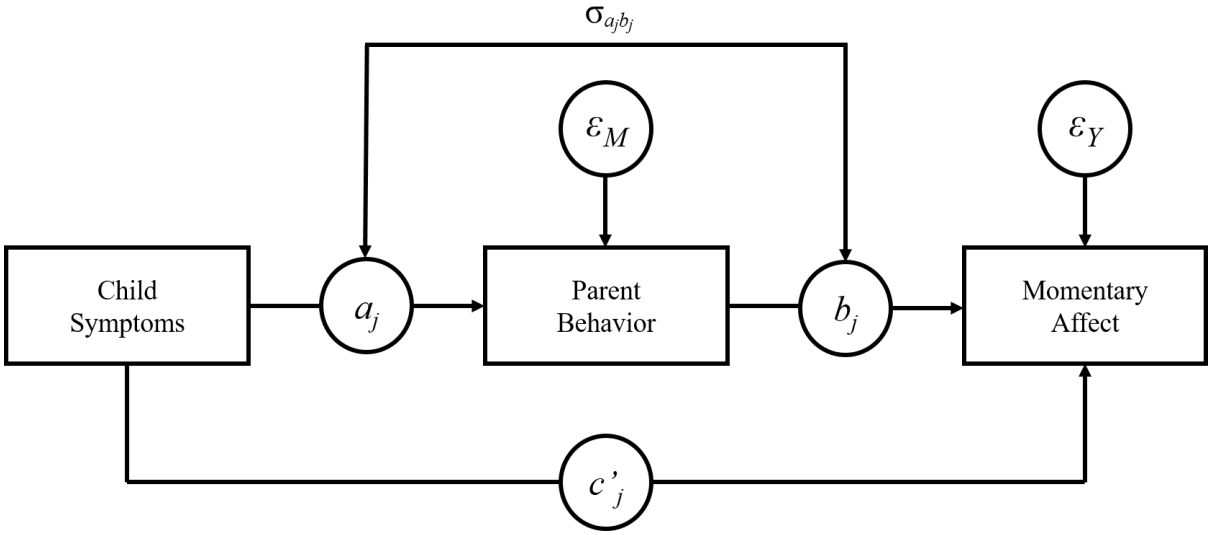
Level 1 Predictors	Dependent Variable	*B* (Intercepts)	*SE*	*p*	95% CI LL	95% CI UL
Child Symptoms						
	Negative Parent Behavior	.650	.085	.000*****	.484	.817
	Positive Parent Behavior	-.451	.106	.000*****	-.658	-.243
	Child Negative Affect	.172	.086	.046	.003	.341
	Child Positive Affect	-.290	.167	.082	-.618	.037
Positive Parent Behavior						
	Child Negative Affect	-.064	.057	ns	-.175	.047
	Child Positive Affect	.082	.078	ns	-.071	.236
Negative Parent Behavior						
	Child Negative Affect	-.057	.050	ns	-.155	.041
	Child Positive Affect	.059	.163	ns	-.260	.378

Note. CI= confidence interval; LL = lower limit; UL = upper limit. *N* = 108 parent-child dyads.

* $p \leq .001$ after Bonferroni-Correction for multiple hypotheses testing.

Figure 1

Within-Subject Mediation Analyses



Note. Figure based on Bolger & Laurenceau (2013), p. 192.

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9 Study III: Daily Family Experiences and HPA-Axis Regulation in Children with ADHD

Objective. The HPA-axis is calibrated throughout childhood to adaptively match the setting (Boyce & Ellis, 2005; Del Giudice et al., 2011), and reacts to everyday experiences (Belsky et al., 2009). To which extent positive and negative daily family interactions and child symptoms of ADHD or comorbidities are associated with HPA-axis functioning, has not yet been assessed through at-home cortisol sampling. In the presence of child ADHD and other forms of externalizing behavior, children are at higher risk to cause and experience negative family interactions (Whalen et al., 2011). The goal of this study was to investigate associations between naturalistically assessed interactions, including parent-perceived child symptoms in everyday family environments and diurnal cortisol in school-aged children, partly with ADHD and comorbidities.

Methods. 122 children (n= 53 with ADHD diagnosis) aged 7-16, provided saliva samples in the afternoon and evening over seven days from Monday – Sunday. Sample collection timing adherence was monitored using the MEMs Cap device as well as time-stamped photos. Using a smartphone application, children and one of their parents answered momentary assessment questions in the afternoon and evening around the time of saliva sampling, later assayed for cortisol. Children rated the perceived interaction quality with parents and parents and rated their perceptions of child symptoms as well as their negative behavior towards the child.

Results. Parents' self-report of negative behavior towards the child, as well as child-rated quality of interactions with mothers did not predict cortisol levels. Parent-rated child ADHD and comorbid symptoms were significantly associated with child cortisol, namely difficulties with forgetfulness, to start a task, cope with changes, listening as well as

aggression. All symptoms were related to decreased child cortisol, except for forgetfulness, which was associated with increased cortisol.

Conclusion. Specific symptoms of ADHD and comorbid externalizing problems are related to child cortisol. This is the first study linking ADHD and comorbid symptoms, assessed through daily diary report over multiple days in the family home setting, to at-home cortisol sampling. Children's experiences in everyday family life are important for our understanding of HPA-axis adaptation to the environment and stress-health links in children.

Daily Family Experiences and HPA-Axis Regulation in Children with ADHD

From early infancy, the primary caregivers help to shape self-regulation and the physiological stress response of the Hypothalamic–pituitary–adrenal (HPA)-axis (Lupien et al., 2009; Gunnar & Cheatham, 2003). The stress response systems, and their context-dependent calibration, are adaptively evolved psychobiological mechanisms that respond to specific features of childhood environments, matching the setting (Boyce & Ellis, 2005). This calibration to context has the potential of positive effects under conditions of protection and support (Marsmann et al., 2012; Slopen et al., 2014) or negative health effects under conditions of adversity (Saxbe et al., 2012).

The family plays a key role in the child's environment, due to the high amount of time children usually spend with the family members. Because the HPA-axis responds to daily experiences in the environment (Adam et al., 2006). Family interactions might offer important insights into potential associations between behavioral components and short-term changes in HPA-axis indices (Kuhlmann et al., 2016).

Whether or not children display symptoms of Attention Deficit-/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD) has a major influence on family functioning and family interactions (Campbell, 1994; Harpin, 2005; Paschall & Mastergeorge, 2016). The higher risk of distressed parent-child interactions due to child symptoms could potentially influence the HPA-axis response compared to children without symptoms. Children without externalizing symptoms may also cause difficult interactions and conflict at home, but these interactions are likely less laden with aggression or negative affect than interactions of children with ODD/CD symptoms. Children without externalizing behavior might therefore neither cause nor experience as much conflict characterized by aggressive interactions and oppositional behaviors. Children with ADHD or ODD/CD symptoms are therefore likely to cause or experience more distress in social

interactions. Daily experiences in the family may be an important variable to explain the link between child symptoms and individual characteristics with HPA-axis regulation and later health related outcomes (Adam et al., 2017).

This study evaluates whether daily experiences in the family have a direct, short-term effect on the HPA-axis. Family interactions, specifically child reported interaction quality, parent perceptions of child symptoms and self-reported parent behavior towards the child are evaluated at the time of child salivary cortisol sampling, the major circulating hormone of the HPA-axis. The investigation considers families of children with ADHD or ODD/CD as well as comparison families.

Physiological Stress System

Physiological stress levels are regulated through the social environment (Gunnar & Donzella, 2002). Researchers highlight the need for future studies about familial risk factors and adverse parenting to predict changes in HPA-axis regulation in children, especially those with behavioral problems like ADHD (Freitag et al., 2009). Children who grow up in disparaging conditions make more stressful experiences and show a heightened risk to fail to develop the self-regulatory skills needed to manage challenging interpersonal situations and stressful events. This affects the physiology of the stress system and can lead to long-term health effects, such as heart disease, cancer and other serious medical conditions (Miller, Chen, & Parker, 2011; Repetti, Robles, & Reynolds, 2011; Russek & Schwartz, 1997; Wegman & Stetler, 2009). Both, hypo- as well as hypercortisolism have been linked to health problems (Adam & Kumari, 2009; Piazza et al., 2013). A body of research has therefore addressed, how early-life psychosocial stress is associated with later physical and mental health problems (Gluckman and Hanson, 2006; Matthews and Gallo, 2011; Matthews, 2005; Repetti et al., 2002; Shonkoff et al., 2012). Long-term consequences of chronic adversity can be seen in lower basal cortisol level, which is described as a protective mechanism for the organism

(Fries et al., 2005; Saxbe et al., 2012). An expected short-term consequence of negative experiences would be increased cortisol, while positive experiences could be associated with decreased cortisol (Chrousos and Gold, 1992; De Bellis, 2001; Dockray & Steptoe, 2010; Grassi-Oliveira et al., 2008; Miller et al., 2007). However, inconsistencies of when to expect cortisol increase or decrease persist (De Bellis, 2001, Dockray & Steptoe, 2010; Grassi-Oliveira et al., 2008, Gunnar, 1992; Zhang et al., 2016). For family functioning specifically, parent-child conflict and negative experiences with parents predict lower cortisol at wakeup and a reduced diurnal slope as well as higher overall daily cortisol output (area under the curve, AUC) and increased bedtime cortisol (Engert et al., 2011; Kuhlman et al., 2016; Lippold et al., 2014; Slatcher & Robles, 2012). Similarly, positive daily interactions were shown to predict HPA-axis' and cortisol responses (Dockray & Steptoe, 2010; Sin, 2017; Lippold et al., 2014; Marsman et al., 2012).

Family Environment

Prior research shows a direct influence of family context for physiological and psychological child development. Experiences with primary caregivers are thereby particularly relevant (Keller et al., 2005; Marsman et al., 2012). Positive as well as negative parent-child experiences are thought to fluctuate throughout the day (Lippold, 2014). Lasting daily family conflict has been associated with a change in cortisol levels throughout populations of various age spans (Karlamangla et al., 2013; Zhang et al., 2016). Frequent and high-intensity forms of conflict and negative interactions can render families an environment of physiological and psychological stress (Repetti et al., 2002).

Stress can evoke bi-directional mechanisms, where higher parental stress being associated with maladaptive parenting practices, which promote conflict laden parent-child relationships (Webster-Stratton, 1990). Parental stress –eventually caused by a child's behavior or symptoms- can affect children's HPA-axis functioning (Korpa et al., 2017). The quality and

valence of parent-child interactions are not static, but vary over the day in accordance with child contact and parenting challenges and difficulties (Whalen et al., 2006). Interactions within the core family are thus suitable target points for investigations of a contextual HPA-axis response. Child and parent behaviors are likely bi-directional, mostly described as a transactional model, where child symptoms influence parental behavior and the family environment and vice versa (Sameroff, 1975; Whalen et al., 2011). While parenting can be stressful, parents of children with ADHD experience levels of stress that are further elevated compared to non-ADHD families (Whalen et al., 2011). The effects of child-related stress are amplified with the number of behavioral difficulties and diagnosis, e.g. if children show symptoms of ADHD as well as additional comorbid ODD or CD compared to children with single diagnoses (Wiener et al., 2016).

Child Externalizing Behavior

Children with externalizing symptoms, such as ADHD, ODD or CD are predisposed for showing behavioral problems, and are often more strongly affected by so-called risky family features. These include relationships that lack affection and support as well as frequent conflict and display of anger or aggression (Repetti et al., 2002). Constellations that are characterized by high conflict and stress and may fail to provide a nurturing and safe basis for exploration. Although mostly interconnected with other factors, - like unfavorable socio-economic status (SES) - dysfunctional relationships with primary caregivers can be considered a major risk factor for mental and physical health (Danese et al., 2009; Repetti et al., 2002; Repetti et al., 2011).

The Present Study

This study addresses how behavioral components, assessed via momentary assessments in children's and parents' daily lives are associated with salivary cortisol levels.

We expect potential differences in family interactions (interaction quality, child symptoms and parent behavior) to explain variance in the stress response patterns of children. We considered saliva samples and reports on family interactions to gain insight into daily family exchanges and whether these events would be related to cortisol. We focus on the momentary aspects of social interaction rather than stable contextual conditions that might not change on a daily basis.

Three variables have been identified for their eventual contribution in the association between family interactions and child HPA-axis functioning: First, the quality of interaction from the child's point of view, when being in contact with the mother. Second, self-reported negative parent behavior towards the child (disappointment, roughness, irritability, impatience and anger). Third, parent perceptions of child ADHD and comorbid externalizing behavior symptoms.

We expect that variations in cortisol can be attributed to daily experiences in family life, as measured by the three chosen variables. The majority of prior literature postulates higher cortisol responses in connection to negative emotional experiences and lower cortisol responses in connection to positive emotional experiences. Therefore, we hypothesize children's positive reports of occurring interaction quality to be associated with lower cortisol values, and negative reports of interaction quality to be associated with higher cortisol expression.

For self-reported parent behavior, we assume the occurrence of negative behavior towards the child (disappointment, roughness, irritability, impatience and anger) would be related to higher child cortisol.

In regards to the special population of children with symptoms of ADHD as well as comorbidities we theorize, that the parent-report of externalizing symptoms will be associated with an increase in children's cortisol.

Method

2.1 Participants

N= 122 children (39% girls) between 8 and 16 years of age (M= 11.33, SD= 2.00) and one parent of each child participated in the study. Families were recruited through ADHD specialists (psychologists, psychiatrists, and physicians), parenting organizations and media as well as public schools from 2018-2019. The study accepted siblings to participate (n = 54 children had at least one sibling in the study). Inclusion criteria were as follows: child age between 7-16 years, attending school in Switzerland, absence of clinical diagnoses except for ADHD, ODD or CD. Since we were interested in externalizing symptoms, diagnosis of ODD or CD was an inclusion criterion for the ADHD group as well as the comparison group. Official ADHD diagnosis from a physician or clinician was applicable for n= 53 children. Children without ADHD diagnosis were included in the comparison group. For each child participant, one parent joined the study (94% mothers).

Participating parents reported to be single (17%), divorced/separated (13%), widowed (2%) or married (68%). Nearly 75% of families stated a monthly net (after taxes) household income above the country's average (FSO, 2017) so the majority of participants would be characterized as medium to high SES.

Two children (from the same family) ended participation in the study after completing the first day of saliva sampling, data from this day were included in the analyses.

We observed a lot of missing values, due to participant non-adherence. Not uncommon for momentary assessment studies, participants did not fill out every questionnaire. Some items were dependent on family contact (i.e. the question regarding child's perceived interaction quality with their mother was only displayed upon prior child report of having been in contact with the mother). We applied the strict criterion of maximum 40 minutes time between (parent or child) question responses and cortisol samples for the present analyses. This lead to

the additional exclusion of many events. The final sample for analyses, consistent between n= 38 (child symptoms) and n= 53 (interaction quality and parent behavior) parent-child dyads.

2.2 Procedure

During one calendar week, children and their participating parent answered daily diary questions in the afternoon and in the evening. Around the timing of afternoon and evening questions, children sampled saliva two times each day. Participating families were visited in their homes by research staff. The home visit (approx. 90 minutes) required attendance by the participating children and parents. Study information, smartphones for daily diaries and saliva sampling materials were provided with a training during this visit. Salivettes were sorted and labeled for each day and time point. Following experimenter demonstration, each child exercised handling, and practiced saliva sampling. Daily diary questionnaires and their answering scales were demonstrated on the smartphone device. Data collection took place within the home for seven days following the home visit, always starting on a Monday. Children received a gift card for the equivalent of about 50 US Dollars for their participation at the end of the study. This study was approved by the cantonal ethics review board. All rules of ethical standards and safety were followed. All parents and children above the age of 14 gave written and oral consent; children below the age of 14 gave oral consent to participation. All children gave consent independent from their parents.

2.3 Measures

2.3.1 HPA-Axis Functioning (Salivary Cortisol)

Saliva collection took place within the home for seven days following the home visit, always starting on a Monday. All sampling weeks were scheduled while the children were attending school (not during vacations or school breaks). Child participants were asked to collect saliva samples in the afternoon (around 4:30 pm), and the evening (around 7:00 pm). Children were

not allowed to eat or drink, brush their teeth, or chew gum 30 minutes before each sample. The time of sampling was assessed through: a) parent or adolescent self-report (SR) as well as b) a digital time-stamp collected via either Medication Event Monitoring Systems (MEMS) caps or time-stamped photographs taken by participants. Due to the high costs of caps, not all families were provided with MEMS caps. Approximately half of families were instructed to provide a photograph of the tube label on the empty salivette tube (because salivette was in the child's mouth at this point) for each sample collected as a means of verifying sample collection times.

Saliva was obtained using Sarstedt cortisol Salivettes with instructions to move the swab around the mouth for 1-2 minutes until completely wet. Saliva samples were refrigerated in the participants' home refrigerators until the end of sampling week, then transported back to the University and stored at -30°C until assay. Samples were assayed for salivary cortisol at the Technical University of Dresden, Germany, with immunoassay kits (CLIA, IBL-international, Germany). The intra-assay CV and inter-assay CV were calculated with 4.5% and 5.2%, respectively.

Regarding sample time assessment, less than 10% of self-reported times (SR) were missing. The additional objective time-stamp methods were applied less conscientiously (18% data missing), due to families missing to take the time-stamped photo or not adhering to the opening and closure procedure of MEMS caps before and after each sample. For cases with missing SR times, but present objective time-stamp data, the objective time was used. Sensitivity analyses revealed no change in results for analyses with or without using the objective time. A major concern in salivary bioscience studies conducted in the home, compared to a controlled laboratory setting, is sampling schedule adherence.

2.3.2 Child Symptoms

We considered two different types of variables for analyses: 1) ADHD diagnosis and 2) assessing momentary parent perceptions of child symptoms.

ADHD Diagnosis. Dichotomous grouping variable based on clinician or physician performed assessment with official report confirming diagnosis. ADHD diagnosis was used as a covariate in all statistical models.

Parent Perceptions of Child Symptom. Using a momentary assessment questionnaire, parents rated their child's behavior on typical dimensions of ADHD symptoms (APA, 2013): Start a task ("*My child had difficulties to start with a task*"), forgetfulness ("*My child had difficulties to remember everything*"), coping with changes ("*My child had difficulties coping with new and difficult things*), control ("*My child had difficulties to control his/her words and feelings*"), waiting ("*My child had difficulties waiting his/her turn*"), listening ("*My child had difficulties listening attentively*"). In addition, some aspects of aggressive and disruptive behavior were included in this assessment, as the focus of this investigation are children with ADHD but comorbidity is frequent and therefore of interest, leading to following items: Outburst ("*My child had an outburst of rage or threw a tantrum*"), screaming ("*My child screamed out loudly*"), aggression ("*My child was aggressive*"). Items were answered on a seven-point response scale from 0 "*not at all*" to 6 "*extremely*" and were modelled as separate predictors (but within the same model), in order to test if certain dimensions of behavior would be related to cortisol reactivity, rather than summarizing the different behavioral aspects of ADHD and comorbidities into one summary scale.

2.3.3 Child's Perceived Interaction Quality

If a child stated to be together with their parent at the moment, the question "how did you feel while being with your mother?" was displayed. Answers were given on a three-point response scale (0 "bad", 1 "medium", 2 "good").

2.3.4 Self-reported Parent Behavior

Negative behavior towards the child included the following dimensions: disappointment, roughness, irritability, impatience and anger. Parents were asked to rate whether they had displayed the behavior upon momentary assessment alarm. Answers were given on a seven-point response scale from 0 “not at all” to 6 “extremely”.

2.4 Data analyses

Model testing was carried out with multilevel modeling (MLM) using Mplus 8.4 (Muthèn & Muthèn, 2019). MLM accounts for statistical dependence in the data due to repeated measurements within each participant and nested data. Repeated measures of questions and cortisol (level 1) were nested within children (level 2). We tested non-independence of sibling data on the family level (level 3), however variance components were rather small and non-significant, with an intraclass correlation coefficient (ICC) for siblings in families of .03, indicating that only a small portion of the variance was attributable to shared family factors. For this reason, we ran a two-level model. We estimated random intercepts, and added random slopes for all predictor variables. However, random variances turned out to be small and non-significant, so random slopes were omitted in favor of a greater number of degrees of freedom. As our hypotheses concerned within-person associations (level 1), all predictor variables were centered at the level 2 group mean (which in this case refers to the child’s individual mean). We included two within-subject time covariates: Time series (time of the week) and time since wake (in minutes, from awakening to the respective cortisol sample). The other covariates were modelled as level 2 predictors, considering: ADHD diagnosis, child age and child sex as well as the child’s mean time since wake values. All main effects were modeled and analyzed on level 1, leading to the following equation, here with the example of child’s perceived interaction quality:

Level 1: Child log cortisol$_{ij}$ = β_0 + β_1(time series)$_{ij}$ + β_2(time since wake)$_{ij}$ β_3(child's perceived interaction quality)$_{ij}$ + e$_{0ij}$

Level 2: β_0 = γ_{00}+ γ_{01}(ADHD diagnosis$_i$)+ γ_{02}(child age$_i$)+ γ_{03}(child sex$_i$)+ γ_{04}(mean time since wake$_i$)+ u$_{0i}$

β_1 = γ_{10}+ γ_{11}(ADHD diagnosis$_i$)+ γ_{12}(child age$_i$)+ γ_{13}(child sex$_i$)+ γ_{14}(mean time since wake$_i$)+u$_{1i}$

β_2 = γ_{20}+ γ_{21}(ADHD diagnosis$_i$)+ γ_{22}(child age$_i$)+ γ_{23}(child sex$_i$)+ γ_{24}(mean time since wake$_i$)+u$_{2i}$

β_3 = γ_{30}+ γ_{31}(ADHD diagnosis$_i$)+ γ_{32}(child age$_i$)+ γ_{33}(child sex$_i$)+ γ_{34}(mean time since wake$_i$)+u$_{3i}$

Child Cortisol$_{ij}$ is the cortisol value of child *j* at measurement *i*. The intercept β_0 is the average level of cortisol across children, while u$_{0j}$ reflects the deviation of each child's cortisol average from the overall average. The coefficient β_1(child's perceived interaction quality)$_{ij}$ and according slope deviations u$_{1\text{-}3j.}$ Child's perceived interaction quality$_{ij}$ captures the report of child's perceived interaction quality at measure *i* of child *j*. The same equation is applicable for all other variables under investigation, regarding parent behavior towards the child and parent perceptions of child symptoms in family interactions. The estimate β_2(Time series)$_{ij}$ is a covariate for the time trend over the whole study week while β_3(Time since wake)$_{ij}$ refers to the time (in minutes) since awakening until the respective cortisol sample, and e$_{0ij}$ is the error term. Cortisol data was positively skewed and therefore was log-transformed. In addition, a Robust Maximum Likelihood (MLR) estimator was used for data analyses.

Results

For the final model, main predictors were regressed on log transformed cortisol scores along with the covariates time series (course over whole week), time since waking, ADHD diagnosis, child age and child sex. Model results are summarized in Table 1.

Covariates

The dichotomous covariate ADHD diagnosis signaled a marginally significant association with cortisol output (*B*= .424, *p*=.094), in the model of self-reported parent behavior towards the child. ADHD diagnosis also marginally significantly predicted cortisol in the model of child ADHD symptom reports (*B*= .404, *p*= .091). The time since waking was significantly associated to cortisol only in the interaction quality model, where more time difference (in minutes) from waking up in the morning until concerning saliva sample predicted a decrease in cortisol (*B*= -.004, *p*= .000). Child age, child sex and the time series (over the whole week) covariates were not significantly associated with cortisol across models in this study.

Child's Perceived Interaction Quality

The child-rated quality of maternal interactions was not significantly associated with cortisol (*B*= .279, *p*= .128). The intraclass correlation coefficient (ICC) indicated, that 33% of the variance is attributable between children, we thus observe a high within-child variability for this variable.

Parent Behavior towards the Child

All parent behavior variables of interest (Impatience, Anger, Disappointment, Irritability, and Roughness) were included in the same model. Predictors were correlated between *r*= .39 and *r*= .69. None of the parent behavior variables were related to cortisol, except for anger indicating a marginal trend (*B*= -0.358, *p*=.080). This would suggest that when parents rated higher anger towards their child, child cortisol at the investigated time period was lower. An ICC of .55 indicated high variability between children as well as within-child.

Parent Perceptions of Child Symptoms

The momentary report of parent-perceived child symptoms assessed typical aspects of ADHD. The parent report included difficulties to start a task, forgetfulness, coping with changes, control, waiting, listening, outburst, screaming and aggression. Correlations ranged from r= .37 to r=.66. As displayed at the bottom of Table 1, some symptoms yielded a significant association with cortisol: forgetfulness (B= .243, p= .014), coping with changes (B= -.132, p= .004), difficulties to start a task (B= -.126, p= .003) and listening (B= -.190, p= .003). Control and waiting items were not related to cortisol. While higher ratings of difficulties with forgetfulness were associated with higher cortisol output, higher ratings of difficulties coping with changes, to start a task, and listening are inversely related to cortisol levels, resulting in lower cortisol values. For this set of variables, the variance attributable between children was at 64%, indicating smaller within-child than between child variance in these effects. This is seen as plausible, given that this study considered children with and without ADHD or comorbid symptoms.

In addition to ADHD symptoms, we also assessed typical symptoms of ODD/CD due to the high comorbidity (Bendiksen et al., 2017). A significant association between aggression (B= -.333, p= .000) and cortisol was observed, along with a trend for the symptom screaming B= .276, p= .085). The direction of effect for aggression signifies that higher difficulties with the concerned symptom predicted decreased cortisol values, while higher reports of screaming would suggest higher cortisol values.

Discussion

The goal of the present investigation was to test, whether parent perceptions of child symptoms and everyday family interactions would predict children's cortisol, sampled at the time of symptom and interaction report. The three examined variables were (child-reported)

interaction quality as well as (parent-reported) negative parent behavior and perceptions of child of ADHD and ODD/CD symptoms, rated by parents.

Child's perceived interaction quality

We observed no significant association between child-ratings of interaction quality and child cortisol.

Our finding is in contrast to other studies investigating family experiences; however, the tested concepts and variables vary from ours, with e.g. family conflict (Kuhlman, 2016; Slatcher & Robles, 2012) and youth's daily positive and negative experiences (Lippold, 2014; Sin et al., 2017). This study was designed to also question children on contact with their fathers, however due to the small amount of reported interactions with fathers (less than half as many paternal than maternal interactions), there was not enough power to analyze the quality of paternal interactions. Exploratory analyses did not show an association for child's perceived interactions quality with fathers and cortisol.

Self-Reported Parent Behavior

The hypothesis was that negative aspects of parent behavior directed towards the child (disappointment, roughness, irritability, impatience and anger) would be in connection with a visible modulation of the HPA-axis. None of the negative parent behavior variables were associated with child cortisol in this study, except for a marginally significant association between parental anger and cortisol. The direction of effect would indicate that reports of parental anger are associated with reduced child cortisol. Negative and positive parent behavior have been related to cortisol output before, however only through retrospective reports in young adults investigating basal cortisol (Marsman et al., 2012) or in laboratory settings in the framework of stress tests, where e.g. mother's high expressions of emotions have been associated with increased cortisol in children (Christiansen et al., 2010), not in momentary

assessment. Inconsistencies regarding the direction of effect do persist, as children with ADHD inattentive subtype have been found to show significantly decreased cortisol in reactivity to a stressor (Randazzo, 2008), and thus signaling the direction of effect to be distinct in special populations. Reduced HPA-axis reactivity in relation to stressful stimuli has also been reported by others (e.g. Pesonen et al., 2011). A lower cortisol output is also consistent with other results and theories where, especially because of early childhood or lasting adverse experiences, cortisol would be lower (Kuras et al., 2017; Oh et al., 2018). Contrary to the hypotheses, the variables of impatience, disappointment, irritability, and roughness did not show a significant relation with cortisol output. One important point to note is that the self-report of negative parent behavior probably never comes without bias, as this category of items is subject to social desirability. Self-reporting negative behavior towards one's child holds a high threshold, because it might be viewed negatively (Hutchison et al., 2006).

Parent Perceptions of Child Symptoms

We observed significant associations between some typical symptoms of ADHD and concurrent cortisol output. We assessed parent-reported symptoms around the time of cortisol sampling and tested whether occurred symptoms predict cortisol expression in children. The report of parent-perceived child symptoms was related to HPA-axis functioning in this study. Specifically, the items forgetfulness, coping with changes, start a task and listening significantly predicted cortisol. The items control (over feelings and words) and waiting were not significantly related to child cortisol.

When parents rated more problems of the child's momentary coping with changes, starting a task and listening attentively in smartphone questionnaires, the according child cortisol output was decreased. This is consistent with the hypotheses and in line with the theory of ADHD symptoms being associated with physiological under-arousal (Barkley, 1997; Northover et al.,

2016). The item forgetfulness shows a positive relationship with cortisol, suggesting that higher reports of forgetfulness are associated with elevated cortisol.

Regarding comorbid externalizing behavior, the variables of aggression and – marginally - screaming significantly predicted cortisol. An increased report of aggression was associated with lower child cortisol levels, while screaming was associated with increased cortisol. As we hypothesized a short-term upregulation, these findings are only partly in line with the hypotheses. The exact contribution of child externalizing behavior in family interactions and subsequent salivary cortisol has to be further determined.

Strengths & Limitations

The present study provides a design with high ecological validity. Momentary assessment, using a smartphone application, prompted children and their parents to report on the investigated variables upon a set alarm, and therefore capturing family interactions of everyday life. The data we present was sampled at home, likely capturing true everyday family behavior (Shiffman et al., 2008). Nevertheless, many small events and interactions of family life will not be captured because they might have occurred outside of the timeframe of assessment or just not at the exact moment of the questionnaire alarm.

The timing of momentary assessment alarms was fixed to 4:30 pm and 7:00 pm. All participants were given a 90-minute window to respond, to enhance compliance. The response window was intended to accommodate constraints in family routines or afternoon programs that would prevent participants to answer questions in a busy moment. Given the intense saliva sampling schedule, families were instructed to provide the sample saliva at the timing of questions, but families were still free to schedule their saliva samples earlier or later to prevent missing samples and to enhance adherence of families. We tried to apply analytic criteria, which would avoid mismatching momentary assessment with cortisol samples as much as possible by only allowing a maximum of 40 minutes between question responses and saliva samples. We

validated SR times of cortisol samples with an objective time stamp method and excluded saliva samples for which no valid time report was present. Still, we cannot exclude that within the timeframe of max. 40 minutes between responses and cortisol sampling, different events might have been reported than those that have been captured by cortisol level. Interactions at the time of question response might have been different from the family interactions at the time of cortisol sampling, as situations in the family settings can change quickly. With these constraints in mind, families still participated in an incomparably intense sampling and momentary assessment schedule of seven consecutive days (one calendar week), which enhances the validity of cortisol values (Rotenberg et al., 2012; Stewart & Seeman, 2000), and also makes capturing moments of family interactions more likely compared to fewer days of assessment. Given the intensive study design of several questions a day, most momentary assessment studies report missings due to non-adherence. Concordant cortisol sampling in children, in addition to child and parent momentary assessment, remains a challenge for families and a challenge for researchers to recruit parent-child dyads to participate. The strict criteria for considering events for analyses (e.g. time between child or parent response and saliva sampling) led to an exclusion of almost 75% of events and many child-parent dyads were excluded completely. Out of N= 122 assessed parent-child dyads, only a subsample that fulfilled the strict cutoff of < 40 minutes between questionnaires and saliva samples was considered for the present analyses. This reduced number of participants and data limits the external validity as well as our statistical power. In addition to power issues, which limit the chance to find an effect but also increase the risk for type II error, a small sample size also increases bias and impairs solution propriety (Wolf et al., 2013). This has to be kept in mind when interpreting the results. Our number of participants is in line with the number of participants from other studies with the same design (e.g. Papp et al., 2009), the results should be seen as a foundation for future studies.

We used self-assessment in both, child and parent variables. For children, valid self-report is generally recommended and feasible from age 7, as it takes a certain degree of cognitive development to understand survey questions and the ability of self-reflection (De Leeuw et al., 2004). In general, we endorse child self-report in studies, due to a good feasibility and reliability (Riley, 2004). Therefore, we had parents as well as children themselves report on momentary assessment questionnaires. However, children with ADHD tend to underestimate their own symptoms of ADHD (Wiener et al., 2012). For the present investigation, we thus considered parent-reported symptoms to be preferable, given our special population, who are partly on the edge of the recommended age threshold and the complexity to rate one's own symptoms.

It should be considered, that the parental rating of child symptoms and the observed cortisol output could potentially be connected through possible mediators or confounding variables. We hypothesized a direct association between parent perceptions of child symptoms and HPA-axis functioning, however this does not necessarily exclude possible additional indirect paths in how child symptoms and HPA-axis regulation could be related. Therefore, we want to note, that it could also be that the perception of child symptoms would trigger certain parent behavior. The displayed parental behavior could in turn be more relevant to a child's HPA-axis functioning, than the chance of being a physiological corollary of the child's ADHD symptoms. It remains for future studies, to test a mediation model with parent perceptions of child symptoms, parent behavior and cortisol output.

The generalizability of the results is limited by the rather high SES characteristics of the majority of the sample. We recommend reevaluating the presented results in a sample with more variance regarding SES. We deem it especially important to investigate the here postulated relationships in environments of low SES and related challenges, as there is a clear relationship between low SES and HPA-axis dysfunction (Desantis et al., 2015; Dowd et al., 2009; Matthews and Gallo, 2011).

In contrast to existing literature on HPA-functioning in children with strong environmental adversities like poverty and childhood trauma, as well as severe conflict, our focus was the lower-threshold behavior, as it likely occurs in families on a day-to-day basis. This might partly explain why we were not able to find strong effects for all variables. Another important argument was contributed by Kuhlman and colleagues (2016), who state, that the afternoon and evening regulation of the HPA-axis would be more sensitive to an accumulation of interpersonal experiences across weeks and not days. This study does however contribute in clarifying that specific family behavior can be associated with children's cortisol output. It is possible, that a certain degree or threshold of behavior has to be met in order to provoke a change in HPA-axis activity. Participants' HPA-axes might be more susceptible to certain experiences, depending if it constitutes a rare, extraordinary event or baseline behavior, experienced every day (Granger, 1998).

The introduced variables and items add new information on how family interactions might be related to HPA-functioning. The bidirectional mechanisms between child and parent behavior as well as parent perceptions of child symptoms deserve a closer look in order to clarify the role of child externalizing behavior symptoms and physiological, endocrine functioning.

Conclusions

To our knowledge, this is the first study linking momentarily occurring symptoms of ADHD in children, assessed through daily diary report over multiple days in the family home setting, to at-home cortisol sampling. The present study therefore extends prior literature by investigating family interactions several times a day and through different variables, together with symptoms of child externalizing behavior in direct relation to cortisol sampling. Participating children and their families participated during 7 days, reporting on their family interactions and parent-perceived child symptoms several times a day. By assessing child and parent point of views to family interactions, this study offers insight into the relationship between parent-perceived

symptoms, child rated quality of interactions as well as negative parent behavior and children's HPA-axis functioning. This holds the potential of a better understanding how single aspects of the family environment can be connected to diurnal cortisol expression.

Testing links between daily family interactions and HPA-axis regulation is important to further our understanding of an underlying connection between rearing conditions and later physical and mental health. By comparing children with externalizing behavior to comparison children, we can learn about potential differences and similarities in every day family life, leaving parent-child interactions as powerful targets for intervention and prevention. Identifying key mechanisms within daily parent-child interactions, will improve our understanding of HPA-axis functioning in response to positive and negative family experiences of everyday life.

Further research on symptom characteristics in relation to cortisol could provide new information for clinical practice. Targeting specific symptom expressions therapeutically might help to deter HPA-axis dysregulation consequences. Some symptoms might be more adverse for healthy parent-child relationships and trigger dysfunctional family functioning than others. Identifying key triggers on the endocrine and family level may contribute to a healthier HPA-axis calibration (Miller et al., 2011). We see the family environment as an important source of resilience in the case of positive experiences or vulnerability in the case of present adversity, potentially affecting a child's later mental and physical health.

Tables

Table 1

Summary of Model Results for all Predictors on Child Cortisol within 40 minutes

Within-Level Predictors	*B* (*SE*)	*p*-value	95% CI
Interaction Quality (*n*= 53)			
Child perceived interaction quality	.279 (.18)	.128	[-.080, .637]
Parent Behavior (*n*= 38)			
Impatience	-.182 (.16)	.274	[-.507, .144]
Anger	-.358 (.20)	.080*	[-.758, .042]
Disappointment	.160 (.38)	.675	[-.586, .905]
Irritability	.076 (.29)	.796	[-.502, .655]
Roughness	.111 (.45)	.806	[-.775, .998]
Parent Perceptions of Child Symptoms (*n*= 38)			
Forgetfulness	.243 (.09)	.014**	[.049, .437]
Coping with Changes	-.132 (.04)	.004***	[-.221, -.043]
Control	.018 (.04)	.665	[-.065, .101]
Waiting	-.140 (.08)	.102	[-.308, .028]
Listening attentively	-.190 (.06)	.003***	[-.316, -.064]
Starting a task	-.126 (.04)	.003***	[.209, -.044]
Throwing a Tantrum	-.197 (.14)	.171	[-.479, .085]
Screaming	.276 (.16)	.085*	[-.039, .591]
Aggression	-.333 (.06)	.000***	[-.462, -.205]

Note. CI= confidence interval;
* $p < .10$ ** $p < .05$ *** $p < .01$

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10 General Discussion

The results of the three performed studies were discussed and compared to the findings of previous research efforts in chapters 7, 8, and 9, respectively. This chapter will therefore focus on the presented work's general contribution to the field, including a summary of key findings. Overall strengths and limitations will be reviewed with propositions for future research, followed by a conclusion and implications for clinical practice.

10.1 Findings and Contributions of this Thesis

The present thesis was interested in the lives of children with externalizing behavior and their families. The focus was set on children with symptoms of ADHD as well as disruptive disorders (ODD and CD). The presented research aimed at connecting HPA-axis functioning and family life, including interactions and well-being of children and parents. This approach united 1) Clinical family psychology and 2) Psychoneuroendocrinology, examining the intersection of HPA-axis regulation (cortisol output) and behavior or environmental factors.

To the best of knowledge, this is the first study that executed this combination of fields of research, with the presented methods and data collection from as many as 146 child-parent dyads, across seven days of measurement with three (ambulatory assessment) or five (saliva) daily assessments. This work therefore extends the previous literature in the fields of child pathology, family relationships and HPA-axis functioning. The present design and data signify an improvement of earlier studies, in terms of

a) the number of participating children

b) the assessment of ADHD symptoms as well as ODD/CD comorbidity, compared to non-affected children of the same age

b) the accuracy of child psychopathology assessment with clinical diagnosis and symptom report

c) the validity of salivary biomarker results with more than two or three (weekend) days assessment,

d) using momentary assessment of daily family interactions at home, in families' naturalistic setting compared to laboratory settings

e) the application of appropriate statistical methods allowing to model the nested structure of the data and their interdependence of repeated measures designs

f) the consideration of child and parent report

g) the addition of an objective time stamp method to validate self-report of saliva collection times

h) the examination of a wide age span of 7 to 16 years, including timing of puberty

I) the control for development variables important for research with children: age and stage of puberty

Summary of Findings

The first article examined cortisol samples to investigate the CAR as well as total diurnal cortisol output across the day, both via AUC. Symptoms of ADHD and symptoms of ODD/CD were modeled along with the covariates of child age and stage of puberty, to test a hypothesized reduced CAR and a smaller diurnal cortisol AUC from first (wake) to last (evening) sample. Age and pubertal stage, but not ADHD nor ODD/CD symptoms explained significant variance in the CAR or diurnal AUC. We observed a high variability of cortisol. Differences emerged between children as well as within-child, across days. In addition, the five weekday sampling occasions can be distinguished from cortisol levels at the two weekend days. Experts reached consensus that a minimum of 3-4 (week) days of cortisol sampling should be conducted and six or more days are needed for a stable diurnal rhythm with little measurement error (Stewart & Seeman, 2000). Most studies have implemented a sampling schedule of three days or less. Our data suggests that, depending on the research questions, 3-4 days of cortisol sampling are not enough. To our knowledge, this is the first study sampling cortisol with an intensive schedule across a full week in order to investigate whether ADHD symptoms and comorbidities are related to HPA-axis functioning. Findings highlight the importance of incorporating

covariates specific to development, such as age and stage of puberty, for our understanding of cortisol functioning in children and adolescents as well as a sampling schedule that appropriately accounts for the high variability of cortisol across days.

The second article used momentary assessment to examine daily family interactions in regards to child symptoms. Parent-reported child symptoms were hypothesized to be associated with child and parent well-being. Positive and negative parental behavior was proposed to mediate the relationship between parent perceptions of child symptoms and children's as well as parents' positive and negative affect. Indeed, parent reports of child symptoms predicted less positive and more negative parent behavior towards the child and negative parent behavior predicted more negative affect in parents. The findings connect to earlier research findings of how child pathology can undermine positive relationships and appropriate parent behavior. The findings can be seen as an indication that not only child behavioral difficulties need to be addressed in treatment. Parent behavior and - relatedly - parent well-being can be directly impaired by perceiving child symptoms. Parental well-being and behavior should thus be targeted with support and training from clinical practice.

In the third article, a potential interdependence of HPA-axis functioning and family interactions, including child symptoms, was probed through a synchronized assessment of cortisol output and family events. While child-reported feelings in maternal interactions were not associated with children's cortisol, parental anger towards the child emerged as a trend to be associated with children's cortisol output. Some parent-reported ADHD and comorbid symptoms significantly predicted increases or decreases in children's concurrent cortisol output. This study was the first to link momentary assessment of family interactions and ADHD symptoms to at-home cortisol sampling. The findings provide an encouraging basis for further research. Momentary assessment and concurrent cortisol sampling in children and families with psychopathology is feasible and can provide unique insights into the connection of family experiences and HPA-axis functioning in a naturalistic

environment. Understanding the axis' response to children's family interactions and symptoms is relevant to determine the impact of everyday environmental exposures on child development.

10.2 Limitations & Strengths

For an appropriate classification and integration of results, the limitations and strengths of the presented work will be elaborated. This chapter is dedicated to overall limitations and strengths concerning the content, methods and results of the presented research project. It connects to the notes on limitations and strengths of the respective studies in chapters 7, 8 and 9.

Limitations

One of the objectives was to compare how manifestations of child symptoms are related to HPA-axis functioning. However, the unequal distribution of participant children with ADHD-IN, ADHD-HI or combined subtype did not allow a valid examination of separate ADHD subtypes. Analyses of parent-reported symptoms (versus previous diagnostic report) revealed only few children with purely HI subtype in this sample. Not rare in the case of ADHD, the aspect of hyperactivity/ impulsivity decreases with age and brain maturation (APA, 2013). If the ADHD diagnosis dates back years, the clinical picture might have changed. Other results of ADHD and cortisol rely on samples with more, or even exclusively, children with symptoms of ADHD-HI (Angeli et al., 2018; Blomqvist et al., 2007; Imeraj et al., 2012; Isaksson et al., 2012; Okabe et al., 2017; Vogel et al., 2017). The present thesis questions that children with ADHD show a dissimilar pattern of diurnal cortisol expression (CAR and total diurnal output, via AUC) than children without ADHD. Whether some subtypes of ADHD or combinations with comorbidities show a psychoneuroendocrinologically distinct diurnal HPA-axis regulation has to be determined by future studies with larger sample sizes per ADHD subtype. This would allow to appropriately employing subtype affiliation as a study variable. The same applies to symptoms of ODD/CD, more children with symptoms of ODD/CD would be better to test an association over and on top of ADHD alone.

Regarding the sample size, an a priori power analysis for an estimated medium effect size (f^2 =.15) indicated sufficient power with *N*= 100 participants. Accounting for missing values in the respective studies and variables, the presented analyses have partly been underpowered, especially to detect smaller effects. Where indicated, the presented results have to be interpreted with caution. The number of children taking part in this study can generally be seen as representative, especially in light of the intensive study design. However, some statistical models had to be conducted with a limited number of child-parent dyads, due to a high percent of missings in some variables. After accounting for missings and the exclusion of some participants, the sample size is at the limit for the applicability of multilevel-structural equation modeling analyses. The objective for future studies would be the fulfillment of the recommended sample size, typically *N* > 200 (Kline, 2015). This applies especially for between-subject analyses; modelling the within-subject process benefits from higher power through the intensive repeated measures design.

In light of the external validity, some sample characteristics lead to a limited generalizability of results. By recruiting in public schools and via practitioners seeing children with ADHD, a good representation of the general population was targeted. Nevertheless, a high proportion of our participants are characterized through a high SES. The presented results should be reevaluated in a sample with more variance regarding SES. A reexamination of the relationships postulated by this thesis is especially relevant in environments of low SES and low-income. Families in these settings face more challenges and additional risk factors, leading to higher stress (Noel et al., 2008), strained relationships (Qi & Kaiser, 2003) as well as reduced resources to attend to children (Pinderhughes et al., 2000). Various studies show a strong association between low SES and HPA-axis dysfunction (Clearfield et al., 2014; Desantis et al., 2015; Dowd et al., 2009; Matthews and Gallo, 2011; Zalewski et al., 2012).

In turn, high SES could be a form of protection, potentially promoting resilience. High SES is often linked to higher family income, a safer neighborhood, favorable school system, and higher education of parents', perhaps rendering preferable educational styles more likely. This might be an underestimated part in the puzzle of healthy HPA-axis regulation due to environment interaction. The

intensive study design compared to the low study compensation (CHF 50 for the whole week) might have attracted families with highly involved parents as well as families who handle their daily lives well, despite the child's ADHD or ODD/CD symptoms. Due to limited capacity, very strained parents might have been less likely committed to participate in an intensive study. Future studies putting emphasis on sample environment and comparison of cortisol in high vs. low SES in relation to child psychopathology could advance clarification of such mechanisms.

Not all families succeeded to complete every saliva sample and momentary assessment occasion. Future studies might consider a more incentive-based system, where the total amount of compensation is split and reimbursed in steps (e.g. CHF 2 for every single questionnaire, or CHF 10 for every fully completed study day). Especially children with ADHD struggle with delayed gratification (Gawrilow et al., 2011), which is why shorter-term incentives might work well to further enhance participant compliance.

In studies 2 and 3, we suggest a theoretical model, where parent-perceived child symptoms are thought to predict positive and negative affect as well as positive and negative parent behavior (Study 2) or differences in children's HPA-axis regulation (Study 3). Although the use of momentary assessment holds the advantage of measuring family interactions in their natural setting, we have to note that everyday interactions and psychosocial mechanisms between children and their parents are very complex. Exchanges are happening in a multitude of moments and situations throughout the day. This study encompassed seven days, with questioning three times a day. This enabled gaining insight into family interactions several times a day. However, the momentarily captured exchanges and experiences in the family by this study only show a small excerpt of an occurring situation. Therefore, many other events and interactions of family life will not be captured because they might have occurred outside of the timeframe of assessment or just not at the exact moment of the questionnaire alarm.

In line with Elgar and colleagues (2004), parent-child relationships are likely mediated by many genetic and environmental factors. In regards to the special population of children with ADHD and comorbidities, one of the especially relevant factors might be parent psychopathology. The chance for a child with ADHD to have a parent, who is likewise affected by ADHD, has been stated to be up to 40 to 55% (Smalley et al., 2000; Takeda et al., 2010). Parents of this study were presented with a short screening questionnaire for psychopathology, which did not reveal a parent to show strong signs of depression, anxiety, obsessive-compulsive disorder or eating disorders. Parent ADHD has not been targeted and incorporated in this study as we expected strong associations between child symptoms and parent variables, regardless of a parent's ADHD symptoms. This is in line with previous findings, where the child ADHD symptoms predicted parenting shortcomings, even after controlling for parent ADHD symptoms (Wymbs et al., 2015). It is however acknowledged that the combination of child and parent ADHD will likely add more complexity to family functioning and it is advised to consider parent ADHD in future studies.

Participants were given a 90-minute window to respond to momentary assessment questions to accommodate constraints in family routines or afternoon programs, which could prevent participants from answering questions in a busy moment. This study incorporates child and parent variables within the same models, and parent report as well as child report or saliva sample might not always have occurred at the same time. As situations in the family setting can change quickly, different experiences or events might have been reported by parent and child participants depending when they responded to questions. For study 3, we strictly limited our analyses to events where parent and child assessment (questions & saliva samples) happened within < 40 minutes. Still, the reported interactions at the time of question response might have been different from the family interactions at the time of cortisol sampling.

One approach to better meet this challenge in the future could be the use of Electronically Activated Recorders (EAR; Mehl et al., 2001) as implemented by Slatcher and Robles (2012). Attached to

participant's clothing, the device records whole day audio material, which for their study was coded for the occurrence of family conflict. Momentary questions and cortisol samples at the time of occurred conflict could then be matched with the situations of conflict.

In contrast to existing literature on HPA-axis functioning in children with strong environmental adversities like poverty, childhood trauma or severe conflict, our focus was lower-threshold behavior, as it likely occurs in families on a day-to-day basis. This might partly explain why we were not able to find strong effects. Another important argument was contributed by Kuhlman and colleagues (2016), who state, that the afternoon and evening regulation of the HPA-axis would be more sensitive to an accumulation of interpersonal experiences across weeks and not days. This study does however contribute in clarifying that parent perceptions of child externalizing symptoms can be associated with children's cortisol output and that parent-perceived child symptoms are connected to parental behavior and negative affect. Regarding cortisol output, it is possible, that a certain threshold of behavior (e.g. parent behavior or child symptoms) has to be met in order to provoke a change in HPA-axis activity. Participants' HPA-axes might be more susceptible to rare, extraordinary experiences, compared to baseline behavior, experienced every day (Granger, 1998).

Study II and III modelled the parent-child dyads' within-processes. Yet, the presented results do not allow a causal interpretation. This is for longitudinal study designs to assess, where children and parents can be accompanied for longer periods of time and therefore results could reflect causal mechanisms with higher validity (Johnston & Jassy, 2007). The models presented in this thesis are an attempt to contribute to bridging the gap between physiological and psychological processes in children's lives. However human psychoneuroendocrinological functioning evolves over years or decades of child development. The same applies for behavioral patterns and family dynamics. The explained vicious circles of child and parent behavior often reflect long-term processes, which are best captured by longitudinal research designs.

Strengths

The at-home collection of saliva is reliant on participant adherence (Clow et al., 2004). Cortisol in general is subject to various confounding variables, and probably not even a laboratory setting can capture influences in their entirety. The intensive sampling schedule over multiple days was intended to help reduce measurement error and enhance the validity of cortisol measures by decreasing the influence of short-term HPA-axis susceptibility. Saliva sampling with children and adolescents in general, and especially at home in their family environment, adds an additional challenge of controlling how and when saliva is collected. To enhance compliance and feasibility, individualized sampling schedules were designed for each family, accommodating their needs and routines. Dual measures of recording subjective and objective sampling times were applied to promote adherence.

The present study provides a design with high ecological validity. Momentary assessment holds many advantages such as real-time capture of momentary processes and evading recall bias (Shiffman et al., 2008; Trull & Ebner-Priemer, 2014). Therefore, the presented data that was sampled during everyday situations (avoiding school hours) likely portrays actual everyday family behavior.

Self-reports of both parents and children were considered in this study. For children, valid self-report is generally recommended and feasible from age 7, as it requires a certain cognitive development to understand survey questions and the ability of self-reflection (De Leeuw et al., 2004). Child self-report is endorsed with good feasibility and reliability in studies (Riley, 2004). For child symptoms however, we relied on parent ratings for two reasons: 1) Practicality. In the case of child symptoms, studies found that children tend to underestimate their own symptoms of ADHD (Wiener et al., 2012) as well as ODD/CD (Schoorl et al., 2016). Given our special population and the age-span on the lower edge of the recommended age threshold, we relied on parent-report to rate disordered behavior. 2) Theoretical implications. When assessing parent behavior and well-being in regards to child symptoms, it matters if and how a parent perceives child symptoms. The perception of child symptoms and the evaluation

of their intensity or disturbance is a subjective process. It was thus relevant to capture parent behavior and well-being in regards to a degree of symptoms that parents found noticeable and likely distressing.

In addition to parent ratings of symptoms, all diagnoses of each child were assessed upon recruitment. In order to qualify for participation the ADHD group, an official diagnosis of ADHD from a clinical professional (e.g. psychologist, psychiatrist, and physician, pediatric) had to be present. Experimenters asked to see the clinical report during the home visit and noted the exact wording of the diagnosis (e.g. with or without hyperactivity/impulsivity), the year of diagnosis, as well as the job title or category of the person who diagnosed the child. It was thus possible to compare the symptom report of parents with the presence of an official diagnosis, as an additional means of assessing children correctly.

ADHD often occurs comorbid with symptoms in the spectrum of oppositional defiant disorder or conduct disorder (Larson et al., 2011; Bendiksen et al., 2017), which is why items concerning comorbid symptoms, are often included in questionnaires for ADHD. The ADHD symptom questionnaires used for this study were therefore complemented with typical symptoms of ODD and CD. Aggressive, oppositional or antisocial behavior adds even more strain on family relationships (De Haan et al., 2013) and was therefore relevant for the tested associations in this study. The inclusion of frequently comorbid symptoms in studies of child ADHD symptoms is recommended (Boots & Wareham, 2010). Research in clinical psychology can serve to inform clinical practice and programs for families of children with behavioral difficulties. The presence of comorbid ODD or other forms of disruptive behavior disorders is a clear indicator that interventions and support for parents should be provided (e.g. Sollie et al., 2016).

10.3 Conclusions & Implications for Clinical Practice

To our knowledge, this is the first intensive study design with this amount of study days and samples to investigate ADHD and comorbidities in regards to HPA-axis functioning. While other research has made important contributions on the impact of ADHD and comorbidities on family functioning and

interactions, this thesis adds the combination of child symptoms with parent positive and negative behavior and positive and negative affect in regards to child pathology. It is the first study linking child and parent behavior in respect to symptoms of ADHD and comorbidities using momentary assessment in the family home setting as well as at-home cortisol sampling.

Momentary assessment has allowed us to examine micro-processes that occur during the day and has the potential to further explore and disentangle mechanisms positive as well as negative family mechanisms. By assessing child and parent points of view to family interactions, including child symptoms, this thesis offers insight into the relationship between parent-perceived symptoms, child rated quality of interactions as well as negative parental behavior towards the child in combination with children's HPA-axis functioning. This holds the potential of a better understanding how single aspects of the family environment can be connected to diurnal cortisol expression.

Consistent with other findings, this thesis found that ADHD symptoms might be related to HPA-axis reactivity rather than basal diurnal HPA-axis functioning (e.g. Pesonen et al., 2011). Consistent with previous investigations, the covariates of child age and pubertal stage were significantly associated with cortisol, which underlines the importance of incorporating developmental-specific variables in biopsychological research with children and adolescents. Regarding cortisol reactivity to child symptoms, this thesis revealed, that aspects of parent-perceived child ADHD and comorbid symptoms can be related to the child's HPA-axis activity. Children's cortisol reactivity to everyday family life, including the experience of symptoms and the parent's perception of these symptoms, is thus an example of HPA-axis functioning in regards to the environment. Focusing on the family environment, the results of this thesis show that child ADHD and comorbid symptoms can be connected with parental well-being. Parent perceived symptoms of the child predicted parental behavior and this in turn was related to parental negative affect. Child ADHD significantly predicted an increase of negative parent behavior towards the child and a decrease in negative positive parent behavior, which provides an important basis of information about family dynamics, particularly in families of children with ADHD or externalizing behavior difficulties. Although some effects did not withstand the applied Bonferroni-

correction for multiple hypothesis testing, the results flag a possible connection of child symptoms with parent negative affect, mediated by parental behavior as well as the potential relation between child symptoms and children's own affect. The findings thus emphasize parent behavior as an important aspect of the relation between child symptoms and family well-being.

Family functioning and reciprocal interactions between children with behavioral difficulties and parents are an important focus of research, as a further understanding of the mechanisms at play can help to inform therapy programs. This thesis emphasizes, that the presence of child externalizing symptoms puts families at higher risk for dysfunctional relationships and negative emotional experiences. ADHD symptoms will likely cause a parental reaction, and strategies of how to deal with symptoms, can be better and worse. Many forms of inappropriate parent conduct displayed towards the child can be harmful for the parent-child relationship. The present results therefore underscore the importance of helping parents train appropriate behavior in families of children with externalizing symptoms.

Further research on behavioral and child symptom characteristics in relation to cortisol could provide new information for clinical practice. The family environment can be an important source of both resilience in the case of positive experiences or vulnerability in the case of present adversity, affecting a child's later mental and physical health (Bauer et al., 2002; Essex et al., 2002; Repetti et al., 2002). Identifying key triggers on the endocrine and family level may contribute to a healthier child HPA-axis calibration (DeMorrow, 2018; Miller et al., 2011; Slopen et al., 2014). In addition to treating child symptoms, the results of this thesis suggest that therapeutically targeting a) parental behavior towards the child in association with child symptoms b) parental emotions that are associated with their own behavior and child symptoms and c) specific symptom expressions, might help to contribute to healthy family interactions and healthy HPA-axis functioning.

The recommended treatment for children with ADHD is behavior therapy (American Academy of Pediatrics, 2011). Therapy can reduce the long-term consequences of dysfunctional family dynamics, including ineffective and inconsistent parenting and negative parental behavior towards the child,

which breaks coercive cycles and enables a healthy parent-child relationship. The interactive process between child and parent behavior is thereby a strong target for interventions, which has to be assessed in a continuous manner (Pearl et al., 2014).

As Hutchison and colleagues (2016) pointed out, the description of a coercive or vicious circle, where a parent's behavior might trigger the child and worsen symptoms can sometimes lead to the impression, that the child's behavior is the parent's fault. This is not the intended claim. Rather, for successful prevention and intervention in clinical practice, it is important to address and target the parental reactions to child behavior. In line with a transactional framework for development, a family systems perspective (Campbell, 1995) is recommended for children with disabilities or behavioral difficulties. To successfully change parent-child patterns of interactions, is not sufficient to only treat the child with behavioral or pharmacologic therapy. The family environment must also be a focused target, in order to appropriately address the manner a parent perceives symptoms and reacts towards their child with behavioral disorders (Hutchison et al., 2016).

Numerous parent-training programs show promising results to promote authoritative parenting, improve dysfunctional behaviors of children and parents, and thus reduce stress (Chronis et al. 2004; Treacy et al. 2005). Especially guidance on how to interact more positively with children with special needs should be pursued. Most trainings are based on cognitive-behavioral therapy (CBT) but incorporate attachment theory, social learning, as well as Baumrind's (1966) developmental theory of parenting. One successful example is the Triple P program (Sanders, 2008) helping parents worldwide, how to effectively and positively parent their children. For children with externalizing and disruptive behavior and disorders, such as ADHD and comorbid ODD, Parent-Child Interaction Therapy (PCIT) has been developed (Lienemann et al., 2017). Its evaluated efficacy successfully reduces e.g. conduct-disordered behavior of preschool age children to normal range behavior (Thomas et al., 2017).

Some trainings rely on theoretical workshops with parents only. While this yields good effect sizes (e.g. Nowak & Heinrichs, 2008), it is a likely scenario that valuable skills and techniques will not always be implemented when at home with one's child in the midst of conflict. Modifying behavior takes time

and practice as well as a good transferability of course contents to the family home. Another approach exists with behavioral observation during parent-child interaction in a laboratory setting with one-way mirrors, where a specialist instructs the parent using a bug-in-ear device. This approach, too, shows encouraging improvements of parent and child behavior in evaluations (Ward et al., 2016). Nevertheless, at home the parent in training could be lacking the specialist's instructions. As a concluding opinion, an ideal parenting program could combine elements of teaching or psychoeducation as well as observation-based laboratory training with a trainer and maximize the transfer of skills across settings. In line with Hutchison and colleagues (2016), it is acknowledged that progress in parent-child relationships and child as well as parent behavior needs advanced longitudinal evaluations, with a transactional view, to investigate ongoing exchanges. Training functional parental behavior along with fostering positive experiences is important for child and parent mental health and stress regulation in the context of child ADHD and comorbidities.

Family relationships and daily experiences are important for the healthy development of every child (Belsky & Pluess, 2009; Berry et al., 2016; Essex et al., 2002; Evans & Kim, 2007; Gunnar & Cheatham, 2003; Gunnar & Donzella, 2002 ; Keller et al., 2005 ; Lucas et al., 2018; Marsman et al., 2012 ; Repetti et al., 2002; 2011). Research on the intersection of daily family interactions and HPA-axis regulation contributes to our understanding of the links between childhood environments and later physical and mental health. We have to continue asking how psychosocial stress and experiences in childhood can get 'under the skin' to increase a risk for later diseases (Miller et al., 2011).

As Granger and Hamilton (2020) pointed out, researching biobehavioral processes, such as the psychobiology of the stress-system, enables to explain inter-individual as well as intra-individual differences as determinants of lifelong trajectories with vulnerability or resilience (e.g., Blair et al., 2011; Stroud et al., 2009). Social context, as an important moderator of the relationship between behavior and physiology, can contribute to explaining these inter- and intra-individual differences in human psychobiology (e.g. Booth et al., 2004). By comparing children with externalizing behavior and their parents to comparison children and parents, we can learn about potential differences and

similarities regarding experiences and physiological functioning in everyday family life, leaving parent-child interactions as powerful targets for clinical and family, as well as biopsychological research.

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Curriculum Vitae
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Experience

September 2018	Research visit: University of California Irvine (UCI), USA Prof. Douglas Granger & Prof. Jenna Riis Salivary Bioscience (7 months)
May 2017	Principal Investigator (PI), national project (46 months) Stress regulation in children with ADHD and comorbid symptoms of aggressive, antisocial behavior: Associations with family interactions, University of Fribourg (UNIFR) Funding: Swiss National Science Foundation (Doc.CH)
November 2015	Interdisciplinary project: Family Interactions in Children with ADHD Prof. Dominik Schoebi and Dr. Sandra Hotz, Institute of Family Research & Counseling, UNIFR Scientific Collaborator (20 months)
January 2014	Psychiatric Day Clinic Interlaken, Spitäler fmi AG Clinical Internship (2 months)
December 2013	Research project: Prenatal Diagnostics Dr. Sandra Hotz, Institute of Family Research & Counseling Research Assistant (12 months)
August 2013	Research visit University of California Los Angeles (UCLA), USA Prof. Thomas Bradbury, Intimate Relationships (1 month)
April 2012	Research project: Delinquency in youth, the role of peer influence Dr. Verena Hofmann, Department of Special Education, UNIFR Research Assistant (6 months)
July 2012	School Psychological Services, Canton St. Gallen, Dr. Hermann Blöchlinger (3 Months)
October 2011	Research project: Coronary Heart Disease, Cardiovascular Risk Factors Dr. Livia Thomas, Biological and Health Psychology, University of Bern Research internship (2 months)

Education

Since November 2015	PhD student, Prof. Dominik Schoebi, Clinical Family Psychology, University of Fribourg
June 2015	Master of Science in Clinical Psychology & Health Psychology, University of Fribourg
October 2014	Erasmus exchange semester, University of Vienna, Austria
June 2013	Bachelor of Science in Psychology, University of Fribourg Minors: Neurosciences, Media & Communication

Languages & IT

- German (native language), English, French
- Windows and Mac, Microsoft Office Package, SPSS, MPlus, R

Research Output

Talks

Esslinger, J. & Schoebi, D. (2020). Parent-Child Relationships at Risk: Child ADHD, Dysfunctional Behavior and low Parental Feelings of Competence. *International Association of Relationship Research (IARR) 2020 conference,* Imperial College London, UK. July 30 - August 1, 2019. Postponed to July 29 - August 2, 2021 (Covid-19 Pandemic)

Esslinger, J., Meuwly, N. & Schoebi, D. (2018). Daily Family Relationships of Children with ADHD: Behavior and Emotions in the Parent-Child Dyad. *International Association of Relationship Research (IARR) 2018 conference,* Colorado State University, Fort Collins, USA. July 15, 2018.

Esslinger, J. & Schoebi, D. (2017). Kinder fördern- Eine interdisziplinäre Studie zum Umgang mit ADHS. ADHS im Alltag- eine Verlaufsstudie. *Kinder fördern. Eine öffentliche Tagung zum interdisziplinären Umgang mit ADHS.* Collegium Helveticum, Zurich. September 21, 2017.

Esslinger, J. & Schoebi, D. (2017). Alltag und Verlauf von ADHS. *Workshop "How to support Children. An Interdisciplinary Study on Children with ADHD: First results and discussion".* Fondation Brocher, Geneva, Switzerland. May 23 & 24, 2017.

Esslinger, J., Hotz, S. & Schoebi, D. (2016). Die Erfassung des psychischen und physischen Funktionsniveaus im Alltag - Eine Verlaufsstudie. *4. Nachwuchsworkshop Familienwissenschaften.* Basel, November 9, 2016.

Posters

Esslinger, J. & Schoebi, D. (2019). Parent-child relationships with and without child ADHD: Daily strains and dysfunction. *International Association of Relationship Research (IARR) 2019 conference,* July 18-21, Brighton, UK.

Esslinger, J., Agbayani, C., Stauffer, T., Schoebi, D. & Riis, J. (2019). Time-Stamped Sample Collection in Salivary Bioscience Field Research: Problems and Pitfalls. *UCI Virtual Salivary Conference-Interdisciplinary Institute of Salivary Bioscience Research (IISBR)*. March 11-15, 2019.

Esslinger, J. (2017). Daily Family Relationships of Children with ADHD:
Emotions and Behavior in the parent-child dyad. *12th International Conference on Child and Adolescent Psychopathology.* University of Roehampton, London, UK. July 17-19, 2017.

Esslinger, J., Hotz, S., Risch, L., & Wiedemann, U. (2014). First Experiences with Non-Invasive Prenatal Testing (NIPT) in Switzerland. *64th American Society of Human Genetics (ASHG) Annual Meeting in San Diego, CA.* October 18-22, 2014.

Scientific outreach, articles in popular magazines
Magazine for parents of children with ADHD (ELPOS) (65, June 2018)
Parent Magazine Fritz + Fränzi: Stress Regulation (5/May 2018)
Parent Magazine Fritz + Fränzi: Aggressive Children (11/November 2017)
Parent Magazine Fritz + Fränzi: Multilingual Education (8/August 2017)
Parent Magazine Fritz + Fränzi, ADHD Series: ADHD and Diagnosis (4/April 2016)

Interviews in Newspapers/Magazines
Tages-Anzeiger Wissen & Der Bund (22.05.2018, Matthias Meili): Ein Labortest für Zappelphilippe
Freiburger Nachrichten (12.12.2017, Jean-Claude Goldschmid): Es begann mit dem Zappelphilipp

Teaching

Lectures
University of Fribourg
Course: Clinical Child- and Adolescent Psychology I (Psychopathology and Classification)
Topic: ADHD (22.03.2018), for Prof. Simone Munsch

Course: Classification, Etiology and Therapy of Psych. Disorders
Topic: Neurodevelopmental Disorders (3.12.2017) for Dr. Annette Cina

University of California, Irvine
Course: Salivary Bioscience
Topic: Guest lecture (25.01.2019)

Co - Supervision of Students
Master-theses:

1. Aurélie Christinaz, «Impact des symptômes de type hyperactif/impulsif sur les relations familiales», 2019
2. Morgane Bulliard, «Effet de facteurs environnementaux sur la sévérité des symptômes TDAH. », 2019
3. Alexia Marcou, «The Link Between Parents' Attachment Styles in Adult Relationships, Their Relationship to Their Child and Child Impulsivity», 2019
4. Mara Puttini, « L'impact de deux différentes formes de malveillance et leur interaction sur la fréquence des symptômes attentionnels du TDAH», 2019

5. Vanessa Pinto Martins, «Y a-t-il un cercle vicieux entre l'exacerbation des symptômes du TDA(H) provoquée par le fonctionnement familial et un impact dans le fonctionnement familial provoqué par les symptômes du TDA(H)?», 2019
6. Brigitte Leuenberger, «Subjective Well-Being of Children with ADHD in Switzerland: Factors and Processes », 2018
7. Maja Odermatt, «Elternschaft bei Kindern mit AD(H)S: Wie sich Persönlichkeit, Rejection Sensitivity und Pathologie auf Kompetenz und negative Zuwendung auswirken», 2018
8. Jessica Jeria Hevia, «L'impact du TDAH sur la famille: le lien entre la relation parentale, la satisfaction conjugale et le sentiment de compétence parentale», 2017
9. Nathalie Zinniker, «Le TDAH dans les yeux de l'insécurité: Le style d'attachement du parent biaise-t-il sa perception du trouble du déficit de l'attention/hyperactivité de son enfant?», 2017

Bachelor-theses:

1. Aline Garbani, «Kompetenzüberzeugungen und Stress bei Eltern von Kindern und Jugendlichen mit der Diagnose ADHS und komorbidem oppositionellem Trotzverhalten», 2019

Supervised Research Interns:

Aline Garbani (2017/2018), Editë Krasniqi (2018), Nelli Rotzer (2017/2018), Sarah Schmidt (2018)

Institutional Responsibility

- Member of the Department Council (2015-2018)
- Departmental Ethics Commission (2015 to 2016)
- President of the Student Council (academic years of 2010 to 2012)

Volunteer Work

- Special Assistance Team Swiss (Swiss Int. Air Lines, emergency psychology and emergency organization)
- Crewmember on the Tallship Sailing Vessel "Alexander von Humboldt II", Sail Training International Foundation

Mentoring Programs

Reseau Romand de Mentoring pour Femmes (2019)
Mentor: Prof. Tatjana Aue, University of Bern

International Association of Relationship Research (IARR) (2017)
Mentor: Prof. Jennifer Harmann, Colorado State University

Starting Doc Mentoring for Women (2015)
Mentor: Prof. Evie Vergauwe, University of Geneva

Ich erkläre ehrenwörtlich, dass ich meine Dissertation selbständig und ohne unzulässige fremde Hilfe verfasst habe und sie noch keiner anderen Fakultät vorgelegt habe.

Ort, Datum

Urbana, 21.10.2020

Unterschrift

J. Esslinger

Jacqueline Esslinger