Child Maltreatment, the Hypothalamic-Pituitary-Adrenal Axis, and Psychopathology

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The present dissertation encompasses the following studies:

Study 1

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Study 2

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Abstract

Findings from epidemiological studies increasingly show that adult mental disorders may have their roots relatively early in life, that is, in childhood and/or adolescence. Both genetic predisposition and adverse environmental factors are known to play a central role in the developmental trajectory of psychopathological outcomes. Among the environmental factors associated with the emergence of mental disorders are experiences of abuse and neglect early in life, collectively referred to as child maltreatment. According to the biological embedding model, such adverse early life experiences are assumed to cause biological scars – i.e., changes in essential biological systems – which in turn are thought to influence vulnerability to mental disorders later in life. More specifically, following corresponding adverse experiences, alterations in biological systems centrally involved in the processing of stress and emotional regulation – including the hypothalamic-pituitary-adrenal (HPA) axis – have been suggested. As a result, extensive research has been conducted to examine associations between child maltreatment experiences and long-term changes in the functioning of relevant biological systems, including studies of changes in cortisol secretion – the main effector hormone of the HPA axis. To date, however, mostly inconsistent results have been observed with regard to cortisol metabolism.

The aim of the present thesis was therefore to systematically investigate the biological embedding of altered HPA axis activity following child maltreatment. Particular attention was paid to the potential moderating/interfering influence of psychopathology. This because, on the one hand, child maltreatment experiences are strongly associated with mental disorders, and on the other hand, altered cortisol secretion has been observed in patients with mental disorders as well. Accordingly, in a first step, the potential association between the experience of child maltreatment and HPA axis functioning, including different measures of cortisol secretion (i.e., cortisol assessed in the context of the circadian rhythm, cortisol assessed in response to awakening, in response to the perception of a stressor, in response to pharmacological challenges, as well as cumulative measures of cortisol secretion), was thoroughly investigated by means of a comprehensive systematic review and meta-analysis. In a second step, differences in pituitary gland volume (PGV) – an approach to assess long-term HPA axis activity – between adolescents engaging in non-suicidal self-injury (NSSI) and healthy controls, were examined. NSSI represents a psychopathological behavior that typically develops/exacerbates during periods of elevated stress and that has been found to be strongly associated with child maltreatment experiences. In this context, particular attention was paid to whether potential structural changes could be better explained by child maltreatment or psychopathology.

The meta-analytic study conducted revealed a blunted cortisol stress reactivity in individuals exposed to child maltreatment compared to those without such experiences. Importantly, although less pronounced, participants with a history of child maltreatment who did not report a mental disorder at the time of measurement likewise showed an attenuated cortisol stress response. No overall differences, however, were found in any of the other measures of HPA axis activity (with the exception of evening cortisol). With regard to the second study, no evidence was found for overall volumetric differences in

PGV between healthy control participants and adolescents engaging in NSSI, recognizing that small effect size differences could not be detected in this study. Group membership, however, significantly interacted with age in predicting PGV. In particular, while PGV increased linearly with age in healthy controls, no such association was found in NSSI patients. Child maltreatment neither explained significant variance in PGV nor interacted with age in predicting PGV.

The present synopsis aims to integrate these findings into the context of the biological embedding model and discusses methodological limitations as well as considerations for the conduct of future studies.

Contents

1. Conceptual Framework

1.1. Mental disorders, environmental stressors, and the long-term health consequences of child maltreatment

Mental disorders are highly prevalent (Schaefer et al., 2017; Steel et al., 2014; Wittchen et al., 2011) and account for a significant proportion of disability worldwide (James et al., 2018). They are associated with an increased risk of all-cause mortality (Chesney et al., 2014; Gili et al., 2019; Walker et al., 2015) and impose enormous economic costs on societies (Trautmann et al., 2016). According to the results of a recent large-scale meta-analysis, about 60% of all mental disorders develop before the age of 25, with a peak age of onset observed at 14.5 years (Solmi et al., 2021). These findings strongly suggest that the majority of adult mental disorders may have their roots relatively early in life, that is, already in childhood and/or adolescence.

Childhood and adolescence, in turn, are characterized by important changes in brain development (Gogtay et al., 2004; Lenroot & Giedd, 2006), with increasing evidence linking aberrant brain maturation trajectories and concomitant changes in brain connectivity and functioning, respectively, to various psychiatric disorders (Goodkind et al., 2015; Paus et al., 2008; Vanes et al., 2020). While brain development critically depends on the finely controlled expression of genes (Douet et al., 2014), and family and twin studies clearly demonstrate that genetic variation accounts for a substantial portion of the risk for mental disorders (e.g., Smoller et al., 2019), it is also well known that environmental experiences are critically involved in shaping brain maturation and functioning (e.g., Lupien et al., 2009). Accordingly, environmental factors have also been shown to increase the risk for various mental illnesses (Uher & Zwicker, 2017).

Perhaps one of the most recognized environmental risk factors for psychopathology in general is the experience of stress (or stressful life events; e.g., A. B. Miller et al., 2019), particularly the experience of chronic stress early in life (e.g., Grant et al., 2004; Snyder et al., 2019). To date, a substantial body of research has linked the experience of chronic or severe stressful life events during childhood and adolescence – also referred to as early life stress or early life adversity – to the development of a broad variety of mental disorders later in life (e.g., Clark et al., 2010; Danese et al., 2009; Dube et al., 2001; Hughes et al., 2017). The National Scientific Council on the Developing Child (e.g., Shonkoff et al., 2012) has proposed a taxonomy that distinguishes between the following three distinct types of environmental stressors (or stress responses, respectively): Positive, tolerable and toxic. "Tolerable" stressors include those that present a high level of adversity or threat, such as the death of a family member or a contentious divorce; however, when buffered by a protective adult, the risk that these types of circumstances will lead to long-term health consequences is thought to be greatly reduced. "Toxic" stress experiences, on the other hand, include those that occur in the absence of a supportive adult relationship and may cause strong, frequent, or prolonged activation of the body's stress response system. A strong, frequent, or prolonged stress response, particularly, a strong, frequent or prolonged

activation of the *hypothalamic-pituitary-adrenals (HPA) axis*, in turn, has been shown to have a great potential to disrupt brain circuitries (e.g., abnormal maturation of specific brain networks; Chen & Baram, 2016), especially when experienced during sensitive developmental periods. Consequently, such toxic stress experiences are assumed to increase the risk of developing mental illnesses later in life (Shonkoff et al., 2012).

Among the various types of early life adversity that can be distinguished (e.g., social isolation, household mental illness, maternal/paternal absence, parental divorce, low socio-economic status, bullying), the experience of child maltreatment – defined by the Centers for Disease Control and Prevention (CDC) as "*any act or series of acts of commission or omission by a parent or other caregiver that results in harm, potential for harm, or threat of harm to a child*" (Leeb et al., 2008, p. 11) – is thought to represent a particularly toxic experience. This because the offender is, by definition, one or both parents/caregivers. Thus, these experiences typically lack the buffering protection from supportive adult relationships (Shonkoff et al., 2012). Child maltreatment experiences such as physical, sexual and emotional abuse, as well as any form of neglect, are indeed strongly associated with later disease risk (e.g., Dube et al., 2001) and represent an important transdiagnostic risk factor for the development of a wide range of mental and physical disorders as well as deficits in neurocognitive functioning (Bonoldi et al., 2013; Clemens et al., 2018; Cowell et al., 2015; Infurna et al., 2016; R. T. Liu et al., 2018; Norman et al., 2012; Porter et al., 2020; R.-Mercier et al., 2018). In this context, it is worth noting that several publications suggest a dose-dependent relationship – i.e., those who have suffered from more severe experiences or report more types of child maltreatment overall showing stronger associations with later health impairments (Clemens et al., 2018; Kendler et al., 2000; Norman et al., 2012). Results obtained from a large observational study including a total of 2,292 children and adolescents showed that the different types of child maltreatment had equivalent psychiatric and behavioral outcomes (Vachon et al., 2015), suggesting a shared variance in driving maltreatment effects on mental health (Cecil et al., 2017). In addition, the findings from Vachon et al. (2015) revealed that the majority of children and adolescents were typically exposed to several types of child maltreatment, indicating that most subtypes of maltreatment actually frequently co-occur, which is in line with other reports (e.g., Cecil et al., 2017; Herrenkohl & Herrenkohl, 2009).

Given the high number of children exposed to child maltreatment (bearing in mind the marked differences in prevalence rates observed between informant and self-report data; i.e., Stoltenborgh et al., 2015: sexual abuse: 0.4% respectively 7.6% (boys), 18.0% (girls); physical abuse: 0.3% respectively 22.6%; emotional abuse: 0.3% respectively 36.3%) and the non-specific associations with a wide range of adverse outcomes, it is perhaps unsurprising that the economic burden of child maltreatment is substantial and constitutes a major problem for public-health and social-welfare (Fang et al., 2012). But how is it possible that an adverse environmental experience, such as child maltreatment, can increase the lifelong risk for a wide variety of negative health outcomes – or, in other words, how does child maltreatment "get under the skin"?

1.2. Child maltreatment and developmental programming of biological systems – the biological embedding model

As noted above, there is growing evidence that environmental stressors, particularly when experienced early in life or during specific windows of developmental plasticity, can induce stable, long-term developmental consequences – for example, on brain architecture – that may in turn influence the susceptibility to develop a variety of chronic diseases, including mental disorders, later in life (for an overview see e.g., Heim et al., 2019; Heindel et al., 2015; Shonkoff et al., 2009). This process of lasting changes in biological functioning through life experiences with the potential to affect health and well-being in the long term is also known as *biological embedding* (e.g., Aristizabal et al., 2020). The exact mechanisms underlying biological embedding are, however, not yet understood in sufficient detail. Among the various processes that might be involved, one proposed mechanism is epigenetic programming (Aristizabal et al., 2020). Epigenetic programming is known to cause changes in gene expression, especially in combination with specific risk alleles, and thus has the potential to alter biological processes, including, as just mentioned, brain development and brain functioning (Berens et al., 2017; Heim et al., 2019; Jacoby et al., 2016; Smith & Mill, 2011). By impacting on structural and functional aspects of brain development, lasting effects on physiology, cognition, emotional experiences, and behavior are in turn likely to be expected (e.g., Roth & Sweatt, 2011). Over time, these changes in experience and behavior may combine to critically influence vulnerability to mental disorders.

Interestingly, as one of the body's primary stress response systems, the HPA axis, with its effector hormone cortisol (one of the major glucocorticoids), is not only well-known to be involved in mediating the stress response to toxic stressors such as child maltreatment (e.g., Shonkoff et al., 2012), but has also been shown to be an important driver of epigenetic changes in tissues such as the brain (McEwen et al., 2015; Zannas & Chrousos, 2017). Importantly, beyond its role in contributing to stress-induced epigenetic changes, there is growing evidence indicating that HPA axis functioning may itself be altered by related processes (e.g., R. S. Lee & Sawa, 2014). Studies in rats, for instance, have shown that pups whose mother exhibited low licking and grooming and arched-back nursing behavior (which serves as a paradigm for and can be interpreted as exposure to adverse early life experiences) had higher methylation levels at a transcription factor (NGFI-A) binding site of the glucocorticoid receptor (GR) gene promoter in hippocampal neurons, which in turn was associated with reduced GR expression in the hippocampus and prolonged HPA axis activity (Weaver et al., 2004). Since then, similar findings of epigenetic modifications in genes involved in HPA axis regulation including the GR gene (Palma-Gudiel et al., 2015; Radtke et al., 2015; Romens et al., 2015; Tyrka et al., 2016), as well as many other candidate genes known to be important in the development of mental disorders (Cecil et al., 2020), have been found in humans as well.

Overall, studies of the biological embedding of early life adversity suggest the development of a phenotype with alterations in brain circuits involved in stress processing and emotion regulation, and

associated changes in core stress response systems, including the HPA axis (Berens et al., 2017; Chen & Baram, 2016; Heim et al., 2019; Jacoby et al., 2016; Teicher & Samson, 2013). Indeed, various reviews highlight findings of alterations in brain morphology, functioning, and connectivity (e.g., Bick & Nelson, 2016; Teicher et al., 2016), as well as changes in key components of the stress response system (e.g., Hakamata et al., 2022; Koss & Gunnar, 2018; Sigrist et al., 2021) in relation to the experience of child maltreatment. These biological changes, in turn, may influence the lifelong risk, presumably as a function of later life environment (e.g., Daskalakis et al., 2013), to develop a wide range of adverse outcomes over time (e.g., Heim et al., 2019).

1.3. The HPA axis and its effector hormone cortisol

In summary, on the one hand, there is increasing evidence that the HPA axis is centrally involved in mediating the biological embedding of child maltreatment. On the other hand, evidence suggests that the functioning of the HPA axis itself may be altered in the long term by this process. Before discussing this in more detail, a brief overview of this essential neuroendocrine system involved in the human stress response will follow.

The HPA axis, in keeping with its name, consists of the hypothalamus, the anterior pituitary gland, and the adrenal glands, each of which contains cells that secrete specialized hormones. Activation of the HPA axis leads to the release of the corticotropin releasing hormone (CRH) from the hypothalamus, which in turn triggers the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH ultimately induces the de novo synthesis and release of cortisol from the adrenal glands. Cortisol is released into the systemic circulation and binds to specific blood proteins (primarily corticosteroid binding globulin; CBG) to circulate throughout the body. Only about 10% of cortisol is free and therefore biologically active. Immediately upon release, cortisol inhibits its own further release by feeding back at the level of the pituitary gland and the hypothalamus (for a comprehensive review, see Spencer & Deak, 2017).

While cortisol is involved in the regulation of a plethora of physiological processes important for maintaining and restoring homeostasis (or allostasis), it is best known for its ability to elevate blood glucose levels and for important anti-inflammatory and immunosuppressive functions (e.g., Sapolsky et al., 2000). In addition, effects on brain morphology and functioning, particularly in limbic brain areas such as the amygdala, the hippocampus, and the prefrontal cortex – brain regions that have a high density of GRs – are well documented (McEwen et al., 2015; Shirazi et al., 2015). Cortisol released during a stress response, for instance, is known to enhance the consolidation of new memories but interferes with the retrieval of information stored in long-term memory (e.g., de Quervain et al., 2017).

The effects on target cells are mainly mediated by binding to two specific receptors, the GR (NR3C1; Oakley & Cidlowski, 2013) and the mineralocorticoid receptor (MR, NR3C2; Gomez-Sanchez & Gomez-Sanchez, 2014). These two receptors are differentially expressed in the body and have different binding affinities for cortisol. Due to the much higher affinity of cortisol for the MR, this

receptor is mostly occupied under basal conditions, whereas the GR becomes increasingly occupied during a stress response or at the peak of the circadian cycle. The effects on cells are mostly genomic and occur within minutes to hours upon receptor binding (e.g., Spencer & Deak, 2017). In the brain alone, cortisol regulates the transcription of various genes involved in the regulation of a multitude of different cellular processes, such as inflammation, growth, or energy production (Juszczak & Stankiewicz, 2018).

1.4. Various measures of HPA axis activity

Consistent with its central role as a stress response system, HPA axis activity is typically triggered by various stressors (e.g., pain, chemical, metabolic, or psychosocial stimuli; Lu et al., 2021) – also referred to as the cortisol stress reactivity. The marked increase in cortisol following a stressor helps to adapt to the homeostatic challenge and thus has different functions depending on the biological system under investigation (e.g., cardiovascular system, immune system; Nicolaides et al., 2015; Sapolsky et al., 2000). Stressors such as pain or specific homeostatic signals, which represent real sensory stimuli, can induce a so-called reactive cortisol response and are mainly mediated by brain structures with direct connections to the hypothalamus such as several brainstem and other hypothalamic nuclei. On the other hand, stressors such as social challenges, which lack primary sensory stimuli signaling homeostatic disruption, often induce an anticipatory cortisol response. Structures involved in controlling these anticipatory responses include limbic brain regions such as the hippocampus, the amygdala and the prefrontal cortex, all of which have indirect connections to the hypothalamus (for a detailed review, see Herman et al., 2003). Interestingly, all of these limbic structures are known to be affected by the experience of child maltreatment (e.g., McEwen, 2012). To date, several studies have examined the relationship between aberrant cortisol stress reactivity and mental health. A series of meta-analyses on the association between borderline personality disorder (BPD) and HPA axis functioning, for instance, found a blunted cortisol stress response in patients with BPD compared to healthy and clinical controls (Drews et al., 2019). Another meta-analysis showed aberrant stress reactivity in patients with depression, patients with anxiety disorders, and patients with schizophrenia, with the direction of dysfunction partially mediated by sex (Zorn et al., 2017). Finally, female adolescents who engage in non-suicidal self-injury (NSSI), a behavior that is clearly linked to the experience of child maltreatment (Serafini et al., 2017), and that typically develops/exacerbates during periods of elevated stress (A. B. Miller et al., 2019) – comparably to the findings from the BPD literature – have been found in some studies to show an attenuated cortisol response to acute psychosocial stress (Kaess et al., 2012; Klimes-Dougan et al., 2019).

In addition to its central role as a stress response system, levels of cortisol strongly increase following the first 30-45 minutes after awakening. This surge in cortisol is closely associated with awakening and is therefore called the cortisol awakening response (CAR). Brain structures heavily involved in regulating the CAR are the central pacemaker – the suprachiasmatic nucleus (SCN) – and

the hippocampus, with the hippocampus playing an important role in inhibiting pre-awakening cortisol secretion (for a comprehensive review, see Clow, Hucklebridge, Stalder, et al., 2010). However, the exact biological function of the CAR is still unknown. It is assumed, that the strong rise in cortisol may be important for the transition from sleep to full alertness, for preparing a person for the demands of the upcoming day, and for switching the immune system form nighttime Th1 to daytime Th2 dominance (Clow, Hucklebridge, & Thorn, 2010). In addition, peak levels may also reflect a timing signal that helps regulate other local tissue clocks and thus rhythmic physiology (Spencer et al., 2018). A meta-analysis synthesizing existing data on the association between the CAR and various psychosocial factors, found that an increased CAR was related to both job and general life stress, whereas a blunted CAR was associated with exhaustion, burnout, and fatigue (Chida & Steptoe, 2009).

In addition to this closely linked release to awakening, the activation of the HPA axis, and thus the release of cortisol, exhibits an important circadian rhythm, with the highest cortisol levels measurable in the early morning hours (typically not including the CAR). Thereafter, levels decline, reaching their nadir during the first half of the night. This circadian pattern is primarily regulated by the SCN (and is therefore tightly linked to the sleep-wake schedule), changes in adrenal sensitivity to ACTH influenced by the autonomic nervous system, and a local adrenal molecular clock system, influencing circadian cortisol synthesis. Changes in cortisol concentrations caused by these rhythms appear to be important for optimal metabolic and cognitive functioning, as well as for an adequate stress responsiveness (for a comprehensive review, see Spiga et al., 2014). The difference between bedtime cortisol levels and awakening levels, called the diurnal slope (DSL), represents an attempt to measure some aspects of these circadian rhythms in humans (e.g., Adam & Kumari, 2009). In the past, various negative health outcomes, including mental disorders, have been associated with a flatter DSL (Adam et al., 2017).

Aside from the assessment of cortisol following the perception of a stressor and in relation to circadian signals, HPA axis functioning and reactivity can be probed by pharmacological challenge tests. These include the dexamethasone suppression test (DST; B. J. Carroll et al., 1981), the combined dexamethasone-corticotropin releasing hormone (Dex-CRH; Watson et al., 2006), and the corticotropin releasing hormone (CRH; Gold et al., 1986) test. These tests, especially the DST, were initially developed as laboratory screening tests for the diagnosis of endogenous Cushing's syndrome, a syndrome associated with cortisol hypersecretion (e.g., Nugent et al., 1965), but were also increasingly used in psychiatry as initially promising diagnostic tools for depression, mainly melancholia (B. J. Carroll et al., 1981). Oral administration of dexamethasone, a synthetic glucocorticoid, causes the suppression of ACTH release from the pituitary gland and thus the release of cortisol by binding to GRs, mainly in corticotrophic cells. Therefore, the measurement of cortisol after the administration of dexamethasone represents a method to measure the negative feedback mechanism of the HPA axis. Intravenous administration of CRH, on the other hand, measures the responsiveness of the pituitary to CRH. Changes in cortisol release following these stimulation tests have been associated with different

and sometimes opposing alterations for various mental disorders (for a comprehensive review, see Leistner & Menke, 2018).

In addition to the aforementioned HPA axis activity measures, cortisol can also be measured in either urine or hair, reflecting cumulative measures of cortisol secretion. Twenty-four-hour urinary free cortisol (24-hour UFC) reflects the excretion of unmetabolized (free) cortisol via urine over a 24-hour period and can be used to assess cortisol excess (Deutschbein et al., 2011; Moore et al., 1985). It is not affected by diurnal variation or by CBG levels (Turpeinen & Hämäläinen, 2013). Cortisol measured in hair (hair cortisol concentration, HCC) reflects another relatively recent methodological development to assess long-term cortisol secretion. It is suggested that cortisol is incorporated into the growing hair; the exact mechanism, however, is not yet fully elucidated. Given that the average growth rate of hair is approximately 1 cm/month, it is proposed that 3 cm of hair reflects the integrated cortisol exposure of the last three months (for review, see Meyer & Novak, 2012; Stalder & Kirschbaum, 2012). A meta-analysis on stress-related and basic determinates of HCC showed that the experience of chronic stress was associated with higher HCC levels, especially when the stressor was still ongoing. Those individuals with absent/past chronic stress, on the other hand, showed a tendency for reduced HCC (not statistically significant). The authors also found reduced HCC in patients with posttraumatic stress disorder (PTSD), but inconsistent results were found for mood disorders (Stalder et al., 2017).

Finally, a more indirect approach to assessing long-term HPA axis activity is to assess the pituitary gland volume (PGV) – an inherent structure of the HPA axis – using structural magnetic resonance imaging (MRI). Compared to the biochemical characterization (i.e., measuring cortisol in blood or saliva), this approach is much less state-dependent, reflects a more proximal trait, and allows the investigation of the potential origin of altered HPA axis output (Anastassiadis et al., 2019; Kaess et al., 2018). Although believed to be less state-dependent, the pituitary gland can undergo volumetric changes in response to functional demands (e.g., Dinč et al., 1998; Wong et al., 2014). For instance, increased HPA axis activity has been found to be related to hypertrophy of ACTH secreting pituitary cells in rats (Westlund et al., 1985). Overall, PGV has been considered a measure of chronic HPA axis functioning (e.g., Farrow et al., 2020; Ganella et al., 2015; Kaess et al., 2018), and structural differences in PGV have been found in various stress-related mental disorders, although again there is considerable inconsistency in findings (Anastassiadis et al., 2019).

1.5. Child maltreatment, biological embedding, the HPA axis and aberrant cortisol release

To summarize, the experience of child maltreatment reflects a well-documented environmental risk factor for the development of a wide range of mental and physical disorders later in life. According to the *biological embedding model*, such adverse experiences are assumed to cause lasting changes in biological functioning, including changes in biological systems involved in stress and emotion regulation, which are thought to be maintained through processes such as epigenetic programming. The resulting "biological scars", in turn, are thought to influence the lifelong risk for a variety of health

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disparities. One essential system that appears to not only be involved in mediating the biological embedding of child maltreatment, but may also be altered in its own functioning in the long run, thereby increasing the risk for various diseases later in life, is the HPA axis. This vital neuroendocrine system, triggered by both the perception of stressors and circadian signals, is involved in the regulation of a plethora of physiological processes important for maintaining and restoring homeostasis (or allostasis). In light of findings of epigenetic changes in genes important for regulating HPA axis activity, as well as findings of altered brain morphology, functioning, and connectivity in brain areas known to be involved in controlling cortisol secretion (i.e., the amygdala, the hippocampus, and the prefrontal cortex), long-term changes in the functioning of this system in individuals exposed to child maltreatment are indeed likely to be expected. In addition, supporting the notion that altered HPA axis functioning may be a risk factor for psychopathology, there are now numerous studies indicating that cortisol release is altered in several adverse health conditions, including various mental disorders; keeping in mind, however, that overall results are quite heterogeneous and inconsistent.

Drawing from the preceding considerations, it is perhaps not surprising that the association between child maltreatment and changes in cortisol secretion, including the various measures of HPA axis activity mentioned above, has been extensively studied in the past. However, similar to the psychopathology literature, the findings to date have been predominantly inconsistent – especially with respect to the direction of the reported change (hypercortisolism versus hypocortisolism; e.g., Carpenter et al., 2007; Heim et al., 2000). Both conditions, hypercortisolism and hypocortisolism, on the other hand, are associated with health impairments, as shown by the two rare diseases Cushing's syndrome and Addison's disease (Betterle et al., 2019; Feelders et al., 2012). Importantly, in addition to suggesting a "programming effect", the *biological embedding model* does not anticipate the form of the potential change in HPA axis functioning (e.g., Young et al., 2021).

2. Present Thesis

Accordingly, within the scope of the present thesis, in a first step, the *biological embedding model* of altered HPA axis activity, including all of the previously introduced measures of cortisol secretion (exception: PGV) following the experience of child maltreatment, was thoroughly investigated by means of a comprehensive systematic review and meta-analysis. In this context, the influence of several potential moderators known to influence cortisol secretion was examined. Among the various moderators investigated, the potential influence of psychopathology on the effect of child maltreatment on changes in cortisol secretion was of particular interest, as several studies have shown altered cortisol secretion in patients with mental disorders as well (e.g., Drews et al., 2019; Kaess et al., 2012; Klimes-Dougan et al., 2019; Zorn et al., 2017). Due to the close relationship between the experience of child maltreatment and psychopathology, these studies cannot rule out the possibility that the observed changes in cortisol secretion were actually caused by childhood adversity and may have been present even prior to the development of the respective mental health conditions. Specific polymorphisms of

those genes involved in the regulation of HPA axis activity, which are known to be epigenetically regulated by the experience of chronic stress, for instance, have also been found to be related to an increased risk of developing psychopathology (e.g., Fan et al., 2021; Ising et al., 2008; Mahon et al., 2013). In addition, brain structures known to regulate HPA axis activity (i.e., hippocampus, amygdala, prefrontal cortex) have been found to be similarly altered in individuals with mental disorders (e.g., McEwen, 2012). Accordingly, psychopathology might also be related to HPA axis dysregulation, independent of childhood adversity. Or, as an additional possibility, changes in HPA axis activity might to be observed only in those who develop a mental disorder and not in those who remain healthy over time (i.e., only those who develop a mental disorder show the biological embedding of child maltreatment in terms of changes in HPA axis activity; the others remain resilient). Thus, psychopathology may confound or moderate the relationship between child maltreatment and cortisol and should therefore be considered carefully. In a second step, differences in PGV between adolescents engaging in NSSI and healthy controls were examined. As previously indicated, child maltreatment reflects an important risk factor for NSSI (Serafini et al., 2017), the behavior typically develops/exacerbates during periods of elevated stress (A. B. Miller et al., 2019), and studies have found alterations in the cortisol stress response in these patients as well (Kaess et al., 2012; Klimes-Dougan et al., 2019). Thus, in the context of this study, we were interested in whether structural alterations could be found at the level of the pituitary gland and whether the potential alterations could be better explained by the experience of child maltreatment or psychopathology.

2.1. Manuscript

Child maltreatment and hypothalamic-pituitary-adrenal axis functioning: A systematic review and meta-analysis

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Highlights

- Changes in HPA axis functioning assumed as a result of child maltreatment (CM).
- This meta-analysis revealed blunted cortisol stress reactivity in CM exposed group.
- No overall effects were found for any other HPA axis activity measure.
- Sex and study quality accounted for some of the between-study heterogeneity.
- Methodological flaws of primary studies hamper comprehensive conclusion.

Abstract

Alterations in hypothalamic–pituitary–adrenal (HPA) axis and its effector hormone cortisol have been proposed as one possible mechanism linking child maltreatment experiences to health disparities. In this series of meta-analyses, we aimed to quantify the existing evidence on the effect of child maltreatment on various measures of HPA axis activity. The systematic literature search yielded 1,858 records, of which 87 studies ($k = 132$) were included. Using random-effects models, we found evidence for blunted cortisol stress reactivity in individuals exposed to child maltreatment. In contrast, no overall differences were found in any of the other HPA axis activity measures (including measures of daily activity, cortisol assessed in the context of pharmacological challenges and cumulative measures of cortisol secretion). The impact of several moderators (e.g., sex, psychopathology, study quality), the role of methodological shortcomings of existing studies, as well as potential directions for future research are discussed.

1. Introduction

Child maltreatment is a widespread phenomenon that affects the lives of millions of children worldwide (Stoltenborgh et al., 2015; Witt et al., 2017). Despite extensive research on the consequences of the experience of child maltreatment, surprising heterogeneity exists across studies with respect to its operational definition (Cicchetti & Toth, 2005; Leeb et al., 2008; Manly, 2005). Researchers, however, generally agree that child maltreatment involves both acts of commission – including physical, sexual, and emotional (psychological) abuse – as well as acts of omission (i.e., any form of neglect) by a parent or other caregiver that results in harm, potential for harm, or threat of harm to a child (usually interpreted as up to 18 years of age; Gilbert et al., 2009; Leeb et al., 2008). Typically, maltreated children experience multi-type maltreatment, suggesting that the different forms of maltreatment often co-occur (Herrenkohl & Herrenkohl, 2009; Vachon et al., 2015). While inconsistencies exist between studies in terms of its definition, extensive research, including findings from prospective and retrospective cohort studies (e.g., Clark et al., 2010; Danese et al., 2009; Dube et al., 2001) as well as twin studies (Kendler et al., 2000; Nelson et al., 2002), has shown that the experience of child maltreatment represents a profound, non-specific risk factor for the development of a broad variety of mental (e.g., Bonoldi et al., 2013; Carr et al., 2013; Dube et al., 2001; Infurna et al., 2016; R. T. Liu et al., 2018; Norman et al., 2012; Porter et al., 2020; Teicher & Samson, 2013) as well as physical disorders (e.g., Clemens et al., 2018; Hemmingsson et al., 2014). Importantly, most publications indicate a dose-dependent relationship between the experience of child maltreatment and the risk for health impairments, with those reporting more severe experiences or an increasing number of different types of child maltreatment showing stronger associations (Clemens et al., 2018; Dube et al., 2001; Hemmingsson et al., 2014; Kendler et al., 2000; Norman et al., 2012).

One proposed mechanism by which child maltreatment might affect later disease risk involves epigenetic programming – a mechanism known to cause long-lasting changes in gene expression, especially in combination with specific risk alleles, thereby inducing long-lasting changes in biological functioning (i.e., biological embedding; Heim et al., 2019; Jacoby et al., 2016; Smith & Mill, 2011). It is assumed that particularly the expression of several genes relevant to stress regulation might be affected, ultimately leading to the development of a phenotype with core dysfunctions in circuits of the brain involved in the processing of stress and emotion regulation, and related changes in core outflow stress response systems, including – and this will present the focus of the current meta-analysis – the hypothalamic-pituitary-adrenal (HPA) axis (Chen & Baram, 2016; Heim et al., 2019; Jacoby et al., 2016; Koss & Gunnar, 2018; Strüber et al., 2014). In turn, these core dysfunctions might then increase the lifelong risk for the development of a wide range of adverse outcomes later in life (e.g., Heim et al., 2019).

As an important stress response system, HPA axis activity and associated cortisol secretion – i.e., *cortisol stress reactivity* – serves various functions, depending on the system under investigation (e.g., cardiovascular system, immune system), together being important for survival and restoring

homeostasis (adapting to a homeostatic challenge; Nicolaides et al., 2015). Importantly, structures centrally involved in controlling stress-induced HPA axis activity (particularly anticipatory responses to social challenges) include limbic brain regions such as the hippocampus, the amygdala, and the prefrontal cortex (for a detailed review, see Herman et al., 2003), structures also well-known to be affected by chronic stress such as the experience of child maltreatment (e.g., McEwen et al., 2015, 2016; Shirazi et al., 2015; Teicher et al., 2016). Interestingly, an aberrant cortisol stress response has been observed in patients with various mental health problems including borderline personality disorder (BPD), anxiety disorders, depression, and schizophrenia (e.g., Drews et al., 2019; Zorn et al., 2017).

Aside from its central role as a stress response system, HPA axis activity and associated cortisol secretion, in addition to stressors, is also triggered by other regulatory control factors, including circadian signals (for a comprehensive overview, see Spencer & Deak, 2017). Accordingly, in addition to the well-known cortisol stress response, several other measures of HPA axis activity can be distinguished. These include the *cortisol awakening response* (*CAR*; Clow, Hucklebridge, Stalder, et al., 2010; Fries et al., 2009; Spencer et al., 2018), *diurnal cortisol* (*DC*; Adam & Kumari, 2009; Segerstrom et al., 2014; Spiga et al., 2014), cortisol assessed following pharmacological challenge tests (i.e., the *dexamethasone suppression test* (*DST*), the *combined dexamethasone-corticotropin releasing hormone test* (*Dex-CRH*), and the *corticotropin-releasing hormone test* (*CRH*); B. J. Carroll et al., 1981; Gold et al., 1986; Watson et al., 2006), as well as cumulative measures of cortisol secretion including *24-hour urinary free cortisol* (*24-hour UFC*; Deutschbein et al., 2011; Moore et al., 1985) and *hair cortisol concentrations* (*HCC*; for an overview, see Meyer & Novak, 2012; Stalder & Kirschbaum, 2012). Interestingly, similar to findings related to the cortisol stress response, alterations in these other HPA axis activity measures have been associated with various mental and physical health problems as well, although substantial inconsistencies exist among findings (e.g., Adam et al., 2017; Berger et al., 2016; Chida & Steptoe, 2009; Leistner & Menke, 2018; Stalder & Kirschbaum, 2012).

To summarize, a growing number of studies indicate associations between the experience of child maltreatment and epigenetic changes in key genes involved in stress regulation. Interestingly, epigenetic changes have been found in genes important for the regulation of HPA axis activity, such as in the GR gene, the FKBP5 gene and the CRH gene (Hoffmann & Spengler, 2012; Klengel et al., 2013; Palma-Gudiel et al., 2015; Turecki & Meaney, 2016). Together with findings of altered brain morphology, functioning and connectivity, especially in brain regions involved in the regulation of HPA axis activity (e.g., McCrory et al., 2010; Teicher et al., 2016), long-lasting changes in the regulation of this system in individuals exposed to child maltreatment are suggested. If additionally, the manifold biological effects of cortisol are considered (e.g., Sapolsky et al., 2000), a dysregulation in the release of this hormone might increase the susceptibility for a wide variety of negative health outcomes, particularly in combination with other stressful experiences later in life. As discussed above, alterations in several measures of HPA axis activity have indeed been linked to various health conditions including psychopathology. Accordingly, the association between child maltreatment and alterations in cortisol

secretion has been widely investigated, including various measures of HPA axis activity. However, findings are inconclusive, with inconsistencies reported (similarly with findings related to psychopathology), specifically regarding the direction of alteration (hyper- versus hyposecretion). To date, three meta-analyses have investigated the association between adverse childhood experiences and aberrant cortisol secretion (Bernard et al., 2017; Bunea et al., 2017; Fogelman & Canli, 2018), whereby two of them focused on early life adversity (ELA) in general and one specifically on child maltreatment. With respect to cortisol stress reactivity, the meta-analysis conducted by Bunea and colleagues (2017) revealed a blunted cortisol stress response to social stressors in those with a history of ELA. In contrast to these findings, the two other meta-analyses failed to show alterations in circadian rhythms, including measures such as the diurnal slope (DSL) as well as the CAR (Bernard et al., 2017; Fogelman & Canli, 2018).

When examining the relationship between child maltreatment and HPA axis activity, careful control of several potential moderators may be of particular importance. As mentioned previously, various mental disorders have been linked to alterations in HPA axis functioning (e.g., Chida & Steptoe, 2009; Stalder et al., 2017; Zorn et al., 2017). The meta-analysis conducted by Zorn et al. (2017), for instance, was able to show that women with major depressive disorder (MDD), women with an anxiety disorder and patients with schizophrenia show a blunted cortisol stress response to psychosocial stressors compared to healthy control participants. The meta-analysis conducted by Drews et al. (2019) similarly found evidence for an overall attenuated cortisol stress response in patients with BPD. Due to the close association between the experience of child maltreatment and psychopathology, these studies, however, cannot rule out the possibility that the observed endocrinological alterations were actually caused by childhood adversity and may have been present even before the development of the respective mental health conditions. Moreover, beyond the epigenetic changes found in genes important for the regulation of HPA axis activity that are likely caused by the experience of chronic stress, such as the experience of child maltreatment, specific polymorphisms of respective genes associated with differences in cortisol secretion independent of child maltreatment have also been found to be related to an increased risk of developing mental disorders (Fan et al., 2021; Ising et al., 2008; Mahon et al., 2013). Accordingly, psychopathology may interfere with or moderate the relationship between child maltreatment and cortisol, and should therefore be considered carefully. In addition, several lines of evidence suggest that women are generally more prone to mental disorders, particularly stress-related disorders, and that sex hormones might account for some of these findings (S. H. Li & Graham, 2017). Interestingly, marked sex differences have also been reported with respect to HPA axis functioning (Foley & Kirschbaum, 2010; Stalder et al., 2016; Stalder & Kirschbaum, 2012; Zänkert et al., 2019), indicating that in order to accurately capture the relationship between child maltreatment and cortisol, the influence of sex should be considered as well. Furthermore, there is some support that hormonal activity is elevated at stressor onset (e.g., at the time of child maltreatment) and reduces with passing time (e.g., with increasing age; G. E. Miller et al., 2007), implying that the age of the population studied

may likewise be important. Finally, ethnic differences in HPA axis functioning have been found (Boileau et al., 2019), keeping in mind, of course, that minorities are generally exposed to more adversity (e.g., M. O'Connor et al., 2020), which in turn may explain this association.

A number of variables related to the measurement of child maltreatment may also be important when investigating the association between child maltreatment and HPA axis functioning. These include the assessment modality employed (e.g., informant versus self-reports), the various approaches to defining the presence of child maltreatment (e.g., records, cut-offs, specifications), the age at maltreatment onset, as well as the chronicity of the maltreatment experiences. For instance, a nationally-representative birth cohort study, the Environmental Risk (E-Risk) Longitudinal Twin Study, demonstrated that retrospective self-report data of child maltreatment were more strongly associated with adult psychopathology than prospective informant reports (Newbury et al., 2018). Chronic maltreatment starting early in life is generally associated with poorer neurocognitive functioning and worse psychopathology (Cowell et al., 2015; Jaffee & Maikovich-Fong, 2011; Kaplow & Widom, 2007). In addition, findings suggest that chronic exposure to stress hormones can impact brain structures differently, depending on the timing and duration of the exposure (Lupien et al., 2009). Thus, effects on HPA axis functioning might vary depending on the age of first child maltreatment experience and/or the chronicity of these experiences.

Furthermore, studies vary widely regarding the assessment of cortisol. Depending on the HPA axis activity measure of interest, some of these variations may account for additional variability in the child maltreatment cortisol relationship. Variables that have been associated with different cortisol findings include, for instance, sample type (blood versus saliva; Spencer & Deak, 2017), slope type, and whether morning samples were collected at awakening for diurnal cortisol (Adam et al., 2017; Ryan et al., 2016), as well as the type of stressor in the context of the cortisol stress reactivity (social-evaluative versus other; e.g., Dickerson & Kemeny, 2004; Zänkert et al., 2019), and differences might emerge depending on how well a task can elicit a cortisol response. In addition, the variation in dosage of dexamethasone in pharmacological stimulation tests (0.5 mg versus 1.0 mg) might account for variability as well (Leistner & Menke, 2018).

Finally, several aspects of methodological quality need to be considered when attempting to quantify the relationship between the experience of child maltreatment and HPA axis functioning. Besides matching the child maltreatment and the control group with respect to age, sex, and psychopathology, and ensuring that no one from the control group was exposed to child maltreatment experiences, these include instructions for sampling and collection, the day and timing of sampling, as well as controlling for specific state covariates such as being sick or experiencing any current stress at the time of testing, with these methodological variables differing to some extent between the various HPA axis activity measures. For a comprehensive overview and corresponding references, see Appendix B Tables B1–B7. Finally, there are certain disease states (e.g., addictions, endocrine diseases), various drugs (e.g., glucocorticoids, psychoactive medications), and sex hormone-dependent variables (e.g.,

menstrual cycle, oral contraceptive intake, pregnancy) that can strongly influence cortisol levels (e.g., Foley & Kirschbaum, 2010; Granger et al., 2009; Kudielka et al., 2012; Kudielka & Wüst, 2010; Locatelli et al., 2009; Stalder et al., 2016; Zänkert et al., 2019). Considering that participants with experiences of child maltreatment are more likely to suffer from medical conditions, are at increased risk for substance abuse, and more often experience unintended teenage pregnancy (e.g., Hughes et al., 2017), factors related to altered cortisol secretion (e.g., Foley & Kirschbaum, 2010; Stalder et al., 2016; Stalder & Kirschbaum, 2012), careful assessment and matching between groups (i.e., maltreated versus control group) on these variables is of major importance.

Thus, in this comprehensive systematic review and meta-analysis, we aimed to quantify existing evidence on the effect of child maltreatment on cortisol metabolism, including all of the previously mentioned measures of HPA axis activity. In contrast to existing meta-analyses, we were particularly interested in the potential influence of psychopathology in interfering or moderating the effect of child maltreatment on changes in cortisol secretion. Accordingly, psychopathology, and especially the matching of the groups (psychopathology versus no psychopathology) was recorded thoroughly. Furthermore, we were interested in a range of other factors likely to moderate the effect of child maltreatment on cortisol regulation, such as age at the time of study participation, sex, ethnicity, child maltreatment assessment method (informant versus self-report), child maltreatment grouping method (i.e., cut-off scores, child protective services (CPS) records, other), age at the time of child maltreatment onset, chronicity of the child maltreatment experiences, as well as variables related to the assessment of the corresponding HPA axis activity measure. We considered different indices for each HPA axis activity measures, at least including one index of total cortisol production and one index reflecting change in cortisol over time (sensitivity of the system; Pruessner et al., 2003). In contrast to the existing meta-analyses, the present investigation sought to determine whether aberrant cortisol secretion patterns following child maltreatment can be observed in both of these largely independent components of HPA axis activity. Finally, a comprehensive quality assessment based on expert guidelines was developed for each activity measure, and several elements of methodological quality and their potential moderating role were investigated.

2. Methods

2.1. Systematic literature search

Articles were identified by searching the electronic databases Pubmed, PsycINFO, Web of Science (WOS) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from their inception to June 2018. The search consisted of titles and abstracts and used the following search string: ("maltreatment" OR "neglect" OR "emotional abuse" OR "sexual abuse" OR "physical abuse" OR "childhood trauma") AND ("hypothalamic–pituitary–adrenal" OR "HPA" OR "cortisol" OR "adrenocorticotropic hormone" OR "ACTH"). Moreover, the reference lists of the prior meta-analyses

on HPA axis functioning and child maltreatment (or ELA) were checked, as were studies proposed by authors who were contacted in the context of data collection.

2.2. Selection criteria

Studies were included if they: (1) involved human participants of all ages; (2) reported on at least one measure of child maltreatment (e.g., self-report [questionnaire, interview], report by an outside source [CPS record, parental report] or self-identification), whereby child maltreatment was defined according to the definition provided by the Centers for Disease Control and Prevention ("*any act or series of acts of commission or omission by a parent or other caregiver that results in harm, potential for harm, or threat of harm to a child*"; Leeb et al., 2008, p. 11) including the subtypes emotional, physical, sexual abuse, as well as neglect; (3) reported measuring cortisol levels, either as indicator of daily activity (DC, CAR), in response to a stressor (cortisol stress reactivity) or pharmacological challenges (DST, Dex-CRH, CRH), or as a cumulative index (24-hour UFC or HCC). All assessment methods, i.e., saliva, blood (serum, plasma), urine and hair, were eligible. Additionally, several preconditions were formulated for the various measures of HPA axis activity: With respect to DC at least two sampling time points, one cortisol assessment in the morning (best with reference to awakening) and one in late afternoon/evening, had to be available (Segerstrom et al., 2014). In case of the CAR, only studies that collected at least two samples, with the first sample anchored to awakening and a second sample between +30 min or +45 min post-awakening, were included (Stalder et al., 2016). With regard to the cortisol stress reactivity, studies needed to collect at least one cortisol baseline measure (before being introduced to a stressor) as well as a sample between +20 and +40 min post-stressor onset to capture the peak of the cortisol stress response (Dickerson & Kemeny, 2004). UFC had to be collected over a period of 24 h (Moore et al., 1985) and studies assessing HCC needed to focus on the first 3 cm hair segment (Meyer & Novak, 2012). No restrictions were applied to studies involving pharmacological stimulation tests. Articles were excluded for one or more of the following reasons: (1) evaluated a non-human sample; (2) were not written in English or German; (3) did not contain primary data (e.g., systematic reviews, meta-analysis, book chapters); or (4) were not peer reviewed (e.g., dissertations, master-theses, conference abstracts). Additionally, studies that included (5) participants with substance abuse (e.g., alcohol, cocaine); (6) individuals who suffered from a medical condition (e.g., endocrine disorder, chronic fatigue, chronic pain); or studies including (7) pregnant women or women in the postpartum period (up to 6 months) were excluded, given the well-known effects of these factors on HPA axis activity (e.g., Stalder et al., 2016; Zänkert et al., 2019). Studies were first screened based on their title and abstract and then further examined in full text in case of suitability.

2.3. Data extraction

As mentioned earlier, for each of the HPA axis activity measures (exception: 24-hour UFC and HCC) several outcome indices were defined, including at least one measure for total cortisol production and

one measure reflecting changes in cortisol over time. For DC, these included waking (morning) and bedtime levels (for total cortisol) as well as the delta between bedtime and waking cortisol samples (reflecting change over time; DSL). For the CAR, the following assessment time points or indices were extracted: waking cortisol, peak cortisol (expected between +30 and +45 min post awakening), end cortisol (assessed +60 min post awakening), peak reactivity (delta between the peak and the waking cortisol sample) as well as the area under the curve with respect to the ground (AUC$_g$; reflecting total cortisol production) and the area under the curve with respect to increase (AUC$_i$; reflecting changes over time; for more details regarding these two formulas, see Pruessner et al., 2003). Similarly, the following assessment time points or indices were extracted for the cortisol stress reactivity, the CRH- and the Dex-CRH-test: baseline cortisol (before being introduced to a stressor; before CRH injection), peak levels, recovery levels (last sample assessed), peak reactivity (defined as delta between peak and baseline levels), AUC$_g$ and AUC$_i$. In some of the studies, the timing of the peak differed between the child maltreatment and the control group and the values at the individual peak times were extracted for each group. Whenever a peak occurred in only one of the groups, the value at that peak time was extracted also for the other group. There were also studies in which neither group showed a cortisol response following the perception of a stressor. In this case the values were extracted at the time a response would have been expected (around +30 min post stressor onset). For these few studies, however, no peak reactivity values were extracted or included in this meta-analysis. For the DST, cortisol assessed in the morning prior administration of dexamethasone (which was normally administrated at 11 pm) and cortisol measured the next day, as well as the delta between these two measurement time points were extracted. As we were interested in obtaining all of the defined outcome indices from each study, the authors of all studies containing missing information were contacted with a data request. The data request consisted of an excel file containing all the variables of interest. Since we assumed that the requested additional calculations were relatively time-consuming, one option was to send us the raw data, with which we calculated the desired indices. If the data could not be provided, whenever possible, means and standard deviations were extracted from tables or text. If those data were not available, data were extracted from figures using a web-based digitizer (Rohatgi, 2020). Two independent reviewers extracted the data from the corresponding figures and the mean value of both extractions was calculated. If not clearly stated in the text or in the subheading of the figures, we assumed that they represented means and standard errors. Standard deviations were calculated from standard errors or from confidence intervals using the RevMan Calculator provided by the Cochrane group (Drahota & Beller, 2020). If none of these data sources were available, the study was excluded. In case of multiple publications based on the same cohort, the study with the largest sample size or the one that provided extractable data was included. Whenever possible, non-transformed (raw) cortisol data were extracted. In the case of more than two groups described in the paper, we extracted the data from those two groups that best matched in terms of psychopathology, or if the data of two groups could be combined, weighted means and standard deviations were calculated using the StatsToDo software (https://www.statstodo.com/index.

php). If a study included both a clinical and a healthy control group and appropriate measures of child maltreatment were taken in both groups, data were requested or extracted separately for these two subgroups. If the experience of child maltreatment was assessed but grouping was based on other criteria, the authors were asked to (re)group participants based on the presence or absence of child maltreatment or, in case of cut-off scores, in high versus low child maltreatment groups (see Appendix A for details on the respective (re)grouping method of the studies in question). Finally, if a measure did not just assess child maltreatment but other traumatic experiences as well, such as it is the case for the Early Trauma Inventory (ETI; Bremner et al., 2000), authors were requested to group participants including only the subscales which assessed child maltreatment. However, this was not always possible, which is why some of the included studies did not focus on child maltreatment only, but on ELA in general. The few studies to which this applies are marked accordingly. We always asked authors to provide the data including only those without missing cortisol or child maltreatment assessments. Therefore, the data presented in this meta-analysis might not completely correspond to the data displayed in the original studies.

2.4. Coding of study characteristics for moderator analyses

The following details were extracted from each study (1) identifying features (i.e., authors, year of publication, journal), (2) participant characteristics (i.e., sample size, age-range, average age, sex ratio, ethnicity [or race: percentage of Caucasians, non-Caucasians], assessment of psychopathology [clinical sample, healthy controls, mixed, not assessed, as well as the percentage of participants meeting criteria for a current mental disorder]), (3) trauma related information (i.e., measurement method [self-report, informant report, mixed], instrument used, grouping method [cut-off scores, record, other], type of child maltreatment [emotional, physical, sexual abuse, neglect], average age of first child maltreatment report and average duration of child maltreatment), (4) cortisol related information (i.e., type of sample [blood, saliva, urine, hair], measurement unit [e.g., nmol/l, µg/dl], time points of sampling, number of samples, reliability of measure [sampling over one day, two-days, more], minutes to peak, duration of stressor, type of stressor [social-evaluative, other], whether a cortisol response was observed [yes, both groups, only in one group, no], dose of the respective stimulant in case of the pharmacological stimulation tests) and (5) data related information (source of data [paper, provided] and whether the data were (re)grouped or not). Some of these variables were viewed as potential moderators that might account for variability in the child maltreatment cortisol relationship (see moderator analyses).

2.5. Risk of bias in individual studies

In order to quantify the risk of bias for each individual study and to examine the potential moderating role of several elements of methodological quality, a quality assessment tool was developed. This quality assessment tool covered the following three key domains: (1) variables associated with the selection of participants (including the measurement of child maltreatment and the matching of the two groups with

respect to age, gender and psychopathology), (2) variables associated with the measurement of HPA axis activity, and related to, the (3) assessment of important confounders. These quality criteria, particularly those related to the assessment of cortisol and associated confounders, were developed based on expert guidelines and differ to some degree between the various HPA axis activity measures (see Appendix B for corresponding references). The risk of bias assessment for each HPA axis activity measure was conducted by two independent reviewers, with disagreements being resolved through discussion. In case of (re)grouped data or missing statistics (e.g., t-test or fisher's exact test), corresponding group comparisons were conducted based on available means and standard deviations using QuickCals from GraphPad (https://www.graphpad.com/quickcalcs/). As the data of some articles were (re)grouped, the information with respect to some quality items was no longer available at the group level. In this case, a conservative approach was followed and the corresponding point was not awarded (marked accordingly in the corresponding tables of Appendix B). In certain cases, the assessment of a quality item was not meaningful, e.g., scoring the matching between the child maltreatment and the control group with respect to oral contraceptive intake in an all-male sample, and in those cases the corresponding items were coded as NA (not applicable). For each of the three quality domains (selection of participants, appropriate assessment of the corresponding HPA axis activity measure, appropriate control for confounders), a score derived from the mean of all associated items (excluding the NA items) multiplied by 100 was calculated. In addition to these domain-specific scores, we also calculated an overall total score. These scores were then used in corresponding meta-regression analyses.

2.6. Statistical analyses

All analyses were run using R and R studio (version 3.6.2 2019–12-12), packages: meta, metafor, dmetar) and were guided by the online book "A Hands-on Guide" from Harrer et al. (2019). Effect sizes for the primary studies were estimated using the Hedge's g coefficient corrected for small sample sizes (Hedges, 1982). In order to calculate the overall effect, random-effects models for the different HPA axis activity measures and the various outcome indices were performed, applying the Restricted Maximum-Likelihood (REML) method to estimate the variance of the distribution of the true effect sizes (tau^2; Veroniki et al., 2016). Between-study heterogeneity was evaluated focusing on the Cochran's Q statistics (with a $p < 0.05$ indicating the presence of statistical heterogeneity), the Higgins's and Thompson's I^2 measure (with I^2: 25% = low heterogeneity, 50% = moderate heterogeneity, 75% = high heterogeneity) and the prediction interval (Higgins, 2003; Higgins & Thompson, 2002; IntHout et al., 2016). By means of the find.outliers (meta package) and inf.analysis function (Leave-One-Out-method; dmetar package), studies with extreme effect sizes (outlier studies) and studies exerting a high impact on the overall result (potential influential studies) were identified and excluded in the context of corresponding sensitivity analyses (Harrer et al., 2019; Viechtbauer & Cheung, 2010). Additionally, meta-regression and subgroup analyses (mixed/fixed-effects model) were conducted to examine the

influence of several predefined moderator variables. For some studies, cortisol data were available for a lower number of participants than reported in the original paper, with information on the various moderator variables only available for the original sample. Despite this, these original values were included in corresponding moderator analyses. To our best knowledge, we marked this in the tables describing the characteristics of the included studies. In case of substantial between-study heterogeneity ($I^2 > 50\%$), meta-regression and subgroup analyses were based on the sensitivity model excluding outlier studies. Finally, in order to evaluate the presence of publication bias, funnel plots were visually inspected and the Egger's test for funnel plot asymmetry was performed (Egger et al., 1997; Peters et al., 2008).

3. Results

3.1. Search results

The literature search yielded a total of $N = 1,858$ records of which $n = 575$ duplicates were removed. Screening of reference lists of existing meta-analyses on HPA axis functioning and child maltreatment (or ELA), as well as studies proposed by authors who were contacted in the context of data collection, yielded an additional $n = 9$ studies. After title and abstract screening, $n = 1,025$ articles were discarded because they did not meet inclusion criteria. The remaining $n = 267$ studies were assessed in full-text. Of these, another $n = 120$ publications were excluded for the following reasons (1) no appropriate HPA axis measure ($n = 52$), (2) all participants experienced child maltreatment ($n = 8$), (3) unusual measure of child maltreatment ($n = 6$), (4) intervention study with no baseline assessment ($n = 3$), and (5) samples used in multiple studies ($n = 51$). Additionally, $n = 60$ articles had to be excluded due to missing relevant statistics, leaving a total of $n = 87$ independent studies included in this series of meta-analyses (for full process of study selection, see Fig. 1). Of the $n = 87$ studies, $n = 14$ studies included two subgroups, one study contained three subgroups, and $n = 18$ articles collected data on more than one HPA axis activity measure (with DC and CAR most frequently jointly assessed), leaving a total of $k = 132$ group comparisons. Since some studies collected data on various HPA axis activity measures, it was possible that an effect size (e.g., cortisol measured at awakening) was included in two different random-effects models relating to two different outcome indices (e.g., morning cortisol in the context of DC and awakening cortisol in the context of the CAR). With respect to the various HPA axis activity measures, $n = 23$ studies reported on DC ($k = 26$), $n = 22$ on the CAR ($k = 27$), $n = 35$ on cortisol stress reactivity ($k = 39$), and $n = 19$ studies assessed cortisol following pharmacological challenges (DST: $n = 11$ ($k = 17$); Dex-CRH test: $n = 8$ ($k = 10$)). Only two studies examined cortisol after the CRH test, which is why these two studies were combined with the data reported for the Dex-CRH test. With respect to the cumulative measures, $n = 8$ studies reported on HCC ($k = 9$) and $n = 4$ studies on 24-hour UFC. Overall, data from $n = 41$ studies were provided by the respective authors, of which $n = 23$ data sets ($k = 29$) were (re)grouped for the purpose of this meta-analysis (see Appendix A). For three studies including

large sample sizes (Hibel et al., 2019; Lovallo et al., 2019; Vreeburg et al., 2009) from which we obtained data, the publications that best described the respective samples and not those that appeared in the initial literature search were chosen as references.
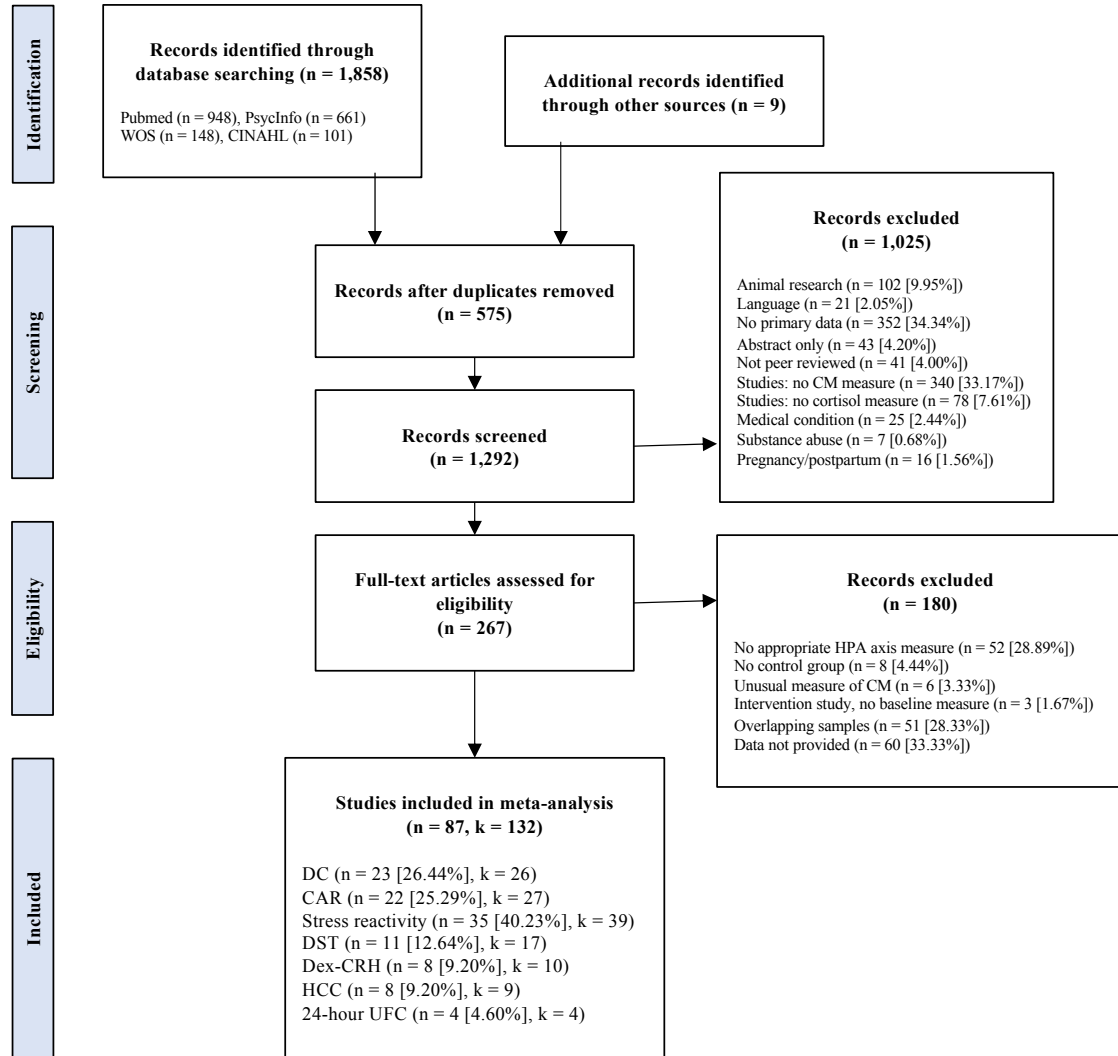
Fig. 1. PRISMA flow diagram describing the process of study selection. WOS = Web of Science; CINAHL = Cumulative Index to Nursing and Allied Health Literature; CM = child maltreatment; HPA axis = hypothalamic–pituitary–adrenal axis; DC = diurnal cortisol; CAR = cortisol awakening response; DST = dexamethasone suppression test; Dex-CRH = dexamethasone-corticotropin releasing hormone; HCC = hair cortisol concentrations; 24-hour UFC = 24-hour urinary free cortisol; n = number of studies; k = number of group comparisons.

3.2. Synthesis of results

3.2.1. Diurnal cortisol

3.2.1.1. Included studies

In total, our systematic search strategy identified $n = 40$ studies that assessed waking (or morning) and evening cortisol to measure some aspects of the circadian rhythm of cortisol secretion. Of these, $n = 23$ studies, including $k = 26$ comparisons involving a total of $n = 5,248$ participants were retained for

quantitative synthesis. Owing to a lack of statistical information, data from the remaining $n = 17$ studies that were eligible for inclusion could not be considered. The mean age of the total sample was 26.89 ($SD = 14.99$) years, the majority of studies included predominantly female subjects (with the percentage of females ranging between 33.1 and 100.0%, $M = 65.4\%$, S$D = 24.0\%$; $k = 5$ comparisons with a purely female sample), and the percentage of Non-Caucasians ranged between 0.0 and 81.7% ($M = 30.0\%$, $SD = 30.7\%$; $k = 14$ not reporting on ethnicity). Most studies ($k = 16$) were conducted with adults only, with fewer studies involving children or adolescents ($k = 10$). With respect to psychopathology, $k = 8$ comparisons included healthy participants, $k = 5$ involved participants all fulfilling diagnostic criteria for a mental disorder, $k = 6$ comparisons comprised participants with at least some fulfilling the diagnostic criteria for a mental disorder (range: 17.5–96.0%; with $k = 2$ not matched in terms of psychopathology), and $k = 7$ did not report on psychopathology at all. The majority of studies used self-reports to assess the presence of child maltreatment ($k = 17$) and $k = 9$ comparisons relied on informant reports. The assessment of child maltreatment and the grouping of participants into a child maltreatment and a control group varied across the studies. This refers both to the instruments used as well as to the grouping procedure applied (e.g., cut-off scores, specific definitions, presence of records). Three studies ($k = 4$) not only focused on child maltreatment but also included participants with other types of ELA (Carrion et al., 2002; Faravelli et al., 2010, 2017). In terms of reliability, the fewest studies assessed cortisol over more than two days ($k = 5$). In total, we received data from 13 studies ($k = 16$), of which the respective authors of six studies ($k = 8$) regrouped or grouped their data based on the available assessment of child maltreatment (or, in case of raw data, the (re)grouping was performed by us). For further details on the characteristics of the included studies, see Table 1.

Table 1
Summary characteristics of included studies that reported on diurnal cortisol (DC).

Study	Total Sample					CM Sample			Control Sample			CM Assessment				Cortisol Assessment						Data	
	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Type of sample	Unit	Time points	Slope	Rel.	Indices	Source	Data (re)grouped
Bernard et al., 2010	435	1.08 (0.58)	46.4	72.6	no	340[a]	1.00 (0.56)	47.9	95	1.34 (0.55)	41.1	informant (record)	CPS	other (record)	NA	saliva	µg/dl	awak., bedtime	NA	2	morning, evening	provided, group	no
Carrion et al., 2002[b]	82	10.78 (1.79)	41.5	36.6	yes*, PTSD	51	10.70 (1.90)	41.2	31	10.90 (1.60)	40.6	self-report (quest.)	PTSD Reaction Index	other (spec.)	EA, PA, SA, N, loss/sepa-ration[◊]	saliva	µg/dl	pre breakfast, pre bed	NA	3	morning, evening	paper, table	no
Cicchetti et al., 2010	553	10.02 (1.87)	47.6	81.7	NA	265[c]	10.00 (1.86)	38.9	288	10.08 (1.89)	55.6	informant (mixed)	MCS (CPS), MMCI	other (record)	EA, PA, SA, N	saliva	log	9am, 4pm	NA	3	morning, evening	paper, table	no
Faravelli et al., 2010	93[d]	43.60 (15.40)	50.2	NA	yes, mixed	32	NA	NA	61	NA	NA	self-report (mixed)	CECA-Q, self-dev.	other (not spec.)	PA, SA, loss[◊]	saliva	nmol/l	8am, 8pm	other	1	all	paper, table	no
Faravelli et al., 2017a	102	43.46 (12.24)	48.0	0.0	NA	40	43.50 (12.51)	42.0	62	43.43 (12.16)	52.0	self-report (mixed)	CECA-Q, FPI	other (spec.)	PA, SA, N, loss[◊]	saliva	nmol/l	30min post-awak., 8pm	other	1	all	provided, group	no
Faravelli et al., 2017b	54	43.74 (10.51)	44.0	0.0	yes, psych.	30	42.20 (11.35)	47.0	24	45.66 (9.23)	42.0	self-report (mixed)	CECA-Q, FPI	other (spec.)	PA, SA, N, loss[◊]	saliva	nmol/l	30min post-awak., 8pm	other	1	all	provided, group	no
Fisher et al., 2007	177	4.40 (0.83)	46.3	11.0	NA	117[e]	NA	46.2	60	NA	47.0	informant (record)	CWA	other (record)	EA, PA, SA, N	saliva	µg/dl	30min post awak., 30 min pre bedtime	other	2	all	paper, table	no
Fuchs et al., 2017	82	35.38 (5.07)	100.0	NA	NA	37	36.47 (4.92)	100.0	45	34.48 (5.06)	100.0	self-report (quest.)	CTQ	cut-offs	PA, SA	saliva	nmol/l	awak., 8pm	other	2	all	provided, group	no
Hibel et al., 2019[f]	248	4.91 (1.14)	49.6	74.6	NA	165	4.93 (1.15)	49.7	83	4.86 (1.13)	49.4	informant (mixed)	MCS (CPS), MMCI	other (record)	EA, PA, SA, N	saliva	µg/ml	awak., bedtime	wake-to-bed	2	all	provided, group	no
Keeshin et al., 2014	36	14.97 (1.40)	100.0	NA	yes*, mixed	24	15.04 (1.45)	100.0	12	14.84 (1.34)	100.0	informant (record)	medical record	other (record)	SA	saliva	log	awak., between 4-6pm	NA	3	morning, evening	paper, table	no
Klaassens et al., 2009	22	47.58 (11.70)	100.0	NA	no	10	47.80 (12.10)	100.0	12	47.40 (11.90)	100.0	self-report (quest.)	CTQ[g]	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 11pm	NA	2	morning, evening	paper, figure	no
Kuhlman et al., 2015	79	12.73 (2.27)	40.5	22.0[h]	yes, mixed	60	12.91 (2.26)	41.2	19	12.16 (2.27)	36.8	informant (quest.)	ETI	other (spec.)	EA, PA, SA,	saliva	µg/dl	awak., pre bed	wake-to-bed	2	all	provided, group	yes
Kumsta et al., 2017	57	24.02 (0.85)	61.4	NA	NA	44[i]	24.15 (0.90)	68.2	13	23.55 (0.45)	38.5	informant (NA)	no instr. used	institution-alization	N	saliva	nmol/l	awak., 8pm	wake-to-bed	2	all	provided, group	no
Kuras et al., 2017	61	33.80 (2.30)	49.2	NA	no[°]	29	NA	NA	32	NA	NA	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., awak. + 13h	NA	2	morning, evening	paper, figure[+]	no
Lindley et al., 2004	16[j]	40.00 (11.17)	87.5	6.2	yes, PTSD	9	34.56 (9.28)	88.9	7	47.00 (9.78)	85.7	self-report (quest.)	THS	other (spec.)	PA, SA	saliva	µg/dl	8am, 10pm	other	1	all	provided, raw	no
Lopes et al., 2012	38[k]	40.29 (8.69)	100.0	NA	yes, MDD	16	41.06 (6.46)	100.0	22	39.73 (10.12)	100.0	self-report (quest.)	CTQ	other (not spec.)	EA, PA, SA, N	saliva	nmol/l	8am, 8pm	NA	1	morning, evening	paper, figure[+]	no
Lovallo et al., 2019[l]	699	23.70 (3.14)	55.9	20.3	no	335	23.90 (3.26)	63.0	364	23.50 (3.02)	49.5	self-report (interview)	C-DIS-IV	other (spec.)	EA, PA, SA	saliva	µg/dl	awak., bedtime	wake-to-bed	1	all	provided, group	yes
Puetz et al., 2016	40	10.55 (1.71)	47.5	35.0	yes, mixed	17	10.88 (1.65)	29.0	23	10.30 (1.74)	61.0	informant (record)	SSR (medi-cal record)	other (record)	EA, PA, N	saliva	nmol/l	30min post awak., 30min pre sleep	NA	2	morning, evening	paper, table	no

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Table 1
Summary characteristics of included studies that reported on diurnal cortisol (DC).

Study	Total Sample					CM Sample			Control Sample			CM Assessment				Cortisol Assessment						Data	
	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Type of sample	Unit	Time points	Slope	Rel.	Indices	Source	Data (re)grouped
Reichl et al., 2016a	25	16.25 (1.12)	96.0	NA	no	3	16.55 (1.34)	100.0	22	16.20 (1.12)	95.5	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., pre bed	wake-to-bed	3	all	provided, raw	yes
Reichl et al., 2016b	25	16.30 (1.30)	92.0	NA	yes, mixed	17	16.60 (1.29)	94.1	8	15.65 (1.14)	87.5	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., pre bed	wake-to-bed	3	all	provided, raw	yes
Schreuder et al., 2016	114	26.75 (2.85)	45.6	NA	yes, mixed	16	27.81 (2.90)	43.8	98	26.58 (2.81)	45.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	µg/dl	awak., 10pm	wake-to-bed	1	all	provided, group	yes
Smeets et al., 2007	22[m]	40.50 (11.63)	100.0	NA	no°	13	38.77 (11.38)	100.0	9	43.00 (12.21)	100.0	self-report (interview)	self-dev.	other (spec.)	SA	saliva	nmol/l	awak., 8pm	wake-to-bed	2	all	provided, raw	no
Steudte et al., 2013	30[n]	37.87 (12.04)	90.0	0.0	no	4	42.50 (11.39)	100.0	26	37.15 (12.19)	88.5	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., bedtime	wake-to-bed	1	all	provided, group	yes
van der Vegt et al., 2009	529	30.83 (1.22)	33.1	NA	NA	235[o]	30.87 (1.24)	51.9	294	30.80 (1.20)	18.0	informant (interview)	self-dev.	other (spec.)	N	saliva	nmol/l	awak., bedtime	NA	1	morning, evening	paper, table	no
Vreeburg et al., 2009a[p]	1131	42.67 (12.27)	66.3	NA	yes, mixed[q]	645	43.92 (11.68)	70.9	486	41.02 (12.83)	60.3	self-report (interview)	NEMESIS CTI	other (spec.)	EA, PA, SA, N	saliva	nmol/l	awak., 11pm	wake-to-bed	1	all	provided, group	yes
Vreeburg et al., 2009b[p]	498	42.88 (14.46)	61.3	NA	no[r]	120	47.62 (12.64)	73.3	369	41.33 (14.69)	57.5	self-report (interview)	NEMESIS CTI	other (spec.)	EA, PA, SA, N	saliva	nmol/l	awak., 11pm	wake-to-bed	1	all	provided, group	yes

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder, * = groups are not matched with respect to psychopathology, ° = no gold-standard diagnostic tool was named; PTSD = Posttraumatic Stress Disorder; psych. = psychosis; MDD = Major Depressive Disorder; CM = child maltreatment; n = sample size; quest. = questionnaire; CPS = Child Protective Services; MCS = Maltreatment Classification System; MMCI = Maternal Maltreatment Classification Interview; CECA-Q = Childhood Experiences of Care and Abuse Questionnaire; self-dev. = self-developed (the authors used a scale developed by themselves); FPI = Florence Psychiatric Interview; CWA = Child Welfare Agency; CTQ = Childhood Trauma Questionnaire; ETI = Early Trauma Inventory; no instr. used = no instrument used; THS = Trauma History Screen; C-DIS-IV = Computerized version of the Diagnostic Interview Schedule-IV; SSR = Social Services Record; NEMESIS CTI = Netherlands Mental Health Survey and Incidence Study Childhood Trauma Interview; spec. = specification (authors applied a specific definition of CM); N = neglect; EA = emotional abuse; PA = physical abuse; SA = sexual abuse; ◊ = The grouping of participants was not just based on CM experiences but also included other traumatic experiences; awak. = awakening; Rel. = reliability, whereby the following definitions have been used: 1 = cortisol assessed over only one day, 2 = cortisol assessed over two days, 3 = cortisol assessed over more than two days; all = morning, evening, delta (evening minus morning value). [a] The two groups CPS-involved, stayed with birth parents and CPS-involved, placed in foster care were combined into one group. [b] This article did not appear in the initial search, but was suggested by the respective author as best suited for citation in this meta-analysis. [c] The two groups early physical/sexual abuse and maltreated without early abuse were combined into one group. [d] Comparison between patient groups with and without early trauma. [e] The two groups Multidimensional Treatment Foster Care for Preschoolers (MTFC) and Regular Foster Care (RFC) were combined into one group. [f] This article did not appear in the initial search but was suggested by the respective author as best suited for citation in this meta-analysis. [g] Authors also administered ETI, but grouping was based on CTQ. [h] Percentage of non-Caucasians refers to total sample (N = 127). [i] Deprived adoptees were combined into one group and were compared to the non-deprived UK adoptees. [j] Comparison between PTSD patients with childhood sexual or physical abuse and those reporting no history of childhood sexual or physical abuse. [k] Comparison between MDD patients with early life stress and those without corresponding experiences. [l] This article did not appear in the initial search but was suggested by the respective author as best suited for citation in this meta-analysis. [m] Exclusion of repressed memory group; CM sample: recovered and continuous memory group, control sample: control group. [n] The data were regrouped including only the traumatized control subjects and the non-traumatized control subjects (remark: some in the control sample may have experienced other traumatic events). [o] The two groups some neglect and severe neglect were combined into one group. [p] The data are from the Netherlands Study of Depression and Anxiety, a large cohort study; this article did not appear in the initial search but was suggested by the respective author as best suited for citation in this meta-analysis. [q] Patient group: dysthymia, MDD, social phobia, panic with/without agoraphobia, generalized anxiety disorder. [r] No one of the participants fulfilled the diagnostic criteria for dysthymia, MDD, social phobia, panic with/without agoraphobia, or generalized anxiety disorder in the past 6 months. [+] It is not clearly stated in the text or in the subheading of the figure whether means and standard deviations or means and standard errors were presented; we assumed standard errors.

3.2.1.2. Risk of bias assessment

Studies received an average total score of 51.9/100.0 ($SD = 12.7$, range: 27.6–76.7). With respect to the selection of participants ($M = 61.0/100.0$, $SD = 15.5$), the majority of studies used an established instrument to assess the experience of child maltreatment and matched their participants with respect to age, sex, and psychopathology (assessed with a gold-standard diagnostic tool). However, less than half of the comparisons ($k < 13$) assured that all participants in the child maltreatment group were exposed to child maltreatment, while none of the participants in the control group were, and only four studies ($k = 5$) used two different sources to establish the presence of child maltreatment. Relating to the appropriate assessment of DC ($M = 53.5/100.0$, $SD = 17.4$), most studies did report on clear sampling instructions (including prohibitions of certain behaviors before sampling as well as clear information about how to collect, where to place, and how to return samples) and provided details on their test protocol as well as on missing data and/or handling of outliers. However, only few studies provided clear instructions regarding the day of sampling ($k = 9$), assured that the time of awakening did not differ between the groups ($k = 7$), assessed sampling time adherence ($k = 7$), rescheduled sampling if participants were sick ($k = 5$), reported on batch analysis ($k = 8$), and assured that participants were not under any current extraordinary stress ($k = 2$). Finally, as shown by the relatively low scores related to the control of confounding variables ($M = 40.4/100.0$, $SD = 24.6$), less than half of the comparisons ($k \leq 13$) excluded participants with a medical condition or participants working night shifts, assessed smoking, menstrual cycle, oral contraceptive, and medication use (especially medications affecting the central nervous system (CNS)) and thus assured that participants did not differ in these respects, and only $k = 2$ comparisons assured that participants did not differ with respect to other ELA or adult adversity. It should be noted, however, that several studies would have assessed some of the variables of interest, but since the data of six studies ($k = 8$) were (re)grouped, the corresponding information at the group level was no longer available for all of these studies. For details on individual scoring results of the primary studies as well as a summary of the average risk of bias scores, see Appendix B Table B8 or Table B1 for individual quality items.

3.2.1.3. Meta-analysis

The results of the meta-analyses for the three indices of circadian activity (morning, evening, DSL) revealed no overall differences for morning (Hedges' $g = -0.02$, 95% CI [-0.11; 0.06], $p = 0.586$) and DSL cortisol (Hedges' $g = 0.00$, 95% CI [-0.11; 0.11], $p = 0.987$) between the child maltreatment and the control sample (this also held true for the corresponding sensitivity analyses; for further details, see Table 2). In contrast, participants in the child maltreatment group had slightly elevated evening cortisol levels compared to their respective control group (Hedges' $g = 0.10$, 95% CI [0.03; 0.18], $p = 0.008$). For corresponding forest plots, see Appendix C Figs. 1.1–1.3. Between-study heterogeneity was in the low range for all outcome indices ($I^2 < 30\%$, Q-statistics all $p > 0.05$) and visual inspection of traditional

and counter-enhanced funnel plots as well as Egger's regression test of funnel plot asymmetry implied absence of small-study bias (all $p > 0.05$; for funnel plots, see Appendix C Figs. 1.1–1.3).

Table 2
Summary statistics for random-effects models of included studies that reported on diurnal cortisol (DC), displayed separately for the different cortisol outcome indices.

Outcome indices	Random-effects model					Heterogeneity measures					
	N	k	Hedges' g	95% CI	p	tau^2	I^2	Q	p	Pred. int.	Egger's Test[a]
Morning cortisol	5212	26	-0.02	-0.11; 0.06	0.586	0.01	29.1%	35.27	0.083	-0.25; 0.21	-0.268 (0.514)
Morning cortisol sensitivity analysis *	3646	24	-0.00	-0.09; 0.08	0.939	0.01	21.5%	29.29	0.171	-0.21; 0.20	-
Evening cortisol	5188	26	0.10	0.03; 0.18	0.008	0.01	2.0%	25.51	0.434	-0.08; 0.29	0.621 (0.067)
Evening cortisol sensitivity analysis *	2949	23	0.11	0.02; 0.20	0.013	0.01	0.0%	18.92	0.650	-0.07; 0.29	-
DSL cortisol	3390	17	0.00	-0.11; 0.11	0.987	0.01	23.5%	20.92	0.181	-0.28; 0.28	0.246 (0.609)
DSL cortisol sensitivity analysis *	2259	16	0.01	-0.13; 0.14	0.933	0.02	27.9%	20.80	0.143	-0.34; 0.36	-

Note. DSL = diurnal slope; 95% CI = 95% confidence interval; Pred. int. = prediction interval. [a] Intercept and (p values) displayed. Morning cortisol: * exclusion of influential studies Bernard et al., 2010 and Vreeburg et al., 2009a. Evening cortisol: * exclusion of influential studies Bernard et al., 2010, Lovallo et al., 2019, and Vreeburg et al., 2009a. DSL cortisol: * exclusion of influential study Vreeburg et al., 2009a. See Appendix C Figs. 1.1-1.3 for corresponding forest and funnel plots.

3.2.1.4. Meta-regression and subgroup analyses

We conducted a number of pre-defined meta-regression and subgroup analyses. The summary results for each outcome index and each moderator examined are shown in Appendix D Table D1. In the following section, results for moderators found to significantly influence the main effects are outlined. Despite low heterogeneity in the effect size estimates between studies reporting on morning cortisol (I^2 = 29.1%), the following two continuous moderators influenced the main effect: (1) age at the time of study participation and (2) the sub-domain "appropriate measure of cortisol in the context of DC" of the quality assessment. With respect to the mean age of study participants, studies including older-aged samples reported a tendency for higher morning cortisol (β = 0.006, 95% CI [0.001; 0.010], p = 0.014, R^2 = 73.04%; when comparing the child maltreatment group to the control group) compared to younger samples. Concerning the assessment of cortisol, studies with higher quality scores were associated with lower morning cortisol (β = −0.005, 95% CI [−0.010; −0.001], p = 0.012, R^2 = 85.49%) in the child maltreatment group compared to the control group. In addition, forming subgroups of studies using informant reports and those relying on self-report data to assess the presence of child maltreatment revealed overall reduced morning cortisol in those studies applying informant reports (Hedge's g = −0.114, CI [−0.204; −0.024]), whereas a tendency for increased morning cortisol in the child maltreatment compared to the control group was observed in studies relying on self-report information (Hedge's g = 0.060, 95% CI [−0.026; 0.146]; Q_1 = 7.48, p = 0.006). Since the majority of studies relying on informant reports used the presence of records to group participants, the corresponding subgroup comparison of the different grouping methods applied (records, cut-off scores, other grouping approaches (mainly specifications)) also reached significance (Q_2 = 8.32, p = 0.016). Finally, the subgroup comparison between studies where original data were extracted and those that (re)grouped

their data for this meta-analysis also explained some of the between-study heterogeneity, with studies where original data could be extracted implying overall reduced morning cortisol (Hedge's $g = -0.096$, 95% CI [-0.177; -0.016]) and those with (re)grouped data pointing to slightly increased morning cortisol levels in the child maltreatment group (Hedge's $g = 0.087$, 95% CI [-0.014; 0.189]; $Q_I = 7.72$, $p = 0.005$). However, since the majority of studies ($k = 8$ of $k = 9$) that relied on informant reports to group participants also belonged to the original data subgroup, interpretation of these findings should be done with caution. With respect to evening cortisol ($I^2 = 2.0\%$), studies focusing on other types of ELA showed larger positive effect size estimates than studies focusing on child maltreatment only ($Q_I = 12.24$, $p < 0.001$). Further, studies including original data showed larger positive effect size estimates than studies which provided (re)grouped data ($Q_I = 6.47$, $p = 0.011$). It should be noted that by excluding those three studies ($k = 4$) focusing not only on child maltreatment experiences (but also including participants with loss experiences), the initial model on evening cortisol became insignificant ($p = 0.098$). Finally, with respect to DSL cortisol, no moderator was identified that significantly influenced between-study heterogeneity.

3.2.2. Cortisol awakening response

3.2.2.1. Included studies

A total of $n = 22$ studies, comprising $k = 27$ comparisons, with an overall sample size of $n = 3,545$ participants assessed cortisol in response to awakening. The mean age of the total sample was 27.36 (SD $= 10.45$) years ($k = 8$ comparison involved children/adolescents and $k = 19$ including adults only), and the majority of studies included mainly female subjects (with the percentage of females ranging between 0.0 and 100.0%, $M = 65.4\%$, $SD = 30.0\%$; $k = 7$ comprised a purely female sample). With respect to ethnicity, most studies included samples composed predominantly of an ethnic majority group with percentages of Non-Caucasians ranging between 0.0 and 100.0% ($M = 45.7\%$, $SD = 42.2\%$; with $k = 20$ not reporting on ethnicity). Concerning psychopathology, $k = 9$ comparisons included healthy participants, $k = 6$ involved participants all fulfilling diagnostic criteria for a mental disorder, $k = 6$ comparisons comprised participants with at least some fulfilling the diagnostic criteria for a mental disorder (with $k = 4$ not matched in terms of psychopathology), and $k = 6$ did not report on psychopathology at all. The majority of studies ($n = 18$, $k = 23$) employed self-reports to assess the presence of child maltreatment and only $k = 4$ relied on informant reports. Along with the use of different instruments, the grouping of participants into a child maltreatment and a control group varied, however, with the majority of studies using specific cut-off scores ($n = 13$, $k = 17$). Only one of the included studies (Klaus et al., 2018) not only focused on child maltreatment but also included participants with other types of ELA, including death of a close friend or relative, parental separation or divorce, major illnesses or injuries or other traumatic experiences. Three studies ($k = 4$) assessed the CAR over more than two days, and there were several studies ($n = 8$, $k = 9$) with cortisol sampled at only two time points

(i.e., awakening and +30 min post awakening or +45 min post awakening). In $n = 4$ studies peak cortisol values were not observed at the same assessment time points for both groups. Finally, data from 12 studies ($k = 15$) were provided by the respective authors, of which $k = 10$ comparisons contained (re)grouped data. For further details on the characteristics of the included studies, see Table 3.

3.2.2.2. Risk of bias assessment

Studies which assessed cortisol in response to awakening received an average total score of 52.8/100.0 ($SD = 11.7$, range: 35.7–76.7). With respect to the selection of participants ($M = 65.7/100.0$, $SD = 14.9$), the majority of comparisons ($k > 13$) ensured that all participants in the child maltreatment group were exposed to maltreatment, while none of the participants in the control group was, used an established instrument to assess the experience of child maltreatment and matched their participants with respect to age, sex, and psychopathology (assessed with a gold-standard diagnostic tool; $k = 12$ in case of self-reports). However, only one study used two different sources to establish the presence of child maltreatment. Concerning the appropriate assessment of cortisol in the context of the CAR ($M = 56.8/100.0$, $SD = 12.0$), most studies reported on clear sampling ($k = 22$) and collection ($k = 27$) instructions, provided information on the day of sampling ($k = 14$), collected at least three samples (with one sample between +30 and +45 min post awakening, $k = 18$) over at least two days ($k = 14$), provided information about how samples were collected, stored or analyzed ($k = 27$), and reported on outliers or missing data ($k = 22$). However, less than half of the comparisons ($k < 14$) assessed the time of awakening (thus ensuring that the two groups did not differ in this respect; $k = 13$), assessed sampling time adherence ($k = 8$), reported whether sampling was rescheduled if participants were sick ($k = 7$), reported on batch analyses ($k = 9$), and only $k = 3$ comparisons ensured that participants were not under any current extraordinary stress or whether sampling was rescheduled if participants experienced any stressor during the day of collection. Finally, many of the studies failed to control for several important confounding variables ($M = 38.0/100.0$, $SD = 22.5$). For instance, less than half of the comparisons ($k < 14$) reported whether participants were excluded if pregnant or working night shifts, assessed smoking, menstrual cycle, oral contraceptive, and medication use (especially medications affecting the CNS), thus ensuring that participants did not differ in these respects, and only $k = 2$ comparisons ensured that participants did not differ with respect to other ELA or adult adversity. Again, several studies would have assessed some of the variables of interest, but since the data of eight studies ($k = 10$) were (re)grouped, the corresponding information at the group level was no longer available for some of these studies. For details on individual scoring results of the primary studies as well as a summary of the average risk of bias scores, see Appendix B Table B9 or Table B2 for individual quality items.

Table 3
Summary characteristics of included studies that reported on cortisol assessed in the context of the cortisol awakening response (CAR).

Study	Total Sample N	Age M(SD)	Sex	Ethn.	Psycho-path.	CM Sample n	Age M(SD)	Sex	Control Sample n	Age M(SD)	Sex	CM Assessment Method	Instrument	Grouping	Type	Cortisol Assessment Type of sample	Unit	Time points[a]	Time point peak	Rel.	Indices	Data Source	Data (re)grouped
Bicanic et al., 2013	89	15.89 (1.86)	100.0	NA	yes*, PTSD	52	16.10 (1.98)	100.0	37	15.60 (1.65)	100.0	self-report (interview)	self-dev.	other (spec.)	SA	saliva	nmol/l	awak., 15, 30, 45, 60min	NA	1	AUC$_g$	paper, table	no
Fuchs et al., 2017	82	35.38 (5.07)	100.0	NA	NA	37	36.47 (4.92)	100.0	45	34.48 (5.06)	100.0	self-report (quest.)	CTQ	cut-offs	PA, SA	saliva	nmol/l	awak., 30min	30min	2	awak., peak	provided, group	no
Kaess et al., 2017	66	14.91 (0.43)	42.4	NA	NA	15	14.79 (0.44)	53.3	51	14.95 (0.42)	39.2	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 30, 60min	NA	2	awak., AUC$_g$	provided, raw	yes
Keeshin et al., 2014	36	14.97 (1.40)	100.0	NA	yes*, mixed	24	15.04 (1.45)	100.0	12	14.84 (1.34)	100.0	informant (record)	medical record	other (record)	SA	saliva	log	awak., 30min	30min	3	awak., peak, delta	paper, table	no
Klaassens et al., 2009	22	47.58 (11.70)	100.0	NA	no	10	47.80 (12.10)	100.0	12	47.40 (11.90)	100.0	self-report (quest.)	CTQ[b]	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 30, 45, 60min	30min	2	awak., peak, 60min, AUC$_g$	paper, figure & table	no
Klaus et al., 2018	103	34.54 (10.80)	0.0	0.0	no°	39[c]	35.16 (10.85)	0.0	64[e]	34.17 (10.83)	0.0	self-report (quest.)	CTES	cut-offs	PA, SA, other◊	saliva	nmol/l	awak., 30min	30min	2	awak., peak, delta	paper, figure & table	no
Kuhlman et al., 2015	79	12.73 (2.27)	40.5	22.0[d]	yes, mixed	60	12.91 (2.26)	41.2	19	12.16 (2.27)	36.8	informant (quest.)	ETI	other (spec.)	EA, PA, SA	saliva	µg/dl	awak., 45min	45min	2	awak., peak, delta	provided, group	yes
Kumsta et al., 2017	57	24.02 (0.85)	61.4	NA	NA	44[e]	24.15 (0.90)	68.2	13	23.55 (0.45)	38.5	informant (NA)	no instr. used	institutio-nalization	N	saliva	nmol/l	awak., 30, 45min	45min	2	awak., peak, delta	provided, group	no
Kuras et al., 2017	61	33.80 (2.30)	49.2	NA	no°	29	NA	NA	32	NA	NA	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 30, 60min	30, 60min	2	awak., peak, 60min	paper, figure+	no
L. Li et al., 2015	75	37.92 (11.67)	72.0	46.7	yes*, MDD	38	39.70 (10.90)	68.4	37	36.10 (12.30)	75.7	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	µg/dl	awak., 15, 30, 60min	30min	1	awak., peak, 60min, AUC$_g$	paper, figure	no
Lu et al., 2016a	35	23.80 (3.89)	51.4	100.0	yes, MDD	18	23.70 (4.13)	44.4	17	23.90 (3.75)	58.8	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	ng/ml	awak., 30, 45, 60min	30min	1	awak., peak, 60min, AUC$_g$, AUC$_i$	paper, figure	no
Lu et al., 2016b	45	21.65 (3.46)	62.2	100.0	no	23	21.50 (3.91)	60.9	22	21.80 (3.01)	63.6	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	ng/ml	awak., 30, 45, 60min	30min	1	awak., peak, 60min, AUC$_g$, AUC$_i$	paper, figure	no
Mello et al., 2015[f]	63	10.63 (2.15)	47.6	NA	NA	25	10.40 (2.06)	56.0	38	10.79 (2.22)	42.1	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	µg/dl	awak., 30min	0, 30min	1	awak., peak, delta	provided, raw	yes
Monteleone et al., 2018a	44	26.50 (8.10)	100.0	NA	yes, AN	24	27.90 (8.70)	100.0	20	21.80 (7.10)	100.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 15, 30, 60min	15, 60min	1	all	provided, group	no
Monteleone et al., 2018b	36	28.90 (8.70)	100.0	NA	yes, BN	22	31.00 (9.40)	100.0	14	25.70 (6.80)	100.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 15, 30, 60min	30min	1	all	provided, group	no
Peng et al., 2014a	58	28.61 (7.32)	46.6	NA	yes, MDD	28	28.87 (6.28)	46.4	30	28.37 (8.27)	46.7	self-report (quest.)	CTQ	cut-offs	N	saliva	nmol/l	awak., 30min	30min	2	delta	paper, table+	no
Peng et al., 2014b	51	28.09 (4.69)	47.1	NA	no	22	28.37 (5.28)	45.5	29	27.87 (4.28)	48.3	self-report (quest.)	CTQ	cut-offs	N	saliva	nmol/l	awak., 30min	30min	2	delta	paper, table+	no
Quevedo et al., 2017	55	14.91 (1.64)	63.6	50.9	yes*, MDD[g]	35	14.84 (1.55)	77.1	20	15.04 (1.83)	40.0	self-report (interview)	K-SADS-P	other (spec.)	PA, SA, N	saliva	nmol/l	awak., 30, 60min	30min	3	awak., peak, 60min, delta	paper, table	no
Reichl et al., 2016a	25	16.25 (1.12)	96.0	NA	no	3	16.55 (1.34)	100.0	22	16.20 (1.12)	95.5	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 30, 60min	30, 60min	3	all	provided, raw	yes

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Table 3
Summary characteristics of included studies that reported on cortisol assessed in the context of the cortisol awakening response (CAR).

Study	Total Sample					CM Sample			Control Sample			CM Assessment				Cortisol Assessment						Data	
	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Type of sample	Unit	Time points[a]	Time point peak	Rel.	Indices	Source	Data (re)grouped
Reichl et al., 2016b	24	16.32 (1.33)	91.7	NA	yes, mixed	16	16.65 (1.32)	93.8	8	15.65 (1.14)	87.5	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 30, 60min	30min	3	all	provided, raw	yes
Schreuder et al., 2016	114	26.75 (2.85)	45.6	NA	yes, mixed	16	27.81 (2.90)	43.8	98	26.58 (2.81)	45.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	μg/dl	awak., 30, 60min	30min	1	awak., peak, 60min, delta, AUC_g	provided, group	yes
Smeets et al., 2007	22[h]	40.50 (11.63)	100.0	NA	no°	13	38.77 (11.38)	100.0	9	43.00 (12.21)	100.0	self-report (interview)	self-dev.	other (spec.)	SA	saliva	nmol/l	awak., 15, 30, 45min	30min	2	awak., peak, delta, AUC_g, AUC_i	provided, raw	no
Steudte et al., 2013	30[i]	37.87 (12.04)	90.0	0.0	no	4	42.50 (11.39)	100.0	26	37.15 (12.19)	88.5	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	awak., 30min	30min	1	awak., peak, delta	provided, group	yes
van der Vegt et al., 2009	529	30.83 (1.22)	33.1	NA	NA	235	30.87 (1.24)	51.9	294	30.80 (1.20)	18.0	informant (interview)	self-dev.	other (spec.)	N	saliva	nmol/l	awak., 30min	30min	1	awak., peak	paper, table	no
van Zuiden et al., 2011	317	30.19 (9.69)	0.0	NA	NA	152	30.20 (9.64)	0.0	165	30.17 (9.76)	0.0	self-report (quest.)	ETI-SF	other (spec.)	EA, PA, SA	saliva	nmol/l	awak., 15, 30, 60min	30min	1	awak., peak, 60min, delta, AUC_g	provided, group	yes
Vreeburg et al., 2009a[j]	996	42.35 (12.34)	65.9	NA	yes, mixed[k]	565	43.68 (11.82)	69.6	431	40.60 (12.79)	61.0	self-report (interview)	NEMESIS CTI	other (spec.)	EA, PA, SA, N	saliva	nmol/l	awak., 30, 45, 60min	30min	1	all	provided, group	yes
Vreeburg et al., 2009b[j]	431	42.71 (14.62)	59.4	NA	no[l]	106	47.97 (12.54)	69.8	325	41.00 (14.86)	56.0	self-report (interview)	NEMESIS CTI	other (spec.)	EA, PA, SA, N	saliva	nmol/l	awak., 30, 45, 60min	30min	1	all	provided, group	yes

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder, * = groups are not matched with respect to psychopathology, ° = no gold-standard diagnostic tool was named; PTSD = Posttraumatic Stress Disorder; MDD = Major Depressive Disorder; AN = Anorexia Nervosa; BN = Bulimia Nervosa; CM = child maltreatment; n = sample size; quest. = questionnaire; self-dev. = self-developed (the authors used a scale developed by themselves); CTQ = Childhood Trauma Questionnaire; CTES = Childhood Traumatic Events Scale; ETI = Early Trauma Inventory; no instr. used = no instrument used; K-SADS-P = Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present Version; CECA = Childhood Experiences of Care and Abuse; SF = short form; NEMESIS CTI = Netherlands Mental Health Survey and Incidence Study Childhood Trauma Interview; spec. = specification (authors applied a specific definition of CM); SA = sexual abuse; PA = physical abuse; EA = emotional abuse; N = neglect; ◊ = The grouping of participants was not just based on CM experiences but also included other traumatic experiences; awak. = awakening; Rel. = reliability, whereby the following definitions have been used: 1 = cortisol assessed over only one day, 2 = cortisol assessed over two days, 3 = cortisol assessed over more than two days; AUC_g = area under the curve with respect to ground; delta = peak minus awakening levels; AUC_i = area under the curve with respect to increase. [a] Time points cortisol was sampled. [b] Authors also administered ETI, but grouping was based on CTQ. [c] ELS AA/AG and ELS GG were combed into one group and compared to no ELS AA/AG and no ELS GG group. [d] Percentage of non-Caucasians refers to total sample (N = 127). [e] Deprived adoptees were combined into one group and were compared to the non-deprived UK adoptees. [f] Raw data were provided; participants with sampling adherence of +/- 5 min were included. [g] Patients were matched with respect to MDD but not with respect to PTSD. [h] Exclusion of repressed memory group; CM sample: recovered and continuous memory group, control sample: control group. [i] The data were regrouped including only the traumatized control subjects and the non-traumatized control subjects (remark: some in the control sample may have experienced other traumatic events). [j] The data are from the Netherlands Study of Depression and Anxiety, a large cohort study. The article did not appear in the initial search but was suggested by the respective author as best suited for citation in this meta-analysis. [k] Patient group: dysthymia, MDD, social phobia, panic with/without agoraphobia, generalized anxiety disorder. [l] No one of the participants fulfilled the diagnostic criteria for dysthymia, MDD, social phobia, panic with/without agoraphobia, or generalized anxiety disorder in the past 6 months. + It is not clearly stated in the text or in the subheading of the figure whether means and standard deviations or means and standard errors were presented; we assumed standard errors.

3.2.2.3. Meta-analysis

The pooled effect estimates for the different CAR indices (including corresponding sensitivity analyses) are displayed in Table 4. As shown in the corresponding lines, none of the examined indices suggested a difference ($p > 0.05$) in cortisol assessed in response to awakening when comparing the child maltreatment and the control group. For corresponding forest plots, see Appendix C Figs. 2.1–2.6. Between-study heterogeneity was in the moderate to high range for some of the outcome indices ($I^2 = 41.8\%-73.1\%$), exceeding the level of significance (Q-statistics all $p < 0.05$) for peak, delta, AUC_g, and AUC_i cortisol, suggesting that other variables differing between the included studies might be of importance as well. Visual inspection of traditional and counter-enhanced funnel plots as well as Egger's regression test of funnel plot asymmetry implied absence of small-study bias for all outcome indices examined (all $p > 0.05$; for funnel plots, see Appendix C Figs. 2.1–2.6).

Table 4
Summary statistics for random-effects models of included studies that reported on cortisol assessed in the context of the cortisol awakening response (CAR), displayed separately for the different cortisol outcome indices.

Outcome indices	Random-effects model					Heterogeneity measures					
	N	k	Hedges' g	95% CI	p	tau^2	I^2	Q	p	Pred. int.	Egger's Test[a]
Awakening cortisol	3342	24	-0.04	-0.13; 0.05	0.334	0.01	17.3%	27.82	0.223	-0.24; 0.15	-0.732 (0.054)
Awakening cortisol sensitivity analysis *	2271	22	-0.05	-0.14; 0.04	0.277	0.00	0.0%	19.15	0.576	-0.14; 0.05	-
Peak cortisol	3275	23	-0.02	-0.19; 0.15	0.812	0.10	58.3%	52.72	0.000	-0.71; 0.67	-0.636 (0.254)
Peak cortisol sensitivity analysis °	3204	21	0.02	-0.09; 0.13	0.701	0.02	36.5%	31.48	0.049	-0.28; 0.32	-
Peak cortisol sensitivity analysis *	3239	22	0.04	-0.10; 0.17	0.596	0.04	43.5%	37.16	0.016	-0.38; 0.45	-
60 min post awakening cortisol[◊]	2276	14	0.02	-0.13; 0.17	0.798	0.03	41.6%	22.26	0.052	-0.36; 0.40	-0.095 (0.876)
60min post awakening cortisol sensitivity analysis °	2240	13	0.05	-0.07; 0.16	0.429	0.01	18.2%	14.66	0.261	-0.18; 0.28	-
Delta cortisol[◊]	2536	18	-0.03	-0.17; 0.11	0.719	0.03	41.8%	29.23	0.033	-0.42; 0.36	-0.562 (0.287)
Delta cortisol sensitivity analysis °*	2500	17	0.02	-0.06; 0.10	0.622	0.00	0.0%	15.34	0.500	-0.07; 0.11	-
AUC$_g$ cortisol	2327	15	-0.13	-0.41; 0.15	0.370	0.22	73.1%	51.99	0.000	-1.18; 0.92	-0.963 (0.243)
AUC$_g$ cortisol sensitivity analysis °	2211	12	-0.18	-0.40; 0.05	0.118	0.08	61.9%	28.87	0.002	-0.88; 0.52	-
AUC$_i$ cortisol	1654	9	-0.07	-0.48; 0.33	0.723	0.28	70.3%	26.96	0.001	-1.41; 1.26	-0.359 (0.719)

Note. AUCg = area under the curve with respect to ground; AUCi = area under the curve with respect to increase; 95% CI = 95% confidence interval; Pred. int. = prediction interval. [a] Intercept and (p values) displayed. Awakening cortisol: * exclusion of influential studies L. Li et al., 2015 and Vreeburg et al., 2009a. Peak cortisol: ° exclusion of outlier studies Lu et al., 2016a and Monteleone et al., 2018b; * exclusion of influential study Monteleone et al., 2018b. [◊] Due to convergence problems associated with the Fisher scoring algorithm, the DerSimonian-Laird estimator was used to estimate τ^2. 60 min post awakening cortisol: ° exclusion of outlier study Monteleone et al., 2018b. Delta cortisol: °* exclusion of outlier and influential study Monteleone et al., 2018b. AUC$_g$ cortisol: ° exclusion of outlier studies Lu et al., 2016a, Lu et al., 2016b, and Monteleone et al., 2018b. See Appendix C Figs. 2.1-2.6 for corresponding forest and funnel plots.

3.2.2.4. Meta-regression and subgroup analyses

The summary results for the pre-defined meta-regression and subgroup analyses for each outcome index and each moderator examined are shown in Appendix D Table D2. In the following, the results for moderators found to significantly influence the main effects are outlined. The subgroup comparison between studies where original data were extracted and those that (re)grouped their data for this meta-

analysis explained some of the between-study heterogeneity for awakening cortisol and AUC$_g$ cortisol, with studies where original data could be extracted demonstrating overall reduced morning cortisol (Hedge's $g = -0.169$, 95% CI [-0.323; -0.015] and Hedge's $g = -0.611$, 95% CI [-0.868; -0.355], respectively) and those with (re)grouped data pointing to slightly increased morning cortisol levels in the child maltreatment group (Hedge's $g = 0.054$, 95% CI [-0.036; 0.145] and Hedge's $g = 0.069$, 95% CI [-0.025; 0.164], respectively; $Q_I = 6.02$, $p = 0.014$ and $Q_I = 23.80$, $p < 0.001$, respectively). Since, as noted before, there is a relatively large overlap between studies reporting on morning cortisol assessed in the context of DC as well as on cortisol assessed in response to awakening ($k = 14$), this finding was to be expected. Furthermore, with respect to awakening cortisol, age seems to explain some of the between-study variance ($R^2 = 70.27\%$), but in contrast to morning cortisol (DC), does not represent a significant moderator ($p = 0.338$). For delta cortisol, we identified the proportion of women in the sample as a significant continuous moderator (for peak cortisol: $p = 0.071$, for +60 min post awakening cortisol: $p = 0.096$, and for AUC$_g$ cortisol: $p = 0.058$), with an increase in the proportion of females being associated with lower cortisol when comparing the child maltreatment and the control sample ($\beta = -0.005$, 95% CI [-0.010; -0.000], $p = 0.040$, $R^2 = 0.0\%$). Finally, with respect to AUC$_g$ cortisol the sub-domain "appropriate measure of confounders" of the quality assessment explained some of the variance in the effect estimates, with studies with higher quality scores being associated with lower AUC$_g$ cortisol ($\beta = -0.012$, 95% CI [-0.019; -0.005], $p < 0.001$, $R^2 = 95.17\%$) in the child maltreatment group compared to the control group (for awakening cortisol: $p = 0.086$, $R^2 = 64.43\%$).

3.2.3. Cortisol stress reactivity

3.2.3.1. Included studies

In total, our systematic search strategy identified $n = 73$ studies that measured cortisol in the context of a stressor. Of these, $n = 35$ publications ($k = 39$ comparisons) were included. Owing to a lack of statistical information, the data of $n = 22$ studies that were eligible for inclusion could not be considered. The total sample of the $k = 39$ comparisons consisted of $n = 4{,}284$ (range: 17–699) participants with a mean age of 25.57 ($SD = 12.33$) years and an average of 66.1% females ($SD = 28.5\%$, range: 0.0–100.0%; $k = 2$ studies contained a purely male sample and $k = 13$ a purely female sample). $K = 10$ comparisons involved samples consisting of children and/or adolescents only, $k = 26$ comprised exclusively adult participants, and $k = 3$ studies included both adolescent and adult subjects. Eleven studies ($k = 12$) did not report on percentages of Non-Caucasians, while the percentage of Non-Caucasians in the remaining studies ranged between 0.0 and 88.7% ($M = 35.8\%$, $SD = 27.9\%$). With respect to psychopathology, $k = 10$ comparisons included healthy participants, $k = 6$ involved participants all fulfilling diagnostic criteria for a mental disorder, and $k = 10$ comparisons comprised participants with at least some fulfilling the diagnostic criteria for a mental disorder (with $k = 6$ not matched in terms of psychopathology; however, in two of these studies, the authors were able to show that the presence of the specific mental disorder

did not affect the cortisol data). Finally, $k = 13$ comparisons did not report on psychopathology at all. Various instruments to assess child maltreatment were applied with $n = 7$ studies relying on informant reports, $n = 25$ ($k = 29$) on self-report data, and three studies using both information sources. The most frequently used self-report was the Childhood Trauma Questionnaire (CTQ; $n = 15$, $k = 17$), and accordingly, cut-off scores were mostly used to group study participants in these studies. Nevertheless, several other instruments were also employed, resulting again in various grouping approaches. It should be noted that five studies did not focus on child maltreatment only (Hengesch et al., 2018; Ivanov et al., 2011; Kaiser et al., 2018; Otte et al., 2005; Ouellet-Morin et al., 2011) but also included participants with other ELA experiences. By far, the most frequently applied stress task was the Trier Social Stress Test (TSST) or the TSST-C ($n = 18$, $k = 21$) and the majority of studies contained some social-evaluative aspects ($k = 29$; for an overview of the different tasks applied in the various studies, see Appendix E). The average duration of the stressors used was about 19.02 ($SD = 16.94$) min ($k = 27$ between 10 and 20 min). In $n = 3$ studies no cortisol response following the onset of the corresponding stressor was observed. Interestingly, these studies all applied stressors that did not contain any social-evaluative challenges. In $k = 29$ comparisons a cortisol response was observed in both groups (with different peak times found for $k = 5$ comparisons), and finally in $k = 7$ comparisons, the response was observed only in one but not in the other group ($k = 6$ only in the control sample, $k = 1$ only in the child maltreatment sample). On average, the time between the onset of a stressor and peak cortisol levels being reached was 29.84 ($SD = 15.98$) min, with the majority of studies reporting that the peak was reached between +20 and +40 min post stressor onset ($k = 26$). The vast majority of studies used saliva samples to assess cortisol. Baseline, peak and recovery data were reported by most publications, with considerably fewer studies reporting on AUC_i or AUC_g indices. Finally, the data of $n = 19$ ($k = 20$) studies were provided by corresponding authors, with the data of $k = 13$ comparisons being (re)grouped. For further details on the characteristics of the included studies, see Table 5.

Table 5
Summary characteristics of included studies that reported on cortisol assessed in the context of a stressor (cortisol stress reactivity).

Study	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Task	Duration stressor	Time point peak	Cortisol response	Type of sample	Unit	Indices	Source	Data (re)grouped
							Total Sample										CM Sample			Control Sample			CM Assessment		Stressor				Cortisol Assessment			Data	
Alexander et al., 2018	200	23.72 (2.85)	50.0	0.0	no	32	23.81 (3.01)	56.3	168	23.70 (2.83)	48.8	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	15min	25min peak ident.	yes, both	saliva	nmol/l	all	provided, group	yes
Ali & Pruessner, 2012	37	25.77 (5.37)	51.4	NA	no	20	25.95 (5.61)	50.0	17	25.56 (5.22)	52.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	20min	30min peak ident.	yes, both	saliva	nmol/l	all	provided, group	no
Buchmann et al., 2014	195	19.00 (0.00)	53.9	NA	yes*, mixed	15	19.00 (0.00)	53.3	180	19.00 (0.00)	53.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	20min	20min peak ident.	yes, both	blood	ng/ml	bl, peak, end, delta	provided, group	yes
Carpenter et al., 2007	50	29.11 (11.31)	66.0	24.0	no	23	35.00 (12.90)	74.0	27	24.10 (6.60)	59.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	25min	30min peak ident.	yes, both	blood	nmol/l (adj. for age)	bl, peak, end, delta	paper, table	no
Carpenter et al., 2011	110	30.45 (11.13)	100.0	NA	yes*, mixed	20	36.50 (12.50)	100.0	90	29.10 (10.40)	100.0	self-report (quest.)	CTQ	cut-offs	PA	TSST	25min	45min peak ident.	yes, both	saliva	nmol/l	bl, peak, end	paper, figure[+]	no
Cook et al., 2012	175	15.36 (1.01)	51.8	NA	NA	86	15.39 (1.03)	55.4	89	15.30 (0.97)	48.2	self-report (quest.)	CTQ	cut-offs	EA, PA, N	TSST-C	15min	33min NA	yes, both	saliva	NA	delta	paper, table	no
England-Mason et al., 2017	120	32.20 (4.26)	100.0	NA	NA	25	30.47 (4.36)	100.0	95	32.65 (4.14)	100.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	stroop task	17min	37min peak ident.	yes, only in CG sample	saliva	nmol/l	all	provided, group	yes
Fogelman et al., 2016a	73[a]	63.78 (7.39)	58.9	8.5[c]	no	24	65.00 (9.21)	66.7	49	63.18 (6.33)	55.1	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	15min	25min peak ident.	yes, both	saliva	nmol/l	all	provided, group	yes
Fogelman et al., 2016b	85[b]	23.86 (7.32)	0.0	4.5[d]	no	20	24.65 (7.51)	0.0	65	23.62 (7.30)	0.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	15min	25min peak ident.	yes, both	saliva	nmol/l	all	provided, group	yes
Harkness et al., 2011	71	15.39 (2.11)	67.6	11.0	yes*, mixed	26	15.88 (1.75)	69.2	45	15.11 (2.26)	66.7	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	TSST	30min	30min peak ident.	yes, both	saliva	μg/dl	bl, peak, end, delta, AUC_i	provided, group	yes
Heim et al., 2000a	26	29.77 (6.37)	100.0	38.5	yes*, mixed	14	30.21 (5.46)	100.0	12	29.25 (7.52)	100.0	self-report (interview)	ETI	other (spec.)	PA, SA	TSST	20min	30min peak ident.	yes, both	blood	nmol/l	peak	paper, table	no
Heim et al., 2000b	23	33.35 (6.00)	100.0	13.0	yes*, MDD[e]	13	32.38 (7.64)	100.0	10	34.60 (8.38)	100.0	self-report (interview)	ETI	other (spec.)	PA, SA	TSST	20min	30, 45min peak not ident.	yes, both	blood	nmol/l	peak	paper, table	no
Hengesch et al., 2018	44	22.15 (2.91)	56.8	NA	NA	22[f]	22.50 (3.04)	63.6	22[f]	21.80 (2.80)	50.0	mixed	no instr. used	other (self-ident., agency)	other (insti-tute.[◊])	CPT + PASAT	3min	25min peak ident.	yes, both	saliva	nmol/l	bl, delta, AUC_i	paper, table	no
Ivanov et al., 2011	25	10.55 (1.02)	36.0	88.0	yes, ADHD	10	10.78 (1.12)	50.0	15	10.39 (0.95)	26.7	mixed (quest.)	CLES, PTSRI	other (spec.)	PA, SA, loss[◊]	watching emot. video	11min	end of viewing• no peak	no	saliva	μg/dl	bl, peak, end, AUC_g, AUC_i	provided, raw	no
Kaiser et al., 2018	55	27.62 (6.43)	100.0	43.0[g]	yes*, mixed	42	28.43 (6.65)	100.0	13	25.00 (5.03)	100.0	self-report (interview)	TAQ	cut-offs	PA, SA, WV, peers[◊]	MAST	10.75min	28min peak ident.	yes, both	saliva	ng/ml	bl, peak, end, delta, AUC_g	provided, group	yes
Kuhlman et al., 2015	91	12.75 (2.27)	40.3	22.0[h]	yes, mixed	72	12.91 (2.26)	41.2	19	12.16 (2.27)	36.8	informant (quest.)	ETI	other (spec.)	EA, PA, SA	SE-CPT	5min	25min peak ident.	yes, both	saliva	μg/dl	all	provided, group	yes

Table 5

Summary characteristics of included studies that reported on cortisol assessed in the context of a stressor (cortisol stress reactivity).

Study	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Task	Duration stressor	Time point peak	Cortisol response	Type of sample	Unit	Indices	Source	Data (re)grouped
		Total Sample					**CM Sample**			**Control Sample**			**CM Assessment**				**Stressor**				**Cortisol Assessment**			**Data**
Lovallo et al., 2019[i]	699	23.70 (3.14)	55.9	20.3	no	335	23.90 (3.26)	63.0	364	23.50 (3.02)	49.5	self-report (interview)	C-DIS-IV	other (spec.)	EA, PA, SA	public speaking, arithmet. task	45min	30min peak ident.	yes, both	saliva	μg/dl	bl, peak, end, delta	provided, group	yes
Luecken et al., 2009	76[j]	18.90 (0.97)	48.7	25.0	NA	19	NA	NA	48	NA	NA	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	role-play task	10min	10min peak ident.	yes, both	saliva	μg/dl	all	provided, raw	yes
Luecken & Appelhans, 2006	88	19.30 (1.63)	62.5	22.7	NA	16	19.81 (1.83)	56.3	72	19.18 (1.57)	63.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	speech task	8min	23min peak ident.	yes, only in CG sample	saliva	μg/dl	all	provided, raw	yes
Martinson et al., 2016	50	19.70 (4.19)	100.0	11.8	yes*, mixed	26	21.38 (7.59)	100.0	24	18.92 (1.14)	100.0	self-report (mixed)	self-dev., SCID-I/P	other (spec.)	SA	self-discl. and rel.-build. task	45min	15min peak ident.	yes, only in CG sample	saliva	nmol/l	bl, peak, end	paper, table	no
Mielock et al., 2017	52	27.44 (9.47)	100.0	61.5	yes, MDD	26	26.20 (9.50)	100.0	26	28.70 (9.40)	100.0	self-report (interview)	CAI	cut-offs	PA, SA, WV	TSST	15min	25, 35min peak not ident.	yes, both	saliva	μg/dl	all	provided, group	no
D. B. O'Connor et al., 2018	145	26.93 (9.39)	60.7	26.8	yes, mixed	65	29.95 (10.15)	57.8	80	24.24 (7.59)	63.7	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	MAST	10min	20, 30min peak not ident.	yes, both	saliva	nmol/l	all	provided, group	yes
Otte et al., 2005	76	28.00 (5.00)	13.2	NA	no	16	27.00 (4.00)	6.0	60	28.00 (5.00)	15.0	self-report (interview)	LSC-R	other (spec.)	PA, N, non-int. trauma◊	watching emot. video	20min	40min peak ident.	yes, both	saliva	ng/dl	bl, peak	paper, figure	no
Ouellet-Morin et al., 2011	190	12.00 (0.00)	49.5	8.4	NA	64	12.00 (0.00)	54.7	126	12.00 (0.00)	46.8	informant (interview)	self-develop.	other (spec.)	PA, SA, bully.◊	PST	13min	25, 35min peak not ident.	yes, both	saliva	nmol/l	bl, peak	paper, figure	no
Ouellet-Morin et al., 2018	155	24.10 (3.70)	0.0	NA	NA	56	24.00 (3.60)	0.0	99	24.10 (3.70)	0.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	15min	25min peak ident.	yes, both	saliva	μg/dl	all	provided, group	no
Pierrehumbert et al., 2009	44[k]	33.02 (7.12)	100.0	NA	yes, mixed	27	33.38 (6.01)	100.0	17	32.46 (8.87)	100.0	self-report (interview)	ETI	other (spec.)	SA	TSST	15min	NA peak not ident.	yes, both	saliva	nmol/l	bl, delta, AUC$_i$	paper, table	no
Rao & Morris, 2015	17[l]	18.93 (4.72)	52.9	35.3	yes, MDD	7	18.40 (3.90)	42.9	10	19.30 (5.40)	60.0	mixed (interview)	CAI	cut-offs	PA, SA, WV	TSST	15min	25min peak ident.	yes, only in CG sample	saliva	μg/dl	bl, peak, end, AUC$_g$	paper, table & figure	no
Schalinski et al., 2015	33[m]	34.60 (10.40)	100.0	88.0	yes, mixed	16	34.30 (11.65)	100.0	17	34.90 (9.40)	100.0	self-report (interview)	ETI	other (cluster-ing)	EA, PA, SA	trauma interview	99min	99min peak ident.	yes, only in CG sample	saliva	nmol/l	all	provided, group	yes
Schwaiger et al., 2016	60	52.02 (5.09)	66.7	NA	no	30	52.57 (5.52)	66.7	30	51.47 (4.64)	66.7	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	TSST	15min	25min peak ident.	yes, both	blood	ng/ml	all	provided, raw	no
Seltzer et al., 2014	73	9.54 (1.15)	52.1	47.0	NA	37[n]	9.40 (1.16)	54.1	36[n]	9.68 (1.14)	50.0	informant (mixed)	CPS, CTS	other (record)	PA	TSST-C	16min	31min peak ident.	yes, only in CG sample	saliva	μg/dl	all	provided, raw	no

Table 5

Summary characteristics of included studies that reported on cortisol assessed in the context of a stressor (cortisol stress reactivity).

Study	Total Sample					CM Sample			Control Sample			CM Assessment				Stressor				Cortisol Assessment			Data	
	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Task	Duration stressor	Time point peak	Cortisol response	Type of sample	Unit	Indices	Source	Data (re)grouped
Shenk et al., 2014	104	16.98 (1.18)	100.0	59.0	NA	47	16.75 (1.10)	100.0	57	17.13 (1.21)	100.0	informant (record)	CPS	other (record)	PA, SA, N	perform. and interp. task	15.45min	25.45min• no peak	no	saliva	µg/dl	bl, peak, end, AUCg, AUCi	provided, group	no
Shenk et al., 2010	144	18.09 (3.47)	100.0	45.8	NA	60	18.54 (3.62)	100.0	84	17.76 (3.34)	100.0	informant (record)	CPS	other (record, spec.)	SA	cognitive task	10min	15min peak ident.	yes, both	saliva	µg/dl	AUCi	paper, table	no
Sullivan et al., 2013	64	6.89 (0.95)	52.0	88.0	NA	30	6.98 (0.88)	48.0	34	6.72 (1.08)	56.0	informant (mixed)	CPS, CTS-PC	other (record)	N	self-eval. task	4min	20min after last failed task• no peak	no	saliva	µg/dl	bl, peak, end	paper, table	no
Sumner et al., 2014	158	14.93 (1.39)	53.8	47.0	NA	61	15.30 (1.30)	60.7	97	14.70 (1.40)	49.5	self-report (mixed)	CTQ, CECA	cut-offs, other (spec.)	EA, PA, SA	TSST	15min	20min peak ident.	yes, both	saliva	nmol/l	bl, peak, end, AUCi	paper, figure	no
Suzuki et al., 2014a	41	44.89 (13.06)	58.5	39.0	no	17	44.30 (12.50)	52.9	24	45.30 (13.70)	62.5	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	watching emot. pictures	NA	NA peak ident.	yes, only in CM sample	saliva	nmol/l	bl, peak, end, delta	paper, figure+	no
Suzuki et al., 2014b	38	51.91 (11.30)	71.1	0.0	yes, MDD	20	52.10 (12.00)	80.0	18	51.70 (10.80)	61.1	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	watching emot. pictures	NA	NA peak ident.	yes, both	saliva	nmol/l	bl, peak, end, delta	paper, figure+	no
Trickett et al., 2014	454	10.93 (1.16)	46.7	88.7	NA	303	10.84 (1.16)	50.0	151	11.11 (1.15)	40.0	informant (record)	DCFS	other (record)	EA, PA, SA, N	TSST-C	14min	24min peak ident.	yes, both	saliva	µg/dl	bl, peak, end	paper, table	no
Wingenfeld et al., 2017a	59	34.43 (12.02)	100.0	NA	no	22	36.50 (12.20)	100.0	37	33.20 (11.90)	100.0	self-report (interview)	ETIo	other (spec.)	PA, SA	TSST	15min	40min peak ident.	yes, both	saliva	nmol/l	bl, peak, AUCg, AUCi	paper, table & figure	no
Wingenfeld et al., 2017b	84	35.00 (11.21)	100.0	NA	yes, MDD	32	34.20 (10.50)	100.0	52	35.50 (11.70)	100.0	self-report (interview)	ETIo	other (spec.)	PA, SA	TSST	15min	40min peak ident.	yes, both	saliva	nmol/l	bl, peak, AUCg, AUCi	paper, table & figure	no

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder, * = groups are not matched with respect to psychopathology; MDD = Major Depressive Disorder; ADHD = Attention Deficit Hyperactivity Disorder; CM = child maltreatment; n = sample size; quest. = questionnaire; CTQ = Childhood Trauma Questionnaire; CECA = Childhood Experiences of Care and Abuse; ETI = Early Trauma Inventory; no instr. used = no instrument used; CLES = Codington Life Events Scale; PTSRI = Posttraumatic Stress Reaction Index; TAQ = Traumatic Antecedents Questionnaire; C-DIS-V = Computerized version of the Diagnostic Interview Schedule-IV; self-dev. = self-developed (the authors used a scale developed by themselves); SCID-I/P = Structured Clinical Interview for DSM-IV-TR axis I disorders, research version, patient edition; CAI = Childhood Adversity Interview; LSC-R = Life Stressor Checklist-Revised; CPS = Child Protective Services; CTS-PC = Parent–Child Conflict Tactics scale; DCFS = Department of Children and Family Services; spec. = specification (authors applied a specific definition of CM); self-ident. = self-identification (participants self-identified as victims of CM); EA = emotional abuse; PA = physical abuse; SA = sexual abuse; N = neglect; institute. = institutionalization; non-intent. trauma = non-intentional trauma; bully = bullying; ◊ = The grouping of participants was not just based on CM experiences but also included other traumatic experiences; TSST = Trier Social Stress Test; TSST-C = Trier Social Stress Test for Children; CPT = Cold Pressor Test; PASAT = Paced Auditory Serial Addition Task; SE-CPT = Socially Evaluated Cold Pressor Task; arithmet. = arithmetic's; self-discl. = self-disclosure; rel.-build. = relationship-building; PST = Psychosocial Stress Test; perform. = performance; interper. = interpersonal; self-eval. = self-evaluative; ident. = identical; adj. = adjusted; bl = baseline (if possible, value just prior stressor onset was extracted); delta = peak values minus baseline value; AUCg = Area under the curve with respect to ground; AUCi = Area under the curve with respect to increase; • no cortisol peak was observed in both groups, therefore the time point closest to +25 min post stressor onset was extracted. [a] Community-dwelling older adult sample. [b] Community-dwelling younger adult sample. [c] Percentage of non-Caucasians refers to total sample (N = 82). [d] Percentage of non-Caucasians refers to total sample (N = 88). [e] CM sample and control sample were matched with respect to MDD but not with respect to PTSD. [f] Female and male participants with early life adversity were combined into one group and were compared to female and male control participants. [g] Percentage of non-Caucasians refers to total sample (N = 42). [h] Percentage of non-Caucasians refers to total sample (N = 127). [i] This article did not appear in the initial search but was suggested by the respective author as best suited for citation in this meta-analysis. [j] Demographic data for total sample (age, percentage of females, percentage of Non-Caucasians) refers to N = 76, cortisol data available for N = 67. [k] Demographic data for total sample and CM and control sample refers to N = 44, cortisol data available for N = 35. [l] Comparison between participants with MDD and CM and those with MDD without CM. [m] The data were regrouped, taking into account only the patient group with stress-related disorders. [n] Female and male maltreated participants were combined into one group and were compared to female and male control participants. [o] Authors also administered CTQ, but grouping was based on ETI. + It is not clearly stated in the text or in the subheading of the figure whether means and standard deviations or means and standard errors were presented; we assumed standard errors.

3.2.3.2. Risk of bias assessment

Studies assessing cortisol in the context of a stressor received an average total score of 58.1/100.0 (SD = 12.4, range: 32.1–78.6). With respect to the selection of participants (M = 66.7/100.0, SD = 15.8), less than half of the included studies ensured that all participants in the child maltreatment group were exposed to child maltreatment, while none of the participants in the control group were (k = 18), used at least two different sources of information to establish the presence of child maltreatment (k = 8), and ensured that participants were matched with respect to psychopathology assessed with corresponding self-report questionnaires (k = 19). Most studies, however, employed an established measure to assess child maltreatment and matched their participants with respect to age, sex, and psychopathology (assessed with a gold-standard diagnostic tool). Regarding the appropriate measurement of cortisol in the context of a stressor (M = 61.7/100.0, SD = 13.4), less than half of the included studies reported on whether sampling was rescheduled if participants were sick (k = 9), ensured that all women were tested during a specific period of their menstrual cycle (k = 13), reported on whether samples were analyzed in one batch (k = 7), and only k = 5 comparisons included measures attempting to ensure that none of the participants were under any current stress at the time of testing or if testing was rescheduled if participants experienced any stressor during the respective day. Finally, concerning the appropriate control of potential confounders (M = 44.3/100.0, SD = 24.0), less than half of the included studies made efforts to exclude participants with any medical condition (k = 17) known to influence HPA axis functioning, ensured that the groups did not differ with respect to smoking (k = 14), clearly stated whether pregnant women were excluded (k = 14), ensured that participants did not differ with respect to the intake of medications known to influence the CNS (k = 10), and finally, only k = 5 comparisons took measures to ensure the two groups did not differ with respect to other types of ELA or adult adversity. The detailed quality ratings for the individual studies as well as the detailed description of the individual quality items can be found in Appendix B Table B10 or Table B3.

3.2.3.3. Meta-analysis

The pooled effect estimates for the different indices are displayed in Table 6. The results of the sensitivity analyses (where appropriate) are also presented. As shown in the corresponding lines of Table 6, the results of the meta-analyses on baseline cortisol showed no significant overall differences in cortisol levels assessed prior to the onset of the respective stress task between the child maltreatment and the control sample (holding true for the sensitivity analyses). In contrast, the release of cortisol following the perception of a stressor – expressed as peak, recovery, delta, and AUC_i cortisol – was lower in the child maltreatment group compared to the control sample (with all pooled effect estimates being in the small range), indicating a blunted cortisol stress reactivity (see Appendix C Figs. 3.1–3.6 for corresponding forest plots). For AUC_g, the pooled effect estimate was not statistically significant (p = 0.081). However, when excluding one outlier study (Ivanov et al., 2011), significance was also reached

for this outcome index ($p = 0.021$). Between-study heterogeneity was in the moderate to high range for some of the outcome indices ($I^2 > 50\%$), exceeding the level of significance (Q-statistics all $p < 0.05$) for all but AUC$_i$ cortisol. Visual inspection of traditional and counter-enhanced funnel plots as well as Egger's regression test of funnel plot asymmetry revealed the absence of small-study bias for baseline, peak, AUC$_g$, and AUC$_i$ cortisol levels (all $p > 0.05$). However, the Egger's regression test of funnel plot asymmetry reached significance for delta as well as recovery cortisol levels ($p < 0.05$), suggesting the presence of small-study bias (see Appendix C Figs. 3.1–3.6 for corresponding funnel plots).

Table 6
Summary statistics for random-effects models of included studies that reported on cortisol assessed in the context of a stressor (cortisol stress reactivity), displayed separately for the different cortisol outcome indices.

Outcome indices	Random-effects model					Heterogeneity measures					
	N	k	Hedges' g	95% CI	p	tau^2	I^2	Q	p	Pred. int.	Egger's Test[a]
baseline cortisol	3895	35	-0.12	-0.28; 0.04	0.152	0.18	69.7%	112.38	0.000	-0.99; 0.75	-0.587 (0.411)
baseline cortisol sensitivity analysis °	3780	32	-0.07	-0.19; 0.05	0.278	0.06	52.9%	65.87	0.000	-0.59; 0.46	-
baseline cortisol sensitivity analysis *	3845	34	-0.07	-0.21; 0.06	0.290	0.09	59.9%	82.23	0.000	-0.71; 0.56	-
peak cortisol	3867	35	-0.27	-0.51; -0.02	0.033	0.47	78.3%	156.87	0.000	-1.68; 1.14	-1.088 (0.175)
peak cortisol sensitivity analysis °	3731	31	-0.18	-0.29; -0.08	0.001	0.03	42.6%	52.30	0.007	-0.57; 0.20	-
peak cortisol sensitivity analysis *	3817	34	-0.18	-0.33; -0.03	0.019	0.13	65.6%	95.81	0.000	-0.94; 0.58	-
delta cortisol	2678	24	-0.19	-0.32; -0.06	0.004	0.04	46.1%	42.66	0.008	-0.63; 0.25	-1.475 (0.016)
delta cortisol sensitivity analysis °*	2640	23	-0.14	-0.25; -0.04	0.010	0.02	30.7%	31.76	0.082	-0.44; 0.15	-
recovery cortisol	3407	29	-0.28	-0.48; -0.07	0.008	0.24	73.4%	105.22	0.000	-1.30; 0.74	-1.603 (0.038)
recovery cortisol sensitivity analysis °	3254	25	-0.14	-0.24; -0.04	0.004	0.01	19.1%	29.65	0.197	-0.39; 0.11	-
recovery cortisol sensitivity analysis *	3357	28	-0.19	-0.32; -0.06	0.004	0.06	55.5%	60.65	0.000	-0.69; 0.31	-
AUC$_g$ cortisol	1614	20	-0.17	-0.35; 0.02	0.081	0.11	62.5%	50.72	0.000	-0.89; 0.56	-1.596 (0.257)
AUC$_g$ cortisol sensitivity analysis °	1591	19	-0.20	-0.37; -0.03	0.021	0.08	55.7%	40.62	0.002	-0.81; 0.41	-
AUC$_i$ cortisol	1992	23	-0.22	-0.34; -0.10	0.000	0.03	31.4%	32.06	0.076	-0.58; 0.14	-1.458 (0.156)

Note. AUCg = Area under the curve with respect to ground; AUCi = Area under the curve with respect to increase; 95% CI = 95% confidence interval; Pred. int. = prediction interval. [a] Intercept and (*p* values) displayed. Baseline cortisol: ° exclusion of outlier studies Carpenter et al., 2007, Ivanov et al., 2011, and Suzuki et al., 2014a; * exclusion of influential study Carpenter et al., 2007. Peak cortisol: ° exclusion of outlier studies Carpenter et al., 2007, Heim et al., 2000b, Ivanov et al., 2011, and Suzuki et al., 2014b; * exclusion of influential study Carpenter et al., 2007. Delta cortisol: °* exclusion of outlier and influential study Suzuki et al., 2014b. Recovery cortisol: ° exclusion of outlier studies Ali & Pruessner, 2012, Carpenter et al., 2007, Ivanov et al., 2011, and Suzuki et al., 2014a; * exclusion of influential study Carpenter et al., 2007. AUC$_g$ cortisol: ° exclusion of outlier study Ivanov et al., 2011. See Appendix C Figs. 3.1-3.6 for corresponding forest and funnel plots.

3.2.3.4. Meta-regression and subgroup analyses

We conducted a number of pre-defined meta-regression and subgroup analyses focusing on peak, delta, recovery, AUC$_g$, and AUC$_i$ cortisol. The summary results for each outcome index and each moderator examined are shown in Appendix D Table D3. In the following section, the results for moderators found to significantly influence the main effects are outlined. For delta, recovery, and AUC$_i$ cortisol, we identified the proportion of women in the sample as a continuous moderator (for AUC$_i$: $p = 0.052$), with an increase in the proportion of females being associated with lower cortisol secretion following the perception of a stressor when comparing the child maltreatment and the control sample. Additionally,

for delta cortisol, the proportion of participants fulfilling diagnostic criteria for a mental disorder significantly moderated the summary effect, with an increase of the proportion being associated with a stronger blunting of the cortisol stress response ($\beta = -0.006$, 95% CI [-0.010; -0.002], $p = 0.007$, $R^2 = 99.20\%$). This finding, however, should be interpreted with caution, as only two of the studies that included a purely clinical sample (Schalinski et al., 2015; Suzuki et al., 2014) reported on delta cortisol. In addition, and in contrast to the other studies involving a clinical sample (exception Rao & Morris, 2015), these two studies reported relatively strong negative effects. Nevertheless, despite considerable heterogeneity between the studies, all outcome indices showed stronger effects for studies including purely clinical samples and markedly weaker effects for those studies that involved healthy subjects only (see results subgroup analyses). Furthermore, stronger effects were found for studies that observed a cortisol response in just one of the groups (holding true for all outcome indices) compared to studies that found a response in both groups and those that found no response in either of the groups, with the subgroup comparison reaching significance for delta ($Q_2 = 4.53$, $p = 0.033$) and AUC_i ($Q_2 = 12.33$, $p = 0.002$) cortisol. Comparing studies focusing on child maltreatment experiences only to those involving participants with other types of ELA as well showed that the few studies that also considered other types of ELA overall yielded greater negative effect estimates for all outcome indices, but significant for delta cortisol only ($Q_1 = 3.95$, $p = 0.047$). However, it should be noted that heterogeneity within these studies varied substantially between the different outcome indices and thus depended highly on the included studies. Finally, again depending on the outcome index investigated (and thus on the studies included), the different sub-domains of the quality assessment appeared to explain part of the variance in the effect estimates between studies, although this effect was only significant for AUC_i cortisol (and only for the subdomain: selection of participants: $\beta = 0.009$, 95% CI [0.002; 0.016], $p = 0.011$, $R^2 = 77.45\%$). In general, there was a tendency that a higher study quality was associated with a smaller negative difference in cortisol secretion between the child maltreatment and the control group. As an additional note, although subgroup comparisons between studies with (re)grouped data to those with original data could not explain significant heterogeneity between studies for any outcome indices, those studies with (re)grouped data still showed considerably less pronounced effects.

3.2.4. Pharmacological challenge tests

3.2.4.1. Dexamethasone suppression test

3.2.4.1.1. Included studies

Eleven articles, containing $k = 17$ comparisons, involving a total of $n = 2,222$ participants (range: 16–1,112) assessed cortisol in the context of the DST. Of these, $k = 16$ reported on baseline cortisol levels (cortisol assessed before dexamethasone administration; pre-DST), $k = 17$ on cortisol assessed following the administration of dexamethasone (post-DST), and $k = 9$ contained information on delta values (post-DST cortisol minus pre-DST cortisol). The included studies mainly consisted of adults, with only one

study involving adolescents. The average age was 33.32 (SD = 8.32) years and studies ranged from 45.6 to 100.0% (M = 72.6%, SD = 18.6%) in terms of the proportion of women (k = 3 studies with a purely female sample). Five studies (k = 8) did not report on the percentage of Non-Caucasians, while the percentage of Non-Caucasians in the remaining studies ranged between 0.0 and 100.0% (M = 53.4%, SD = 41.2%). Three out of the k = 17 comparisons involved healthy participants and k = 14 included participants in whom the proportion of people suffering from a mental illness ranged from 13.2 to 100.0% (k = 9 studies involved purely clinical samples and k = 3 involved participants where the child maltreatment and the control sample were not matched in terms of psychopathology). Various instruments to assess child maltreatment were applied, all relying on self-report information. The most common self-report used was the CTQ (n = 5, k = 9). It should be noted that the child maltreatment sample of the study from Faravelli et al. (2010) did not only consist of participants with child maltreatment experiences, but also included several participants with loss experiences. Approximately half of the studies used established cut-off values to group participants in the corresponding child maltreatment and control groups, with the others mostly applying specific definitions. All but three studies (k = 4) used 0.5 mg of dexamethasone and the data of four studies (k = 8) were re-grouped for this meta-analysis (see Table 7 for more details).

3.2.4.1.2. Risk of bias assessment

Studies assessing cortisol in the context of the DST received an average score of 72.1/100.0 (SD = 19.0) for selection of participants, 61.3/100.0 (SD = 12.1) for appropriate assessment of cortisol, and 44.7/100.0 (SD = 20.3) for adequate controlling for confounders, resulting in an average overall score of 58.1/100.0 (SD = 13.3, range: 40.0–76.0). The detailed quality ratings for the individual studies as well as the detailed description of the individual quality items can be found in Appendix B Table B11 or Table B4. None of the studies included used two different sources to establish the presence of child maltreatment, reported whether cortisol was analyzed in one batch and whether participants were excluded when working night shifts, and only one study assessed whether exposure and control groups differed in relation to the experience of other traumatic events during childhood or adulthood. Moreover, less than half of the comparisons reported whether sampling was postponed when participants were sick (k = 7), whether dexamethasone intake was checked (k = 7), whether participants differed in smoking (k = 6), intake of oral contraceptives (k = 7), and their use of medication (with CNS effect; k = 4).

Table 7
Summary characteristics of included studies that reported on cortisol assessed in the context of the dexamethasone suppression test (DST).

	Total Sample					CM Sample			Control Sample			CM Assessment				Cortisol Assessment					Data	
Study	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Type of sample	Unit	Time points[a]	Indices[b]	Dex-dose[c]	Source	Data (re)grouped
Baes et al., 2014	20[d]	38.80 (9.84)	75.0	40.0	yes, MDD	13	39.50 (9.73)	76.9	7	37.40 (11.38)	71.4	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	blood	NA	9am	post	0.5mg 10pm	paper, text	no
Carvalho Fernando et al., 2012a	19	27.05 (6.21)	94.7	NA	yes, BPD	14	27.86 (6.59)	92.9	5	24.80 (4.92)	100.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	7:30am	pre, post, delta	0.5mg 11pm	provided, raw	yes
Carvalho Fernando et al., 2012b	25	32.72 (8.78)	52.0	NA	yes, MDD	12	34.42 (9.55)	66.7	13	31.15 (8.06)	38.5	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	7:30am	pre, post, delta	0.5mg 11pm	provided, raw	yes
Carvalho Fernando et al., 2012c	40	32.70 (10.39)	67.5	NA	no	8	42.63 (6.41)	75.0	32	30.22 (9.73)	65.6	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	nmol/l	7:30am	pre, post, delta	0.5mg 11pm	provided, raw	yes
Duval et al., 2004	28	15.95 (1.93)	82.1	0.0	yes*, PTSD	14	16.20 (1.90)	85.7	14	15.70 (2.00)	78.6	self-report (interview)	SCID-I, checklist	other (self-ident.)	SA	blood	nmol/l	8am	pre, post	1.0mg 11pm	paper, table & figure	no
Faravelli et al., 2010	93[e]	43.60 (15.40)	50.2	NA	yes, mixed	32	NA	NA	61	NA	NA	self-report (mixed)	CECA, self-dev.	other (not spec.)	PA, SA, loss◊	saliva	nmol/l	8am	pre, post	0.5mg 11pm	paper, table	no
Lindley et al., 2004	16[f]	40.00 (11.17)	87.5	6.2	yes, PTSD	9	34.56 (9.28)	88.9	7	47.00 (9.78)	85.7	self-report (quest.)	THS	other (spec.)	PA, SA	saliva	µg/dl	8am	pre, post, delta	0.5mg 10pm	provided, raw	no
Lu et al., 2016a	35	23.80 (3.89)	51.4	100.0	yes, MDD	18	23.70 (4.13)	44.4	17	23.90 (3.75)	58.8	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	blood	ng/ml	8am	pre, post	1.0mg 11pm	paper, table	no
Lu et al., 2016b	45	21.65 (3.46)	62.2	100.0	no	23	21.50 (3.91)	60.9	22	21.80 (3.01)	63.6	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	blood	ng/ml	8am	pre, post	1.0mg 11pm	paper, table	no
Mehta et al., 2011a	63[g]	41.76 (13.12)	68.3	87.5	yes, mixed	22	42.23 (11.53)	72.7	41	41.51 (14.03)	65.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	blood	µg/dl	8-9am	pre, post, delta	0.5mg 11pm	provided, group	yes
Mehta et al., 2011b	32[g]	40.63 (12.85)	71.9	90.5	yes, PTSD	18	41.06 (13.48)	77.8	14	40.07 (12.47)	64.3	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	blood	µg/dl	8-9am	pre, post, delta	0.5mg 11pm	provided, group	yes
Newport et al., 2004a	38	30.90 (7.00)	100.0	36.8	yes*, mixed	19	33.30 (6.40)	100.0	19	28.50 (6.90)	100.0	self-report (interview)	ETI	other (spec.)	PA, SA	blood	µg/dl	8am	pre, post	0.5mg 11pm	paper, table	no
Newport et al., 2004b	26	32.98 (7.87)	100.0	19.2	yes, MDD	16	32.40 (7.80)	100.0	10	33.90 (8.30)	100.0	self-report (interview)	ETI	other (spec.)	PA, SA	blood	µg/dl	8am	pre, post	0.5mg 11pm	paper, table	no
Schreuder et al., 2016	114	26.75 (2.85)	45.6	NA	yes, mixed	16	27.81 (2.90)	43.8	98	26.58 (2.81)	45.9	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	saliva	µg/dl	awak.	pre, post, delta	1.0mg 10pm	provided, group	yes
Stein et al., 1997	40	31.47 (6.70)	100.0	NA	yes*, mixed	19	32.20 (6.70)	100.0	21	30.80 (6.80)	100.0	self-report (interview)	self-dev.	other (spec.)	SA	blood	nmol/l	8am	pre, post	0.5mg 11pm	paper, table	no
Vreeburg et al., 2009a[h]	1112	42.71 (12.24)	65.7	NA	yes, mixed[i]	635	43.92 (11.69)	70.7	477	41.10 (12.78)	59.1	self-report (interview)	NEMESIS CTI	other (spec.)	EA, PA, SA, N	saliva	nmol/l	awak.	pre, post, delta	0.5mg 11pm	provided, group	yes
Vreeburg et al., 2009b[h]	476	42.93 (14.49)	60.7	NA	no[j]	116	47.88 (12.36)	72.4	360	41.34 (14.78)	56.9	self-report (interview)	NEMESIS CTI	other (spec.)	EA, PA, SA, N	saliva	nmol/l	awak.	pre, post, delta	0.5mg 11pm	provided, group	yes

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder, * = groups are not matched with respect to psychopathology; MDD = Major Depressive Disorder; BPD = Borderline Personality Disorder; PTSD = Posttraumatic Stress Disorder; CM = child maltreatment; n = sample size; quest. = questionnaire; CTQ = Childhood Trauma Questionnaire; SCID-I = Structured Clinical Interview for DSM-IV Axis I Disorders; CECA = Childhood Experiences of Care and Abuse; self-dev. = self-developed (the authors used a scale

developed by themselves); THS = Trauma History Screen; ETI = Early Trauma Inventory; NEMESIS CTI = Netherlands Mental Health Survey and Incidence Study Childhood Trauma Interview; self-ident. = self-identification (participants self-identified as victims of CM); spec. = specification (authors applied a specific definition of CM); EA = emotional abuse; PA = physical abuse; SA = sexual abuse; N = neglect; $^{\lozenge}$ The grouping of participants was not just based on the experience of CM but also included loss experiences; awak. = awakening; Dex-dose = dose of dexamethasone administered to participants. [a] Timepoints of cortisol sampling. [b] Indices: pre = cortisol assessed prior dexamethasone administration; post = cortisol assessed after dexamethasone administration, delta = post values minus pre varlues. [c] Dose and timepoint of dexamethasone administration. [d] Comparison between depressed patients with and without early life stress. [e] Comparison between patient groups with and without early trauma. [f] Comparison between PTSD patients with childhood sexual or physical abuse and those reporting no history of childhood sexual or physical abuse. [g] The sample represents a highly traumatized, low-income cohort; data provided separately for those patients all fulfilling diagnostic criteria for PTSD and those patients without PTSD. [h] The data are from the Netherlands Study of Depression and Anxiety, a large cohort study; this article did not appear in the initial search but was suggested by the respective author as best suited for citation in this meta-analysis. [i] Patient group: dysthymia, MDD, social phobia, panic with/without agoraphobia, generalized anxiety disorder. [j] No one of the participants fulfilled the diagnostic criteria for dysthymia, MDD, social phobia, panic with/without agoraphobia, or generalized anxiety disorder in the past 6 months.

3.2.4.1.3. Meta-analysis

The results of the meta-analyses yielded no significant overall differences in pre-DST cortisol (Hedges'g = 0.07, 95% CI [−0.09; 0.23], p = 0.402), post-DST cortisol (Hedges'g = 0.01, 95% CI [−0.18; 0.20], p = 0.936) nor in delta cortisol values (Hedges'g = −0.13, 95% CI [−0.31; 0.06], p = 0.178) between participants with child maltreatment experiences and participants without corresponding experiences. Between-study heterogeneity was in the low to moderate range (all I^2 < 45%) reaching significance for pre- (Q_{15} = 25.21, p = 0.047) and post-DST (Q_{16} = 28.64, p = 0.027) cortisol (see Appendix C Figs. 4.1.1–4.1.3 for corresponding forest plots). Visual inspection of traditional and counter-enhanced funnel plots as well as the results of the Egger's regression tests (all p > 0.316) implied absence of small-study bias (for funnel plots see Appendix C Figs. 4.1.1–4.1.3). Corresponding sensitivity analyses excluding studies with extreme effect sizes and influential studies did not change the overall results (see Table 8 for related statistics).

Table 8
Summary statistics for random-effects models of included studies that reported on cortisol assessed in the context of the dexamethasone suppression test (DST), displayed separately for the different cortisol outcome indices.

Outcome indices	Random-effects model					Heterogeneity measures					
	N	k	Hedges' g	95% CI	p	tau^2	I^2	Q	p	Pred. int.	Egger's Test[a]
pre-DST cortisol	2201	16	0.07	-0.09; 0.23	0.402	0.03	40.5%	25.21	0.047	-0.35; 0.49	-0.096 (0.854)
pre-DST cortisol sensitivity analysis[°]	2163	15	0.12	-0.01; 0.25	0.074	0.01	0.0%	13.50	0.487	-0.14; 0.38	-
pre-DST cortisol sensitivity analysis[*]	613	14	0.03	-0.19; 0.24	0.816	0.05	32.0%	19.10	0.120	-0.53; 0.58	-
post-DST cortisol	2214	17	0.01	-0.18; 0.20	0.936	0.06	44.1%	28.64	0.027	-0.56; 0.57	-0.483 (0.343)
delta DST cortisol	1888	9	-0.13	-0.31; 0.06	0.178	0.02	34.0%	12.12	0.146	-0.54; 0.29	-0.642 (0.317)

Note. 95% CI = 95% confidence interval; Pred. int. = prediction interval. [a] Intercept and (p values) displayed. [°] Exclusion of outlier study Newport et al., 2004a. [*] Exclusion of influential studies Vreeburg et al., 2009a and Vreeburg et al., 2009b. See Appendix C Figs. 4.1.1-4.1.3 for corresponding forest and funnel plots.

3.2.4.1.4. Meta-regression and subgroup analyses

We conducted a number of pre-defined meta-regression and subgroup analyses focusing on post-DST cortisol only. The summary results for each moderator examined are shown in Appendix D Table D4. The only moderator that significantly influenced the main effect was the proportion of women in the respective samples (β = −0.014, 95% CI [−0.022; −0.005], p = 0.003, R^2 = 95.16%), with an increase of the proportion being associated with lower cortisol levels following the administration of dexamethasone (increased cortisol suppression) when comparing the child maltreatment sample with participants from the control sample. Since only one study was included that focused on ELA in general, the significant subgroup result of different pooled effect estimates for studies focusing on child maltreatment only and the study including also other childhood adversities has to be interpreted with caution. None of the methodological quality criteria significantly influenced the pooled effect estimate.

3.2.4.2. Combined dexamethasone-corticotropin releasing hormone test

3.2.4.2.1. Included studies

In total, our search strategy identified $n = 21$ studies that measured the responsivity of the pituitary to CRH. Of these, $n = 6$ studies consisting of $k = 8$ comparisons reporting on cortisol in the context of the Dex-CRH test and $n = 2$ studies reporting on cortisol in the context of the CRH test were included ($k = 10$). Of the included studies, $k = 4$ comparisons reported on baseline cortisol (cortisol assessed after the administration of dexamethasone, before CRH injection), $k = 6$ on peak (after the CRH injection) and delta cortisol (peak minus baseline), $k = 9$ on AUC_g, and $k = 6$ on AUC_i cortisol. There was only one study with available recovery data (in all other studies, the peak value corresponded to the last measurement time point). The total sample of the $k = 10$ comparisons consisted of $n = 561$ participants (range: 21–230) with a mean age of 31.19 ($SD = 12.70$) years and an average of 60.0% females ($SD = 39.6\%$, range: 0.0–100.0%; $k = 2$ comparisons contained a purely male sample and $k = 4$ a purely female sample). Studies reporting on Dex-CRH cortisol consisted of adult samples only, whereas the two studies focusing on the CRH test were conducted with children or adolescents. Four studies ($k = 5$) did not report on ethnicity with the other articles ranging between 34.6 and 57.1% in terms of percentage of Non-Caucasians ($M = 45.9\%$, $SD = 9.3\%$). With respect to psychopathology, $k = 3$ comparisons included healthy participants, $k = 3$ involved participants all fulfilling diagnostic criteria for MDD, $k = 1$ comparison included participants with mixed diagnoses, and $k = 3$ involved participants where the child maltreatment and the control sample were not matched for psychopathology. The authors of the three comparisons in which the subjects were not matched for psychopathology, however, showed that the presence of the specific mental disorder did not affect the cortisol results. Again, various instruments to assess child maltreatment were used, with the majority of studies relying on self-report data ($k = 8$). The grouping of participants also differed, including the use of cut-off scores, thirds, the presence of a CPS record and the utilization of specific definitions. The data of $n = 2$ studies were provided by corresponding authors, with the data of one study being re-grouped. See Table 9 for more details.

Table 9

Summary characteristics of included studies that reported on cortisol assessed in the context of the combined dexamethasone-corticotropin releasing hormone (Dex-CRH) test.

	Total Sample					CM Sample			Control Sample			CM Assessment				Cortisol Assessment						Data	
Study	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Type of sample	Unit	Time points	Indices	Dex-dose	CRH-dose	Source	Data (re)grouped
Carpenter et al., 2009	230	29.23 (10.37)	56.5	NA	no	41	35.90 (11.60)	66.0	189	27.78 (9.52)	54.0	self-report (quest.)	CTQ	cut-offs	EA	blood	nmol/l[a]	2:59pm - 5pm (6 samples)	bl, peak	1.5mg 11pm	100μg 3pm	paper, figure[+]	no
Heim et al., 2008a	21	31.64 (8.76)	0.0	57.1	yes, MDD	15	32.30 (8.70)	0.0	6	30.00 (9.50)	0.0	self-report (interview)	ETI	other (spec.)	PA, SA	blood	μg/dl	2pm - 5pm (9 samples)	peak, delta, AUCg, AUCi	1.5mg 11pm	1μg/kg 3pm	paper, table	no
Heim et al., 2008b	28	30.25 (8.44)	0.0	53.6	yes*, mixed	14	31.40 (8.00)	0.0	14	29.10 (9.00)	0.0	self-report (interview)	ETI	other (spec.)	PA, SA	blood	μg/dl	2pm - 5pm (9 samples)	peak, delta, AUCg, AUCi	1.5mg 11pm	1μg/kg 3pm	paper, table	no
Klaassens et al., 2009	22	47.58 (11.70)	100.0	NA	no	10	47.80 (12.10)	100.0	12	47.40 (11.90)	100.0	self-report (quest.)	CTQ[b]	cut-offs	EA, PA, SA, N	blood	nmol/l	3pm - 4:45pm (7 samples)	AUCg	1.5mg 11pm	100μg 3:02pm	paper, table	no
R. J. Lee et al., 2012	24	33.42 (9.72)	41.7	41.7	yes*, PD	10	39.10 (11.37)	40.0	14[c]	29.36 (5.93)	42.9	self-report (quest.)	CTQ	other (thirds)	EA, PA, SA, N	blood	μg/dl	4pm - 6pm (7 samples)[d]	all	1.5mg 11pm	1μg/kg 4pm	provided, raw	no
Spitzer et al., 2018a	86	35.50 (11.26)	100.0	NA	yes, MDD	35	35.20 (10.90)	100.0	51	35.70 (11.60)	100.0	self-report (mixed)	CTQ, ETI	other (spec.)	PA, SA	saliva	nmol/l	1:30pm - 4:30pm (7 samples)	delta[e], AUCg	1.5mg 11pm	100μg 2:30pm	paper, table	no
Spitzer et al., 2018b	58	34.29 (11.85)	100.0	NA	no	21	34.80 (10.90)	100.0	37	34.00 (12.50)	100.0	self-report (mixed)	CTQ, ETI	other (spec.)	PA, SA	saliva	nmol/l	1:30pm - 4:30pm (7 samples)	delta[e], AUCg	1.5mg 11pm	100μg 2:30pm	paper, table	no
Watson et al., 2007	40[f]	48.63 (7.34)	47.5	NA	yes, mixed	25	49.12 (6.83)	52.0	15	47.80 (8.32)	40.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	blood	nmol/l	3pm - 6pm (9 samples)	all	1.5mg 11pm	100μg 3pm	provided, raw	yes
De Bellis et al., 1994[g]	26	11.65 (2.74)	100.0	42.3	yes*, Dysthymia	13	11.20 (2.60)	100.0	13	12.10 (2.90)	100.0	informant (record)	CPS	other (record)	SA	blood	nmol/l	6pm - 10pm (13 samples)	AUCg, AUCi	no dex adm.	1μg/kg 8pm	paper, text	no
Kaufman et al., 1997[g]	26[h]	9.75 (1.16)	53.8	34.6	yes, MDD	13	9.60 (1.40)	53.9	13	9.90 (0.90)	53.9	mixed	PSS, medical records	other (not spec.)	EA, PA, SA[i]	blood	μg/dl	5pm - 8pm (9 samples)	bl[j], peak, AUCg, AUCi	no dex adm.	1μg/kg 5:30pm	paper, table	no

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder, * = groups are not matched with respect to psychopathology; MDD = Major Depressive Disorder; PD = Personality Disorder; CM = child maltreatment; n = sample size; quest. = questionnaire; CTQ = Childhood Trauma Questionnaire; ETI = Early Trauma Inventory; CPS = Child Protective Services; PSS = Psychosocial Schedule for School Aged Children; spec. = specification (authors applied a specific definition of CM); EA = emotional abuse; PA = physical abuse; SA = sexual abuse; N = neglect; bl = baseline (if possible, sample just prior CRH injection was extracted); AUCg = area under the curve with respect to ground; AUCi = area under the curve with respect to increase. Dex-dose = dose of dexamethasone administered to participants; CRH-dose = dose of corticotropin-releasing hormone administered to participants. [a] All extracted values are adjusted for age, gender, and effects of four other maltreatment subtypes. [b] Authors also administered ETI, but grouping was based on CTQ. [c] The low CTQ PD group and the normal control group were combined and compared to the high CTQ PD group. [d] Sample assessed at -150min prior CRH injection was not included in analyses (therefore 7 instead of 8 samples; baseline sample at 4pm). [e] Delta defined as difference between maximum value after CRH injection and the mean of the three baseline measures. [f] The data were regrouped, taking into account only the patient groups. [g] No dexamethasone was administrated (CRH test only). [h] Comparison between the patient groups with and without abuse. [i] 54% were subjected to ongoing EA. [j] Baseline defined as the mean of the three pre CRH infusion samples. [+] It is not clearly stated in the text or in the subheading of the figure whether means and standard deviations or means and standard errors were presented; we assumed standard errors.

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3.2.4.2.2. Risk of bias assessment

Studies assessing the responsivity of the pituitary to CRH received an average total score of 69.8/100.0 (SD = 8.0, range: 58.3–83.3). All studies, or k = 9 out of 10 comparisons used an established instrument to assess the experience of child maltreatment, matched their participants with respect to age and sex, and made efforts to assess psychopathology (selection of participants: M = 76.3/100.0, SD = 12.4). Additionally, most comparisons rescheduled the sampling when participants were sick (k = 8), provided details on their test protocol (k = 10), and on how cortisol was collected, stored and analyzed (k = 10; appropriate measurement of cortisol in the context of the Dex-CRH: M = 62.3/100.0, SD = 14.8). Finally, as shown by the relatively high scores related to the control of confounding variables (M = 69.0/100.0, SD = 10.3), the majority of studies assessed or controlled for a wide variety of potential influential factors. Overall, however, only a few comparisons used two different sources of information to establish the presence of child maltreatment (k = 2), verified the ingestion of dexamethasone (k = 2), reported on whether samples were assessed in one batch (k = 1), or whether participants were excluded in case of working night shifts (k = 2), and only k = 2 comparisons made any effort to ensure that the exposure and control group did not differ with respect to other types of ELA or adult adversity. For details on individual scoring results of the primary studies as well as a summary of the average risk of bias scores, see Appendix B Table B12 or Table B5 for individual quality items.

3.2.4.2.3. Meta-analysis

The pooled effect estimates for the different indices are displayed in Table 10. For each outcome index the analysis was repeated excluding the studies focusing on the CRH test only. Results of the sensitivity analyses (where appropriate) are also presented. None of the pooled effect estimates were significant, indicating that there is no overall difference in cortisol assessed both before and after the administration of CRH and holding true for all outcome indices (all p > 0.05). Between-study heterogeneity was however in the moderate range (I^2 > 50%), exceeding the level of significance (Q-statistics all p < 0.05) for peak, delta, AUC_g, and AUC_i cortisol. Due to a limited number of studies (k < 10), however, no subgroup analyses and meta-regressions were performed. Visual inspection of traditional and counter-enhanced funnel plots as well as Egger's regression test of funnel plot asymmetry suggested the absence of small-study bias (all p > 0.05). Forest and corresponding funnel plots for AUC_g and AUC_i cortisol are displayed in Appendix C Figs. 4.2.1 and 4.2.2.

Table 10

Summary statistics for random-effects models of included studies that reported on cortisol assessed in the context of the combined dexamethasone-corticotropin releasing hormone (Dex-CRH) test, displayed separately for the different cortisol outcome indices.

Outcome indices	Random-effects model					Heterogeneity measures					
	N	k	Hedges' g	95% CI	p	tau^2	I^2	Q	p	Pred. int.	Egger's Test[a]
pre-CRH cortisol	320	4	-0.08	-0.35; 0.18	0.540	0	0.0%	1.32	0.725	-0.66; 0.50	-1.434 (0.070)
pre CRH cortisol (Dex-CRH studies only)	294	3	-0.04	-0.32; 0.24	0.782	0	0.0%	0.54	0.763	-1.86; 1.78	-
pre CRH cortisol sensitivity analysis*	90	3	-0.26	-0.68; 0.16	0.228	0	0.0%	0.21	0.902	-3.00; 2.48	-
peak cortisol	369	6	0.11	-0.39; 0.61	0.668	0.25	68.3%	15.77	0.008	-1.45; 1.66	3.018 (0.106)
peak cortisol (Dex-CRH studies only)	343	5	0.03	-0.53; 0.60	0.906	0.28	69.0%	12.89	0.012	-1.89; 1.95	-
delta cortisol	257	6	-0.05	-0.42; 0.33	0.804	0.10	50.3%	10.05	0.074	-1.08; 0.98	2.038 (0.393)
AUC$_g$ cortisol	329	9	-0.09	-0.45; 0.26	0.602	0.16	54.8%	17.72	0.023	-1.12; 0.93	1.775 (0.379)
AUC$_g$ cortisol (Dex-CRH studies only)	277	7	-0.12	-0.56; 0.33	0.606	0.22	61.0%	15.39	0.018	-1.46; 1.23	-
AUC$_g$ cortisol sensitivity analysis°	308	8	-0.21	-0.47; 0.05	0.106	0.02	25.3%	9.37	0.227	-0.69; 0.27	-
AUC$_i$ cortisol	163	6	0.18	-0.38; 0.74	0.522	0.31	63.3%	13.64	0.018	-1.56; 1.93	4.839 (0.410)
AUC$_i$ cortisol (Dex-CRH studies only)	111	4	0.21	-0.56; 0.99	0.590	0.45	68.8%	9.60	0.022	-3.14; 3.56	-

Note. AUCg = Area under the curve with respect to ground; AUCi = Area under the curve with respect to increase; 95% CI = 95% confidence interval; Pred. int. = prediction interval. [a] Intercept and (p values) displayed. * Exclusion of influential study Carpenter et al., 2009. ° Exclusion of outlier study Heim et al., 2008a. See Appendix C Figs. 4.2.1-4.2.2 for corresponding forest and funnel plots.

3.2.5. Cumulative measures of cortisol secretion

3.2.5.1. Hair cortisol concentrations

3.2.5.1.1. Included studies

A total of $n = 8$ independent studies, comprising $k = 9$ comparisons, with an overall sample size of $n = 978$ participants, reported on HCC. The sample size ranged from $n = 22$ to $n = 537$ participants and the majority of studies included mainly female subjects (with the percentage of females ranging between 50.7 and 100.0%, $M = 84.4\%$, $SD = 19.2\%$; $k = 3$ contained a purely female sample). Four comparisons included children and/or adolescents and $k = 5$ included adult participants only. The average age was 28.13 ($SD = 14.88$) years with the youngest participant being about 3 years and the oldest around 79 years. With respect to ethnicity, most studies included samples composed mainly of an ethnic majority group with the percentage of Non-Caucasians ranging between 0.0 and 87.2% ($M = 27.0\%$, $SD = 33.8\%$). Three studies did not reporting on ethnicity. Concerning psychopathology, $k = 4$ comparisons included only healthy participants, $k = 2$ consisted of a primarily clinical sample (with 96.0–100.0% meeting diagnostic criteria for a mental disorder), and $k = 3$ comparisons did not report on psychopathology. Only one study used information about child maltreatment from an informant source, with the others all using self-report data. The assessment of child maltreatment and the grouping of participants into a child maltreatment and a control group varied between the studies. This refers to both the instruments used and to the grouping procedure, which included the use of cut-off scores, percentiles, clustering methods, and the use of specific definitions. Of the six studies ($k = 7$) that provided data on

request, the respective authors of four studies ($k = 5$) regrouped or grouped their data based on the available assessment of child maltreatment (or, in case of raw data, the (re)grouping was performed by us). For further details on the characteristics of the included studies, see Table 11.

3.2.5.1.2. Risk of bias assessment

Table B13 in Appendix B provides an overview of the individual scoring results of the primary studies as well as a summary of the average risk of bias scores. The detailed description of the quality items can be found in Table B6. On average a total score of 58.9/100.0 was received ($SD = 16.6$, range: 24.0–76.0). Regarding participant selection ($M = 75.0/100.0$, $SD = 10.8$), the majority of studies assessed child maltreatment with an established instrument and ensured that all the participants in the child maltreatment group did experience child maltreatment, while none of the participants in the control group did. Most studies also matched participants with respect to age, sex, as well as psychopathology. However, only one study used two different sources of information to establish the presence of child maltreatment. With respect to the appropriate measure of HCC ($M = 55.6/100.0$, $SD = 15.1$), most studies obtained hair samples from the posterior vertex of the head and reported on a clear sampling analysis protocol and information about outlying or missing data. The majority of the studies however, neither assessed the experience of any ongoing life stressor ($k = 0$) nor whether HCC samples were assessed in one batch ($k = 2$). With respect to the appropriate control of confounding variables, the quality of the different studies varied quite strongly ($M = 48.3/100.0$, $SD = 33.3$, range: 0.0–88.9). It should be noted, however, that several studies would have assessed the variables of interest, but since the data of four studies ($k = 5$) were regrouped, the information at the group level was no longer available (this is marked accordingly in the table). No studies reported whether participants were excluded if they worked night shifts ($k = 0$) and few reported whether participants in the two groups did not differ with respect to other traumatic experiences in childhood or adulthood ($k = 3$). Moreover, less than half of the comparisons reported whether participants with any type of addiction ($k = 4$) or pregnant women ($k = 4$) were excluded as well as whether participants were comparable with respect to medication use (medications with CNS effects, $k = 4$).

Table 11
Summary characteristics of included studies that reported on hair cortisol concentrations (HCC).

Study	Total Sample					CM Sample			Control Sample			CM Assessment				Cortisol Assessment	Data	
	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Unit	Source	Data (re)grouped
do Prado et al., 2017	57	15.39 (1.81)	57.9	NA	no	30	16.47 (1.25)	50.0	27	14.19 (1.57)	66.7	self-report (quest.)	CTQ	other (percentile)	EA, PA, SA, N	pg/mg	paper, figure	no
S. Fischer et al., 2017	135	50.31 (14.73)	71.9	9.0[a]	NA	43	53.10 (13.90)	81.0	92	49.00 (15.00)	67.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	pg/mg	provided, group	yes
Groër et al., 2016	81[b]	46.17 (10.53)	100.0	45.7	NA	27	47.30 (10.70)	100.0	54	45.60 (10.50)	100.0	self-report (quest.)	self-dev.	other (spec.)	SA	ng/mg	paper, table	no
Morris et al., 2017	22[c]	24.71 (3.38)	100.0	18.2	no	7	22.60 (2.30)	100.0	15	25.70 (3.40)	100.0	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	pg/mg	provided, group	no
Reichl et al., 2016a	24	16.27 (1.10)	91.7	NA	no	3	16.55 (1.34)	100.0	21	16.23 (1.09)	90.5	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	pg/mg	provided, raw	yes
Reichl et al., 2016b	25	16.27 (1.30)	96.0	NA	yes, mixed	17	16.56 (1.30)	100.0	8	15.65 (1.14)	87.5	self-report (interview)	CECA	cut-offs	EA, PA, SA, N	pg/mg	provided, raw	yes
Schalinski et al., 2015	39[d]	34.95 (10.74)	100.0	87.2	yes, mixed	17	33.70 (11.70)	100.0	22	35.91 (10.10)	100.0	self-report (interview)	ETI	other (clustering)[e]	EA, PA, SA	pg/mg	provided, group	yes
Steudte et al., 2013	58[f]	39.16 (13.40)	91.4	0	no	10	42.20 (11.22)	100.0	48	38.52 (13.83)	89.6	self-report (quest.)	CTQ	cut-offs	EA, PA, SA, N	pg/mg	provided, group	yes
White et al., 2017	537	9.98 (3.13)	50.7	2.2	NA	245	9.86 (3.24)	46.1	292	10.08 (3.03)	54.5	informant (mixed)	MCS (CPS), MMCI	other (record & spec.)	EA, PA, SA, N	pg/mg	provided, group	no

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder; CM = child maltreatment; n = sample size; quest. = questionnaire; CTQ = Childhood Trauma Questionnaire; self-dev. = self-developed (the authors used a scale developed by themselves); CECA = Childhood Experiences of Care and Abuse; ETI = Early Trauma Inventory; MCS = Maltreatment Classification System; CPS = Child Protective Services; MMCI = Maternal Maltreatment Classification Interview; spec. = specification (authors applied a specific definition of CM); EA = emotional abuse; PA = physical abuse; SA = sexual abuse; N = neglect. [a] Percentage of non-Caucasians refers to total sample (N = 139). [b] Three outliers in hair cortisol were removed, however it is unclear to which group this applied. [c] Comparison between women with abuse/neglect without recent interpersonal violence exposure and non-trauma controls. [d] The data were regrouped, taking into account only the patient group with stress-related disorders. [e] Grouping was based on k-means clustering method based on ETI sum score excluding the general trauma subscale (remark: the sample represents a refugee's sample with all having experienced some type of trauma during their life). [f] The data were regrouped, taking into account only the traumatized control subjects and the non-traumatized control subjects (remark: some in the control sample may have experienced other traumatic events); data provided for a total sample of N = 58 instead of N = 53 as presented in the paper.

3.2.5.1.3. Meta-analysis

Pooling the results of the $k = 9$ comparisons ($n = 978$), we found no significant effect (Hedges'$g = -0.05$, 95% CI [−0.33; 0.24], $p = 0.749$), suggesting no overall difference in HCC in the child maltreatment sample compared to the control sample (the corresponding forest plot is shown in Appendix C Fig. 5.1). There was significant, moderate heterogeneity in the effect size estimates between studies ($Q_8 = 17.14$, $p = 0.029$, $I^2 = 53.3\%$). The between-study heterogeneity was not caused by extreme effect sizes as there was no such outlier study. However, one study exerting a high influence on the overall effect estimate was identified (do Prado et al., 2017). Traditional and contour-enhanced funnel plots are shown in Appendix C Fig. 5.1 and visual inspection of them suggested absence of small-study bias as did the Egger's regression test of funnel plot asymmetry (*intercept* = 0.970, $p = 0.285$; but attention $k < 10$). Excluding the study from do Prado et al. (2017) as part of the sensitivity analysis, heterogeneity decreased from $I^2 = 53.3\%$ to $I^2 = 10.2\%$ ($Q_7 = 7.80$, $p = 0.351$), yielding a small negative effect, which reached significance ($k = 8$, $n = 921$, Hedges'$g = -0.20$, 95% CI [−0.34; −0.06], $p = 0.004$). Despite varying effects of the primary studies, the result of the sensitivity analysis suggests an overall reduction of HCC in the child maltreatment sample compared to the control sample, with the prediction interval (−0.37; −0.03) pointing in the same direction. However, three of the five studies indicating reduced HCC in the child maltreatment compared to the control group had not used a gold-standard diagnostic tool to assess psychopathology and thus matching in this respect is not properly judgeable.

3.2.5.2. 24-hour urinary free cortisol

3.2.5.2.1. Included studies

Eleven studies assessing cortisol in urine were identified through the systematic search. Of these, only $n = 4$ studies including a total of $n = 110$ participants ($n = 108$ with valid cortisol data) could finally be included. Participants were on average 22.17 ($SD = 12.94$) years old and three out of the four studies comprised female participants only ($M = 85.1\%$, $SD = 29.8\%$). The majority of the participants were Caucasian, with the percentage of Non-Caucasians ranging between 12.0 and 42.3% ($M = 27.6\%$, $SD = 15.2\%$). With respect to psychopathology, most of the subjects in the child maltreatment group met the criteria for a mental disorder, while the subjects in the control group were mainly healthy controls ($n = 3$; $n = 1$ did not report on psychopathology). However, in two of the studies included, the authors were able to demonstrate that the presence of the specific mental disorder did not affect the 24-hour UFC data. Three of the four studies focused exclusively on sexual abuse experiences without collecting information about other types of child maltreatment, and two studies recruited participants solely on the basis of self-identification without using any established measurement to assess child maltreatment. All data were extracted from the respective articles. See Table 12 for further details.

Table 12
Summary characteristics of included studies that reported on 24-hour urinary free cortisol (24-hour UFC).

Study	N	Age M(SD)	Sex	Ethn.	Psycho-path.	n	Age M(SD)	Sex	n	Age M(SD)	Sex	Method	Instrument	Grouping	Type	Unit	Source	Data (re)grouped
		Total Sample					**CM Sample**			**Control Sample**		**CM Assessment**				**Cortisol Assessment**	**Data**	
De Bellis et al., 1994	26	11.65 (2.74)	100.0	42.3	yes*, Dysthymia	13	11.20 (2.60)	100.0	13[a]	12.10 (2.90)	100.0	informant (record)	CPS	other (record)	SA	nmol/m^2 x day	paper, table	no
De Bellis et al., 1999	42[b]	10.46 (1.22)	40.5	28.6	yes*, PTSD	18	10.40 (1.40)	44.4	24	10.50 (1.10)	37.5	mixed	CPS, trauma interview	other (spec.)	PA, SA, WV	µg/day (adj. for SES)	paper, table	no
Lemieux & Coe, 1995	17[c]	35.30 (6.30)[d]	100.0	NA	NA	8	NA	100.0	9	NA	100.0	self-report	no instrument used	other (self-ident.)	SA	µg/day (adj. for conc. creatinine & body weight)	paper, table	no
Lemieux et al., 2008	25[e]	31.25 (6.13)	100.0	12.0	yes*, MDD	13	31.30 (6.50)	100.0	12	31.20 (6.00)	100.0	self-report	no instrument used	other (self-ident.)	SA	µg/day	paper, table	no

Note. N = sample size; M = mean; SD = standard deviation; The sex ratio is indicated as percentage of female participants; Ethn. = ethnicity; The ethnicity ratio is indicated as percentage of non-Caucasians; NA = not assessed; Psychopath. = psychopathology, whereby the following definitions have been used: yes = at least some of the participants met diagnostic criteria for a psychiatric disorder, no = none of the participants met diagnostic criteria for any psychiatric disorder, * = groups are not matched with respect to psychopathology; PTSD = Posttraumatic Stress Disorder; MDD = Major Depressive Disorder; CM = child maltreatment; n = sample size; CPS = Child Protective Services; spec. = specification (authors applied a specific definition of CM); self-ident. = self-identification (participants self-identified as victims of CM); SA = sexual abuse; PA = physical abuse; WV = witnessing domestic violence; adj. = adjusted; SES = socioeconomic status; conc. = concentration. [a] 24-hour UFC available for n = 11. [b] Comparison between PTSD and control children. [c] Comparison between women who experienced childhood sexual abuse without PTSD and controls. [d] Age refers to total sample (N = 28) including PTSD group. [e] Comparison between women with a history of childhood sexual abuse without PTSD and controls; one cortisol specimen was lost due to technical error, however unclear to which group this applied.

3.2.5.2.2. Risk of bias assessment

The risk of bias assessment of the primary studies as well as the average risk of bias scores can be found in Appendix B Table B14. The detailed description of the quality items can be found in the Table B7. On average, a total score of 61.5/100.0 was received (SD = 13.5, range: 42.3–73.1; selection of participants: M = 65.6/100.0, SD = 12.0; appropriate measure of 24-hour UFC: M = 50.0/100.0, SD = 18.4; adequate controlling of confounders: M = 66.5/100.0, SD = 20.7). In all n = 4 studies participants were matched with respect to age and gender. In addition, all four articles provide detailed information on how UFC samples were collected, stored and analyzed and all studies give a relatively good overview of participants' medication use. The n = 3 studies that focused on sexual abuse did not provide information about other maltreatment experiences, reducing the quality of the grouping into a child maltreatment and a clear control group without any types of child maltreatment experiences. In only one of the four studies it was ensured that the participants did not experience any ongoing significant life stressors, assessed UFC over at least three days, provided batch analysis information, and none of the studies ensured that the participants in the two groups did not differ with respect to other traumatic experiences in childhood or adulthood.

3.2.5.2.3. Meta-analysis

Pooling the results of the n = 4 studies (n = 108), the aggregate effect size was Hedges'g = 0.07, 95% CI [−0.83; 0.98], p = 0.874, suggesting no overall difference in 24-hour UFC in the child maltreatment sample compared to the control sample (the corresponding forest plot is shown in Appendix C Fig. 5.2). There was significant, high heterogeneity in the effect size estimates (Q_3 = 14.79, p = 0.002, I^2 = 79.7%), indicating high inconsistencies between studies. No outlier study was detected, but the study from Lemieux et al., (2008) had a high influence on the overall result. Traditional and contour-enhanced funnel plots are also shown in Appendix C Fig. 5.2 and visual inspection of them suggested the absence of small-study bias as did the Egger's regression test of funnel plot asymmetry (*intercept* = -6.898, p = 0.428; but attention k < 10). The sensitivity analysis substantially reduced heterogeneity (I^2 = 79.7% to I^2 = 8.5%) and yielded a medium significant overall effect (n = 83, Hedges'g = 0.56, 95% CI [0.11; 1.00], p = 0.014) with participants in the child maltreatment group showing higher 24-hour UFC concentrations compared to the control sample. However, considering the small sample size and the large prediction interval (−2.33; 3.45), it is unclear what the results of future studies will show. In addition, it should be noted that the study excluded in the context of the sensitivity analysis (Lemieux et al., 2008) received the highest average quality score.

4. Discussion

This series of meta-analyses, based on a systematic review of the literature, examined the existing evidence on the association between child maltreatment and cortisol metabolism including various

measures of HPA axis activity. Measures of interest ranged from cortisol assessed in the context of the circadian rhythm (DC) to cortisol assessed in response to awakening (CAR), in response to the perception of a stressor (cortisol stress reactivity) and pharmacological challenges (DST, Dex-CRH test, CRH test), to cumulative measures of cortisol secretion, namely 24-hour UFC and HCC.

4.1. Main findings

Consistent with the findings of two previous meta-analyses (Bernard et al., 2017; Fogelman & Canli, 2018) we did not find overall differences in any of the indices related to cortisol secretion in the context of circadian activity (with the exception of evening cortisol) as well as in response to awakening (CAR) when comparing individuals with child maltreatment to those without corresponding experiences. The finding of slightly increased evening cortisol in individuals exposed to child maltreatment was mainly driven by a few studies in which the child maltreatment group also included individuals with loss experiences and thus should be interpreted with caution in the context of this meta-analysis. Individuals with a history of child maltreatment, however, appear to show a blunted cortisol stress response. Though not yet evident before being introduced to a corresponding stressor (baseline cortisol), blunting was seen in indices reflecting total cortisol production (peak, recovery cortisol) as well as in indices expressing changes in cortisol over time (delta, AUC_i cortisol) following the perception of a stressor. These findings are consistent with the results of a previous meta-analysis examining the effect of ELA on cortisol response to social stress (Bunea et al., 2017), albeit with somewhat smaller effects observed in our meta-analysis. Interestingly, this blunting was not observed in studies where CRH injections (Dex-CRH test) were used to initiate the secretion of cortisol. However, the number of studies on the Dex-CRH test was much smaller compared to the number of studies assessing cortisol in response to a stressor. In addition, no difference in the negative feedback mechanism of the HPA axis (at least at the level of the pituitary gland), measured by oral administration of dexamethasone, was found between the two groups. Finally, with respect to the few studies reporting on cumulative measures of cortisol secretion including 24-hour UFC and HCC, no differences were observed in both of these measures between those exposed to child maltreatment and those without corresponding adversity. Respective sensitivity analyses excluding influential studies, performed within the context of these two outcome indices, on the other hand, suggest increased 24-hour UFC and slightly reduced HCC in maltreated individuals. However, especially the finding of increased 24-hour UFC should be interpreted with caution, since the overall sample size was small and the large prediction interval of the pooled effect estimate suggests a high degree of uncertainty regarding the results of upcoming studies (for a summary overview about all main findings see Table 13).

Table 13

Summary table of main findings from meta-analyses, meta-regression, and subgroup analyses (mixed/fixed-effects models) for the various HPA axis activity measures and related outcome indices.

	k	N	Meta-analyses Random-effects models	Between-study heterogeneity (I^2)	Moderator analyses Significant moderators (meta-regression)	Significant comparisons (subgroup analyses)
DC	26	5248				
Morning cortisol	26	5212	no overall significant effect	low-moderate (29.1%)	tendency for higher morning cortisol in older-aged samples; tendency for lower morning cortisol with higher study quality (in terms of appropriate measure of DC)	reduced morning cortisol in studies (1) that used informant reports, (2) that applied CPS records or cut-offs, (3) where original data were extracted
Evening cortisol	26	5188	small overall positive effect°	low (2.0%)	-	larger positive effect size estimates in studies (1) focusing on other types of ELA; (2) including original data
DSL cortisol	17	3390	no overall significant effect	low (23.5%)	-	-
CAR	27	3545				
Awakening cortisol	24	3342	no overall significant effect	low (17.3%)	-	reduced awakening cortisol in studies where original data were extracted
Peak cortisol	22	3215	no overall significant effect	moderate-high (59.8%)	-	-
60 min post awakening cortisol	14	2276	no overall significant effect	low-moderate (41.6%)	-	-
Delta cortisol	18	2536	no overall significant effect	low-moderate (41.8%)	tendency for lower delta cortisol in studies with higher proportion of females	-
AUC$_g$ cortisol	15	2327	no overall significant effect	moderate-high (73.1%)	tendency for lower AUC$_g$ cortisol with higher study quality (in terms of appropriate measure of confounders)	reduced AUC$_g$ cortisol where original data were extracted
AUC$_i$ cortisol	9	1654	no overall significant effect	moderate-high (70.3%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
Cortisol stress reactivity	39	4284				
Baseline cortisol	35	3895	no overall significant effect	moderate-high (69.7%)	no meta-regression performed	no subgroup analyses performed
Peak cortisol	35	3867	small overall negative effect*	high (78.3%)	-	-
Recovery cortisol	29	3407	small overall negative effect*	moderate-high (73.4%)	tendency for lower recovery cortisol in studies with higher proportion of females	-
Delta cortisol	24	2678	small overall negative effect*	low-moderate (46.1%)	tendency for lower delta cortisol in studies (1) with higher proportion of females; (2) with a higher proportion of participants fulfilling diagnostic criteria for a mental disorder	stronger negative effect estimates in studies (1) that included clinical samples, (2) involved participants with other types of ELA, (3) that observed a cortisol response in only one of the two comparison groups
AUC$_g$ cortisol	20	1614	no overall significant effect	moderate-high (62.5%)	-	-
AUC$_i$ cortisol	23	1992	small overall negative effect*	low-moderate (31.4%)	tendency for higher AUC$_i$ cortisol in studies with higher study quality (in terms of selection of participants)	stronger negative effect estimates in studies that observed a cortisol response in only one of the two comparison groups
DST	17	2222				
Pre-DST cortisol	16	2201	no overall significant effect	low-moderate (40.5%)	no meta-regression performed	no subgroup analyses performed
Post-DST cortisol	17	2214	no overall significant effect	low-moderate (44.1%)	tendency for lower post-DST cortisol in studies with higher proportion of females	increased post-DST cortisol in studies focusing on other types of ELA
Delta	9	1888	no overall significant effect	low-moderate (34.0%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)

Table 13

Summary table of main findings from meta-analyses, meta-regression, and subgroup analyses (mixed/fixed-effects models) for the various HPA axis activity measures and related outcome indices.

	k	N	Meta-analyses		Moderator analyses	
			Random-effects models	Between-study heterogeneity (I^2)	Significant moderators (meta-regression)	Significant comparisons (subgroup analyses)
Dex-CRH test	10	561				
Pre-CRH cortisol	4	320	no overall significant effect	low (0.0%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
Peak cortisol	6	369	no overall significant effect	moderate-high (68.3%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
Delta cortisol	6	257	no overall significant effect	moderate-high (50.3%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
AUC_g cortisol	9	329	no overall significant effect	moderate-high (54.8%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
AUC_i cortisol	6	163	no overall significant effect	moderate-high (63.3%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
HCC	9	978	no overall significant effect	moderate-high (53.3%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)
24-hour UFC	4	108	no overall significant effect	high (79.7%)	$k < 10$ (no meta-regression performed)	$k < 10$ (no subgroup analyses performed)

Note. DC = diurnal cortisol; DSL = diurnal slope cortisol; CAR = cortisol awakening response; DST = dexamethasone suppression test; Dex-CRH test = combined dexamethasone-corticotropin releasing hormone test; HCC = hair cortisol concentrations; 24-hour UFC = 24-hour urinary free cortisol; CM = child maltreatment; AUC_g = area under the curve with respect to ground; AUC_i = area under the curve with respect to increase; ° Positive effect = overall increased cortisol levels in child maltreatment group compared to their respective control group. * Negative effect = overall reduced cortisol levels in child maltreatment group compared to their respective control group. - No significant moderators or/and subgroup comparisons were identified.

4.2. Between-study heterogeneity and the influence of moderators

Although no overall differences in cortisol secretion were found for the majority of the HPA axis activity measures except for cortisol assessed in response to a stressor across studies, we generally observed a significant degree of variability in the effect estimates between studies (especially for indices reflecting cortisol secretion in the context of awakening, after a stressor and following the Dex-CRH test), suggesting the likely influence of additional variables in moderating the effect of child maltreatment on cortisol regulation. Before discussing some of the moderators that systematically accounted for between-study heterogeneity, holding true for various of the HPA axis activity measures, it should be kept in mind that the majority of studies were conducted with predominantly young, female adults who belonged to an ethnic majority group and in whom child maltreatment experiences were assessed mainly through self-reports. In addition, a considerable number of studies did not report on psychopathology, and studies involving clinical samples were fairly heterogeneous in terms of the predominant mental disorder (e.g., MDD versus posttraumatic stress disorder (PTSD)). Accordingly, our ability to find important moderators or relevant subgroup differences might have been limited.

4.2.1. Influence of participant related characteristics

One of the moderators that explained some of the between-study heterogeneity in effect sizes (in line with findings from Bunea et al., 2017; and Zorn et al., 2017) was the proportion of females in the respective sample, with a higher proportion being associated with a stronger blunting of cortisol secretion (CAR, cortisol stress reactivity, and DST). Corresponding sex differences, particularly with respect to stress reactivity, have been repeatedly reported, with men showing higher cortisol levels to psychosocial stress than women (J. J. W. Liu et al., 2017). Factors that influence corticosteroid binding globulin (CBG) levels and thus the level of free cortisol appear to account for some of these gender effects including the use of oral contraceptives and the production of sex steroids throughout the menstrual cycle (e.g., Foley & Kirschbaum, 2010). Both the intake of oral contraceptives and the assessment of the menstrual cycle were not adequately evaluated in many of the studies included and therefore matching of the two groups in these respects was not properly controlled. Apart from the proportion of women in the respective sample, there was little evidence that the remaining participant related characteristics such as age, ethnicity, and participant diagnosis accounted for variability in the effect estimates among primary studies. Interestingly, even though psychopathology did not account for heterogeneity in the child maltreatment cortisol relationship (at least for the majority of outcome indices), a tendency for stronger blunting in clinical samples compared to healthy controls was observed for indices related to cortisol stress reactivity. Nevertheless, an attenuation of the cortisol stress response was observed in participants with child maltreatment experiences that at the time of measurement did not report a mental disorder, suggesting that alterations in HPA axis activity may be present prior to the development of mental health issues or independent of psychopathology.

4.2.2. Influence of trauma related information

Another fairly consistent moderator accounting for some of the between-study heterogeneity (DC and CAR, tendency for cortisol stress reactivity) was whether or not data were (re)grouped for the purpose of this meta-analysis, with (re)grouped data showing a tendency towards smaller effects. In some of the studies that provided (re)grouped data, grouping of participants into a child maltreatment and a control group was based on relatively low severity thresholds (particularly for cortisol assessed in the context of awakening and circadian activity), which might account for this finding. Indeed, and in agreement with the observed dose-dependent relationship between child maltreatment and health impairments (e.g., Clemens et al., 2018; Norman et al., 2012), the severity of child maltreatment experiences, though difficult to assess (Jackson et al., 2019), might actually be of particular importance in explaining variability between the association of child maltreatment and HPA axis functioning. Interestingly, several studies, especially those which assessed cortisol in response to a stressor, found a stronger blunting in cortisol secretion following the perception of a stressor with an increase in the severity of child maltreatment (Lovallo et al., 2019; Ouellet-Morin et al., 2018; Trickett et al., 2014; Voellmin et al., 2015). Unfortunately, our group comparison approach did not allow us to investigate this association systematically. In line with the difficulties in defining child maltreatment and the possibility to rely on various assessment modalities (Cicchetti & Toth, 2005; Manly, 2005), studies generally differed widely in their child maltreatment assessment and grouping approaches. For instance, studies that relied on established self-reports such as the CTQ or the Childhood Experience of Care and Abuse interview (CECA) grouped their participants based on validated cut-off scores, while other studies applied specific definitions (e.g., Heim et al., 2000: "repeated abuse, once a month or more for at least 1 year"), sometimes based on self-developed assessment tools (e.g., Groër et al., 2016; Martinson et al., 2016; Smeets et al., 2007) and still others relied on the presence or absence of a specific record, such as a CPS record (e.g., Bernard et al., 2010; Cicchetti et al., 2010; Hibel et al., 2019). However, neither the assessment (self-report, informant report, mixed) nor the grouping method (cut-offs, other, record) explained variance in the effect estimates of any of the HPA axis activity outcome indices, with the exception of larger effect sizes found in studies focusing on informant reports compared to self-reports for waking/morning cortisol (which is consistent with findings from Bernard et al., 2017). Since there were far fewer studies using informant reports as opposed to self-reports (a pattern also found among studies on the prevalence of child maltreatment; Stoltenborgh et al., 2015), comparison between these approaches might have been inappropriate and the chances of detecting differences accordingly low. Importantly, some of the included studies failed to sufficiently ensure that control participants were not subjected to any type of child maltreatment. The studies that performed poorly in terms of ensuring maltreatment did not take place in the control group were those that relied on specific records, such as CPS records, and studies focusing on one particular type of child maltreatment. In corresponding studies – besides the absence of a record or the corresponding type of maltreatment – no other measures were applied to ensure that control participants had not experienced any child maltreatment. This may have

influenced our results, since child maltreatment experiences are rather common in the general population, as demonstrated by epidemiological studies (Witt et al., 2017). Neither the role of age at maltreatment onset nor the chronicity of the maltreatment experiences on HPA axis activity could be investigated, as very few studies applied measures that assessed these two factors in the first place – a finding in line with a recent review summarizing research on the operationalization of child maltreatment over the last 10 years (Jackson et al., 2019).

4.2.3. Influence of cortisol related information

In our meta-analysis, neither sample type (blood, saliva), type of stressor (social-evaluative, other), slope type (wake-to-bed, other), whether cortisol was assessed in reference to awakening or not, nor dose of dexamethasone (0.5 mg, 1.0 mg) significantly explained variability in the various effect estimates. The only moderator related to the assessment of cortisol that explained between-study heterogeneity was whether a cortisol response was observed in both, in only one, or in none of the groups following the perception of a stressor, with stronger effects found in those studies that observed a cortisol response in just one of the two groups. This finding might be attributed to the fact that six out of the seven comparisons that observed a response only in one of the two groups, reported an increase in cortisol in the control group only. Overall, there was no evidence to suggest that the two components of cortisol secretion – total cortisol production and change in cortisol over time – which appear to capture different aspects of HPA axis activity (Khoury et al., 2015), are affected differently by child maltreatment. A blunting in cortisol secretion following the perception of a stressor was found in indices reflecting both total and change in cortisol over time. However, as expected, studies generally differed widely with respect to the index or indices reported (e.g., much more studies reported on peak cortisol compared to AUC_i cortisol), making comparisons between the different outcome indices difficult. Along with this, depending on the studies included, different moderators emerged, which in turn complicated the interpretation of the corresponding findings.

4.2.4. Influence of several components of methodological quality

Finally, we did not observe a consistent association between study quality as assessed by our self-developed quality assessment tool (which was based on existing recommendations and guidelines) and reported effect sizes. Although, at least for some outcome indices, the quality of the individual studies seemed to explain some of the between-study heterogeneity. For instance, a tendency towards smaller negative differences in cortisol secretion following the perception of a stressor was observed in studies with a higher study quality and thus a lower risk of bias. Importantly, in studies that (re)grouped participants for the purpose of this meta-analysis – although the majority of these studies used an established instrument (an established source of information) to assess child maltreatment experiences – by (re)grouping their study participants, several other aspects of methodological quality could no longer be assessed. Therefore, our conservative approach of not awarding any points in a given case

may have induced biases. In addition, two studies were able to achieve the same average total score, but scored in completely different quality items. Since we were not able to value the importance of the various quality items, our ability to find associations with the different effect estimates might thus have been limited. Nevertheless, it should be mentioned that several quality-related aspects were generally well implemented in the majority of the studies (holding true for all HPA axis activity measures), whereas others were insufficiently addressed and controlled in most of the included publications. With respect to the selection of participants, for instance, the two comparison groups were generally matched in terms of sex and age, and most studies used an established measurement to assess child maltreatment. While exposure and the control groups were generally balanced in terms of psychopathology in those studies that reported on psychopathology, a substantial number of studies did not evaluate the presence of mental disorders at all, and therefore information about matching in this respect was unavailable for several studies. This is particularly surprising as, on the one hand, child maltreatment experiences are much more common among individuals with a mental disorder and, on the other hand, psychopathology itself has been repeatedly associated with changes in various HPA axis activity measures, with sometimes opposing findings for different mental disorders (e.g., Adam et al., 2017; Chida & Steptoe, 2009; Leistner & Menke, 2018; Stalder et al., 2017; Zorn et al., 2017). Accordingly, in these studies, the presence of a possible confounding effect of psychopathology cannot be ruled out. Interestingly, a recent study examining the effects of comorbidity and adversity on HPA axis functioning in depressed patients was able to show that rather than the diagnostic groups per se, the timing of adversity appears to influence HPA axis functioning in adulthood, putting the importance of psychopathology and especially the role of diagnostic groups somewhat into perspective. In this study, an attenuated HPA axis stress response was only found in those patients with comorbid PTSD from childhood. By contrast, no alterations were seen in those with depression only, or those with depression with comorbid PTSD resulting from adult trauma (Mayer et al., 2020). Thus, these results, consistent with the findings of the present meta-analysis and those of the meta-analysis by Bunea et al. (2017), suggest that adverse experiences during childhood indeed appear to be of particular importance in influencing the HPA axis stress response in adulthood.

Related to participant selection, and as already indicated in the context of the assessment of child maltreatment, several studies inadequately ensured that none of the control participants were exposed to any type of child maltreatment, and only a handful of studies used two different sources to evaluate the presence of child maltreatment. Regarding appropriate assessment of cortisol in the context of the corresponding HPA axis activity measure, most studies reported on clear sampling (prohibitions) and collection instructions (i.e., how they collected, stored, and analyzed samples), provided details on their test protocol, and generally reported on missing and/or outlier data. By contrast, very few studies provided information on whether sampling was rescheduled if participants were sick, on batch analysis or ensured that participants were not under any current stress at the time of testing (sampling), factors known to influence cortisol results (e.g., Adam & Kumari, 2009). Furthermore, only a few studies that

assessed cortisol in the context of daily activity (DC and CAR) ensured that exposure and control groups did not differ in the time of awakening as well as sampling time adherence. This is particularly surprising as the validity of the CAR measurement critically depends on the sampling schedule, with inaccurate sampling strongly biasing CAR (including morning/waking) estimates (Stalder et al., 2016). Moreover, a study investigating the variability and reliability of DC indicated that a 10-day sampling procedure would be required to obtain stable estimates of between-person differences in DSL cortisol (Segerstrom et al., 2014). Similarly, up to six assessment days might be necessary to obtain reliable CAR trait measures (Hellhammer et al., 2007). However, only a few studies included in this systematic review assessed cortisol over more than two days. Lastly, a substantial number of studies failed to adequately assess and thus control for important confounding variables. As mentioned in the context of sex differences, the matching of participants in terms of oral contraceptive use and menstrual cycle timing was insufficient in many studies. Other confounding variables which were generally poorly assessed and controlled for were: smoking, medication intake with known CNS effects, and clear statements about whether pregnant women and participants working night shifts were excluded, factors also known to account for variability in cortisol results (e.g., Kudielka et al., 2012; Locatelli et al., 2009; Stalder et al., 2016; Zänkert et al., 2019). Finally, only a few of the included studies took measures to ensure that participants from the control group were not subjected to any type of ELA other than child maltreatment. According to the National Scientific Council on the Developing Child (e.g., Shonkoff et al., 2012), three types of stressors can be differentiated according to their potential to cause enduring physiological disruptions. These include: positive, tolerable and toxic stressors. "Tolerable" stress experiences include those that present a great magnitude of adversity or threat, such as the death of a family member, or a serious illness or injury. However, when buffered by a supportive adult, the risk that corresponding circumstances will cause long-term consequences for health are suggested to be greatly reduced. In contrast, "toxic" stress experiences include those that are experienced in the absence of a supportive adult relationship and may cause strong, frequent, or prolonged activation of the body's stress response system. Since child maltreatment experiences typically occur in the absence of the buffering protection of stable adult support, these experiences are suggested to be particularly toxic and thus show a great potential to induce long-lasting biological changes. In line with this, child maltreatment experiences do show high associations with later disease risk (e.g., Dube et al., 2001). Nevertheless, ELA and especially the experience of multiple adverse childhood experiences have been related to various health conditions later in life as well (e.g., Clark et al., 2010; Danese et al., 2009; Hughes et al., 2017). In addition, the meta-analysis conducted by Bunea et al. (2017), although slightly smaller effects were observed compared to studies focusing on child maltreatment only, showed that ELA was similarly associated with a blunted cortisol stress response. Thus, considering that experiencing adversity during childhood is rather the rule than the exception (Merrick et al., 2019), for the vast majority of studies, it cannot be ruled out that control participants have experienced other forms of ELA, which in turn may have influenced the results of this systematic review. Considering these methodological shortcomings,

including the limitations associated with this series of meta-analyses, our ability to establish a consistent link between the experience of child maltreatment and HPA axis functioning may indeed be compromised. Finally, it should be noted that we decided to focus on peer-reviewed papers only to allow for a transparent and replicable search of the literature. Appropriate statistical methods (e.g., funnel plots and Egger's regression tests) were applied to evaluate and control for publication bias. Nevertheless, the inclusion of grey literature could have counteracted the problem of including data that are not fully representative of the evidence as a whole.

4.3. Interpretation of the findings in the context of developmental programming of the HPA axis

Nevertheless, taking the above constraints into account, we found evidence of an altered cortisol stress response in individuals exposed to child maltreatment as compared to control participants. The null findings with regard to the other HPA axis activity measures (keeping in mind the various methodological shortcomings as one potential explanation) could also indicate that alterations causing aberrant cortisol secretion are less apparent at the level of the pituitary or adrenal glands, but are rather expressed in brain regions involved in stress processing (e.g., limbic brain areas including the hippocampus, the amygdala, and the prefrontal cortex) and in the connectivity of these brain regions to the hypothalamus (Herman et al., 2003). In line with this idea, a review summarizing findings on the neuronal control of chronic stress adaptation, suggests that changes in HPA axis regulation following severe stress exposure might be traced back to long-term changes in the limbic input to neurons controlling stress responsiveness (Herman, 2013). Additionally, it is well known that limbic brain areas including the hippocampus, the amygdala and the prefrontal cortex widely express GRs, and therefore it is not surprising that acute and chronic stress appear to significantly affect synaptic physiology and connectivity in these regions (e.g., Myers et al., 2014). In contrast, structures involved primarily in the regulation of cortisol release in the context of circadian signals or following awakening (i.e., the suprachiasmatic nucleus, Spiga et al., 2014) might be less affected. Thus, corresponding alterations in HPA axis activity measures that are not primarily activated by stress perception (e.g., DC, CAR, HCC, UFC) might only become apparent when cortisol is measured during periods of high life stress – when stress processing actually becomes relevant for these activity measures as well. Interestingly, findings of a longitudinal study evaluating stress exposure across the lifespan on HPA axis functioning at age 37 provide some support for this assumption (Young et al., 2021). In this study, in accordance with the theory of developmental programming of biological systems – the *biological embedding model* (e.g., Heim et al., 2019; Heindel et al., 2015) – individuals with adversities experienced during early or middle childhood showed a blunted cortisol response to a modified version of the TSST. This blunting of cortisol secretion following the perception of this stressor was independent of whether or not participants were experiencing current life stress. Additionally, similar cortisol stress response patterns were seen in participants with high and low cumulative stress, if these cumulative stress exposures did not involve

early life stress (Young et al., 2021). These findings thus support the notion that when attempting to explain differences in the cortisol stress reactivity, it is not so much stress in general, but early childhood stress in particular that seems to be critical (supporting the biological embedding model). In contrast, flatter DSL profiles were only observed in those individuals who experienced ELA and were currently subjected to high levels of stress (Young et al., 2019). While these DSL results remain consistent with the biological embedding model, they also provide support for the assumption that alterations causing aberrant cortisol secretion likely relate to circuits of the brain involved in the processing of stress, and accordingly, meaningful differences in HPA axis activity measures that in terms of their activation do not per se require the experience of stress, are only to be expected when stress processing actually is involved (i.e., under high current life stress; see also Kuhlman et al., 2016).

4.4. Conclusion and future directions

Taking into account all the findings and difficulties in the context of this series of meta-analyses, including: the unbalanced recruitment of study participants in the primary studies (e.g., predominantly young, female adults who belonged to an ethnic majority group and in whom child maltreatment experiences were assessed mainly through self-reports), the considerable number of studies that did not report on psychopathology, the limitations related to the assessment of child maltreatment (i.e., the use of various definitions and our inability to investigate the role of age at onset and the chronicity of the maltreatment experiences), and the various constraints related to the assessment of the various HPA axis activity measures (i.e., the inadequate control of state factors and confounding variables and limitations related to the reliability of the cortisol outcome measures), it becomes apparent that, on the one hand, a comprehensive conclusion about the functioning of the HPA axis in individuals who have been exposed to child maltreatment cannot be drawn at this time point, and on the other hand, our ability to find important moderators or relevant subgroup differences might have been limited. Nevertheless, child maltreatment appears to be associated with a blunted rather than an exaggerated activity when considering cortisol secretion following the perception of a stressor (while a tendency was also shown for HCC), and several moderators including the proportion of females in the sample, psychopathology, and the study quality (to name a few) have been identified to account for some of the observed between-study heterogeneity. Considering that cortisol, when secreted in excess (e.g., during prolonged stress exposure like it is the case for child maltreatment), can have a variety of deleterious effects (Feelders et al., 2012), particularly in the brain (Sapolsky, 1999; Sapolsky et al., 2000), a corresponding downregulation may indeed serve an adaptive function protecting the body from these various adverse effects, an idea that has been subsumed under the so-called "attenuation hypothesis" (e.g., Kaess et al., 2018; Trickett et al., 2010). While probably adaptive in the first place, there is growing evidence linking not only an exaggerated but increasingly also a blunted cortisol stress response to various adverse behavioral and health outcomes (D. Carroll et al., 2017; de Rooij, 2013; Turner et al., 2020). Cortisol has various important anti-inflammatory and immunosuppressive functions (Sapolsky et al., 2000) and

several studies have shown that an attenuated cortisol stress reactivity (irrespective of cause) is associated with a stronger proinflammatory immune response (Buske-Kirschbaum et al., 2010; Janusek et al., 2017; Schwaiger et al., 2016). Interestingly, a growing number of studies suggest that inflammatory processes may precede the onset of, or be involved in the development of various types of mental disorders (Kivimäki et al., 2014; Melhem et al., 2017; Slavich et al., 2020). Accordingly, future studies should not only pay more attention to the potential moderating influence of current life stress, especially if interested in HPA axis activity measures that are not primarily regulated by stress perception alone, but, if interested in the consequences arising from an altered HPA axis activity, studies specifically should examine how an alerted cortisol secretion might be related to dysfunctions in other biological systems. In addition, by investigating the potentially moderating role of genes and epigenetic changes, knowledge of which individuals are most susceptible to the long-term consequences of child maltreatment (or ELA in general) may be further enhanced (e.g., Heim et al., 2019). However, reliable and reproducible results are only to be obtained if future studies more consistently rely on measurement tools that capture the assessment of various types of ELA, their onset, their chronicity and, in particular, these tools should permit the assessment of the perceived severity of the corresponding experiences. Related to a growing number of studies showing different neurobiological consequences of deprivation and threat experiences (e.g., Colich et al., 2020), a more fine-grained analysis of child maltreatment or adversity in general could further improve our understanding of the functioning of the HPA axis in individuals exposed to corresponding experiences. However, in order to obtain reliable and valid HPA axis activity measures, future studies must focus more consistently on cortisol assessment guidelines, which provide important information regarding various state and confounding variables, as well as information on the reliability of the corresponding outcome activity measures (e.g., Adam & Kumari, 2009; Allen et al., 2017; Foley & Kirschbaum, 2010; Kudielka et al., 2012; Stalder et al., 2016; Stalder & Kirschbaum, 2012; Zänkert et al., 2019).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A-E. Supplementary material

Supplementary material related to this article can be found in the online version, at doi: https://doi.org/10.1016/j.yfrne.2022.100987.

2.2. Manuscript

Pituitary volume in adolescents with non-suicidal self-injury: Preliminary evidence for alterations in pituitary maturation

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Highlights

- Non-suicidal self-injury (NSSI) represents a serious problem among adolescents.
- Alterations in hypothalamic-pituitary-adrenal (HPA) axis functioning are suggested.
- Pituitary gland volume (PGV) as alternative way of assessing HPA axis function.
- The present study found evidence for an age-dependent group effect.
- Linear increase of PGV with age in healthy controls, but not in NSSI patients.

Abstract

Background

Non-suicidal self-injury (NSSI), typically observed in the context of various mental disorders, represents a highly prevalent and serious problem among adolescents. Based on studies linking NSSI with stress, alterations in hypothalamic-pituitary-adrenal (HPA) axis functioning have been suggested to contribute to the development and maintenance of this behavior. While research has mainly focused on cortisol – the main hormonal output of this system – to our knowledge, no study has examined pituitary gland volume (PGV) – an alternative approach of assessing HPA axis functionality that is less state-dependent – in adolescents engaging in NSSI.

Methods

Magnetic resonance imaging (MRI) was performed among $n = 35$ adolescents (aged 12–17 years) fulfilling the diagnostic criteria for NSSI disorder according to DSM-5 and $n = 31$ age-matched healthy controls; PGV was obtained by manual tracing. To test for group differences – our primary aim – a hierarchical linear regression model was computed, controlling for several potential confounding variables. Since adolescence reflects a time period for significant brain development – including changes in PGV – we also tested for an age-dependent group effect. In a second step, we aimed to investigate whether differences in PGV are accounted for by the experience of childhood adversity or psychopathology. Finally, following an exploratory approach, the dimensional association between PGV and various clinical characteristics (e.g., frequency of NSSI) were explored.

Results

No evidence was found for overall volumetric differences between healthy control participants and adolescents engaging in NSSI ($p > 0.05$) – recognizing that small effect size differences could not be detected in the present study – but group membership significantly interacted with age in predicting PGV ($p = 0.02$). Particularly, while PGV increased linearly with age in healthy controls ($B = 61.39$, $SE = 14.94$, $p < 0.01$), no corresponding association was found in NSSI patients ($B = 16.83$, $SE = 12.20$, $p = 0.17$). PGV was not related to adverse experiences during childhood and none of the clinical characteristics (e.g., frequency of NSSI) significantly correlated with PGV ($p > 0.05$).

Conclusion

These results provide preliminary evidence for alterations in pituitary maturation in adolescents engaging in NSSI, although replication in longitudinal studies with larger samples is warranted.

Keywords: *Non-suicidal self-injury; Adolescents; Pituitary gland volume; Magnetic Resonance Imaging (MRI); Manual tracing*

1. Introduction

Non-suicidal self-injury (NSSI) is defined as self-inflicted damage to body tissue without suicidal intent (Nock, 2010). NSSI typically first manifests during adolescence (Plener et al., 2015) and is observed in the context of various mental disorders (Ghinea et al., 2020). While a substantial number of adolescents engage in NSSI at least once (17.2%; Swannell et al., 2014), rates of youths meeting the diagnostic criteria for NSSI disorder (DSM-5; American Psychiatric Association, 2013) and thus presenting with repetitive NSSI behavior are still remarkably high in the general population (6.7%; Zetterqvist et al., 2013). Even more, repetitive NSSI is highly prevalent in the clinical context, with rates of up to 60% observed among adolescent inpatient samples (e.g., Kaess et al., 2013). NSSI seems particularly relevant in the context of borderline personality disorder (BPD), with data from longitudinal studies suggesting that this behavior predicts later BPD features (Ghinea et al., 2019). Critically, a history of NSSI represents an important risk factor for suicidality (e.g., Koenig, Brunner, et al., 2017), highlighting the importance of studying NSSI and its underlying biological mechanisms.

A growing number of findings suggest an important role of stress experiences, including the experience of early life adversity, in the etiology of NSSI (R. T. Liu et al., 2018; A. B. Miller et al., 2019). The experience of stress, in turn, is closely associated with hypothalamic-pituitary-adrenal (HPA) axis activity, one of the body's stress response systems (Nicolaides et al., 2015). As heightened stress typically precedes acts of NSSI and considering that the HPA axis represents one biological system centrally involved in the human stress response, it has been suggested that changes in the functioning of this system may constitute one biological mechanism that contributes to the occurrence and maintenance of NSSI behavior (e.g., Kaess et al., 2021). Providing some support for this assumption, studies have found a blunted cortisol response to psychosocial stress in adolescents engaging in NSSI compared to healthy controls or depressed patients without such behavior (Kaess et al., 2012; Klimes-Dougan et al., 2019). In fact, it has been suggested that NSSI may actually help to compensate for the observed inappropriate cortisol response to psychosocial stressors, as painful stimulation itself represents a powerful trigger for HPA axis activity in adolescents with NSSI (Koenig, Rinnewitz, et al., 2017). There is relatively strong evidence linking a corresponding pattern of HPA axis dysregulation to chronic stress experiences (G. E. Miller et al., 2007), particularly those experiences early in life (Bunea et al., 2017), which, as noted before, represent an important risk factor for the development of NSSI. Accordingly, it is currently unclear whether a blunted cortisol stress response, as it has been observed among adolescents engaging in NSSI, actually represents the result of chronic stress experiences and thus precedes the onset of NSSI, or rather reflects a consequence thereof. When secreted in excess – e.g., under prolonged stress exposure – cortisol can have deleterious effects on the body and the brain (Feelders et al., 2012). Thus, a corresponding downregulation may indeed serve an adaptive function that protects the body from these negative effects, an idea subsumed under the so-called "attenuation hypothesis" (e.g., Kaess et al., 2018). Although likely adaptive at first, there is growing evidence linking a blunted cortisol stress response not only to NSSI, but also to several other adverse behavioral and

health outcomes (Turner et al., 2020). In summary, regardless of the actual underlying cause (e.g., chronic stress or/and genetic predisposition), changes in the activity of the HPA axis may reflect one pathophysiological pathway that contributes to the occurrence and maintenance of NSSI behavior.

While biochemical characterization remains the gold-standard for assessing HPA axis functionality, assessment of cortisol is heavily influenced by state factors (e.g., menstrual cycle, illness) and thus subjected to high inter- and intra-individual variability (Zänkert et al., 2019). Moreover, assessing cortisol in blood or saliva does not reveal information about the origin of the observed dysfunction – i.e., at what level along the axis changes may occur that could explain altered HPA axis output. Assessment of pituitary gland volume (PGV) by structural magnetic resonance imaging (MRI) can be considered an alternative approach of assessing HPA axis function that is less state-dependent and reflects more of a proximal trait. Nevertheless, the pituitary gland can undergo volumetric changes in response to functional demands, including for instance the onset of puberty (e.g., Wong et al., 2014). There are now several longitudinal studies that found greater baseline PGV and accelerated PGV growth in adolescent participants with early life adversity, which has been interpreted by the authors as reflecting a state of HPA axis hyperactivity (Farrow et al., 2020; Ganella et al., 2015). Another longitudinal study was able to show that increased PGV in early-adolescence predicted lower cortisol secretion (cortisol awakening response) in mid-adolescence, but only in those participants with relatively high levels of childhood maltreatment, supporting the previously mentioned "attenuation-hypothesis" (Kaess et al., 2018). Finally, structural changes of PGV have been found in various stress-related mental disorders, although a lot of inconsistencies exist between findings (Anastassiadis et al., 2019). To our knowledge, however, no previous study has investigated PGV in an adolescent patient sample fulfilling diagnostic criteria for DSM-5 NSSI disorder.

Therefore, the first aim of the present study was to test for differences in PGV between adolescents engaging in NSSI and healthy controls, while controlling for several potential confounding variables. Based on the literature linking the experience of prolonged stress to NSSI and HPA axis hyperactivity (at least before a corresponding attenuation may follow over time), as well as findings relating stress, particularly chronic stress, to PGV enlargement, we hypothesized that patients engaging in NSSI show lager PGV compared to healthy control participants. In addition, considering the finding that chronic stress has been related not only to greater PGV assessed at a particular point in time but also to accelerated growth of the PGV over time, and considering that the PGV still increases during adolescence before peaking in size in mid-20s to early 30s and declining thereafter (e.g., Anastassiadis et al., 2019), as part of an exploratory approach, we also tested for an age-dependent group effect. Thus, accordingly, adolescents engaging in NSSI may show lager PGVs at younger ages compared to their healthy control participants. Secondly, based on the literature relating adverse childhood experiences – which typically reflect the experience of chronic stress – to greater baseline PGV or accelerated PGV growth, we aimed to investigate whether differences in PGV would be better accounted for by the experience of childhood adversity or psychopathology (i.e., NSSI). Finally, the third aim of this study,

following an exploratory approach, was to explore dimensional associations between PGV and clinical characteristics of NSSI frequency, suicidality and the number of BPD criteria fulfilled in patients with NSSI.

2. Methods

2.1. Participants

Adolescents between 12 and 17 years who had engaged in NSSI on at least 5 days during the last 12 months were consecutively recruited from the specialized outpatient clinic for adolescent risk-taking and self-harm behavior (AtR!Sk; *"Ambulanz für Risikoverhalten & Selbstschädigung"*) and from inpatient units at the Clinic of Child and Adolescent Psychiatry, University Hospital Heidelberg, Germany. Healthy participants who had never engaged in NSSI and who had neither received a psychiatric diagnosis in their lifetime nor undergone psychiatric treatment were recruited via public advertisement. Adolescents with acute psychotic symptoms, acute suicidality, poor knowledge of the German language, adolescents who were taking glucocorticoid-containing medications, reporting any neurological or endocrinological disorder, or those with a contraindication to MRI (e.g., claustrophobic, pregnant, mental implants, history of brain injury) were not included. The study was approved by the institutional ethics committee of the Medical Faculty, University of Heidelberg and was performed in accordance with the Declaration of Helsinki. All participants and their parents/caregivers gave informed and written consent. For further details on study procedure see Ando et al. (2018) and Reichl et al. (2016; as well as the Supplementary Material).

2.2. Psychological measures

Prior to the MRI scanning session, NSSI and healthy control participants underwent structured clinical assessments by specifically trained clinicians at the University Hospital Heidelberg. During this clinical session, socio-demographic and lifestyle-related information (e.g., age, sex, body mass index (BMI), medication intake, smoking behavior and substance abuse in the past three months and physical activity), data on clinical diagnoses, including BPD symptoms, NSSI history, and information related to the experience of childhood adversity were collected. Psychiatric diagnoses were assessed by means of the *Mini-International Neuropsychiatric Interview for Children and Adolescents* (M.I.N.I.-KID; Sheehan et al., 2010), a semi-structured interview for the assessment of axis I psychiatric disorders according to DSM-IV and ICD-10. BPD symptomatology was assessed with the corresponding module of the German version of the *Structured Clinical Interview for DSM-IV Personality Disorders* (SKID II; Fydrich et al., 1997), with BPD being diagnosed if at least five of the nine criteria were met for a duration of at least one year. Depressive symptoms over the past two weeks were assessed with the German version of the *Beck Depression Inventory II* (BDI-II; Hautzinger et al., 2006) and the occurrence, frequency and characteristics of a variety of suicidal and self-injurious thoughts and

behaviors were assessed with the German version of the *Self-Injurious Thoughts and Behaviors Interview* (SITBI-G; G. Fischer et al., 2014). Finally, early adverse experiences were assessed with the German version of the *Childhood Experiences of Care and Abuse Interview* (CECA; Kaess et al., 2011). We focused on the subscales antipathy, neglect, psychological, physical, and sexual abuse which can be rated on a 4-point scale ranging from 0 (no adversity/abuse) to 3 (severe adversity/abuse). A severity score was calculated by summing up all subscales, with higher scores reflecting more severe adversity. In addition, according to the CECA manual, each subscale can be dichotomized into none/mild versus marked/severe, reflecting the absence or the presence of the corresponding adversity.

2.3. Image acquisition

MRI was conducted on a Siemens Magnetom TrioTim Syngo 3T scanner with a 32-channel head coil (Erlangen, Germany). Anatomical images were acquired in the sagittal plane with the following sequence parameters: repetition time = 1900 ms, echo time = 2.52 ms, flip angle = 9°, generating 192 T1-weighted contiguous 1.0 mm thick slices (voxel size = $1.0 \times 1.0 \times 1.0$ mm).

2.4. Image processing: Pituitary volume

T1-weighted images were visually checked for quality assurance and the pituitary gland was manually traced by two independent researchers (IML, SS) blinded to participant's diagnosis using the MRIcron software package (https://www.nitrc.org/projects/mricron) following training by a board-certified neuroradiologist (NS). First, the pituitary gland (lying just beneath the optic chiasm) was identified in the midsagittal view (with the corpus callosum clearly visible). Then, we changed to the coronal plane, where the boundaries of the pituitary gland (diaphragma sellae, superiorly; the sphenoid sinus; inferiorly; cavernous sinuses, bilaterally) are best visualized (Pariante et al., 2004). All coronal slices, including the hyper-intense region in the posterior pituitary but excluding the infundibular stalk, were traced using the method described by Pariante et al. (2004) and Sassi et al. (2001). Finally, the tracing was checked in sagittal and axial planes and edited if necessary. Pituitary volume estimates (in mm^3) were calculated by summing all voxels of all relevant slices. Finally, a mean of the two independent pituitary volume estimates was calculated for each participant and used in statistical analyses. Inter-rater reliability was good (ICC = 0.89). Total brain volume was obtained from automated structural segmentation of the T1-weighted images using FreeSurfer version 6.0 (Reuter et al., 2010).

2.5. Statistical analyses

All analyses were run using R (version 3.6.2; 2019–12–12). Socio-demographic and lifestyle-related data, clinical characteristics and variables related to childhood aversity were tested for between-group differences using two-sided *t*-tests and χ^2-tests (or Mann–Whitney U test and Fisher's exact test if the respective assumptions were not met). There were no missing data except for total brain volume (*n* =

4). Outliers with respect to PGV at more than 3 standard deviations (SD) above the group mean were excluded from analyses ($n = 1$). All continuous variables were centered prior to respective analyses. For our primary objective, a hierarchical linear regression model was computed. Age, use of hormonal contraceptives, medication intake and physical activity were entered into the first block of predictors (step 1), as these factors have been found to affect PGV (e.g., Anastassiadis et al., 2019). Since NSSI and control participants differed with respect to smoking, this variable was also included in the first block. Illicit drug use was highly correlated with smoking and was therefore omitted. NSSI and control participants did not differ with respect to total brain volume, and total brain volume was not correlated with PGV. Furthermore, as total brain volume is not known to be associated with PGV, it has also been omitted. Group membership (NSSI vs. controls) was entered into the second block (step 2; see Supplementary Material for results of power analysis), and the interaction between group membership and age was entered into the final block of predictors (step 3). For aim two, another hierarchical linear regression model was computed, this time entering the dichotomized CECA score into the second block of predictors (step 2) and again the interaction with age into the final block of predictors (step 3). Finally, spearman correlations were calculated to explore dimensional associations between PGV and various clinical characteristics (i.e., NSSI frequency, suicidality, number of BPD criteria fulfilled) in patients with NSSI.

3. Results

3.1. Demographic and clinical characteristics of participants

Overall, $N = 67$ youths underwent both the clinical appointment and the MRI exam. One patient was excluded from all analyses due to an outlier in PGV (+ 3 SD above the group mean), resulting in a study sample of $n = 35$ adolescents with NSSI and $n = 31$ healthy controls. As presented in Table 1, adolescents were comparable on age, sex, and several lifestyle-related measures (including BMI, regular physical activity, regular alcohol intake, use of hormonal contraceptives and medication intake; all $p > 0.05$) but differed, as expected, with respect to psychopathology. Thirteen (37%) adolescents in the NSSI group fulfilled the diagnostic criteria for BPD, 19 (54%) had attempted suicide at least once, and the mean frequency of NSSI in the past year was 63.31 ($SD = 75.59$, range = 5–300) respectively 3.26 ($SD = 5.32$, range = 0–30) in the past month. Participants from the NSSI group were significantly more likely to come from families with separated or divorced parents and to have experienced various types of childhood adversity. See Tables 1 and 2 for further details.

Table 1
Characteristics of Study Groups

	NSSI (*n* = 35)	Controls (*n* = 31)	*p*
Demographics			
Age; mean ± SD (range)	15.78 ± 1.42 (12.40-17.80)	15.95 ± 1.19 (13.38-17.79)	0.61
Sex; number of females (%)	33 (94%)	31 (100%)	0.49
Relationship status parents; n (%)			
together	16 (46%)	22 (71%)	**0.01**
separated/divorced	19 (54%)	7 (23%)	
separated by death	0 (0%)	2 (6%)	
Lifestyle measures			
BMI; mean ± SD (range)	21.84 ± 3.53 (16.03-31.07)	20.67 ± 2.39 (17.01-27.44)	0.12
Regular physical activity; n (%)	19 (54%)	24 (77%)	0.09
Smoking; n (%)	16 (46%)	1 (3%)	**<0.01**
Regular alcohol intake (past 3 months); n (%)	3 (9%)	0 (0%)	0.24
Illicit drug use (past 3 months); n (%)	10 (29%)	2 (6%)	**0.03**
Use of hormonal contraceptives; n (%)	11 (31%)	6 (19%)	0.40
Regular medication; n (%)	7 (20%)	1 (3%)	0.06
Psychopathology			
Diagnoses; number with mental disorder according to DSM-IV (%)	34 (97%)	0 (0%)	**<0.01**
Fulfillment of BPD criteria; n (%)	13 (37%)	0 (0%)	**<0.01**
Number of BPD criteria; mean ± SD (range)	4.06 ± 2.30 (1-8)	0.10 ± 0.30 (0-1)	**<0.01**
BDI-II score; mean ± SD (range)	28.89 ± 15.17 (3-55)	4.06 ± 3.68 (0-13)	**<0.01**
Suicide attempt (lifetime); n (%)	19 (54%)	0 (0%)	**<0.01**
Early life adversity (CECA)			
At least one adverse experience; n (%)	20 (57%)	1 (3%)	**<0.01**
Severity of adverse experiences; mean ± SD (range)	3.34 ± 2.96 (0-10)	0.45 ± 1.03 (0-5)	**<0.01**
Sexual abuse; n (%)	8 (23%)	1 (3%)	**0.03**
Physical abuse; n (%)	8 (23%)	0 (0%)	**0.01**
Psychological abuse; n (%)	3 (9%)	0 (0%)	0.24
Neglect; n (%)	2 (6%)	0 (0%)	0.49
Antipathy; n (%)	16 (46%)	1 (3%)	**<0.01**

Note. NSSI = non-suicidal self-injury; SD = standard deviation; n = sample size; BMI = body mass index; BPD = Borderline Personality Disorder; BDI-II = Beck Depression Inventory-II; CECA = Childhood Experiences of Care and Abuse. Regular physical activity = physical activity 2 times per week or more; smoker = smoked on at least 3-5 days in the past 3 months; regular alcohol intake = alcohol intake on at least 10 days in the past 3 months; illicit drug use = drug use on at least 1 day in the past 3 months; regular medication intake = antidepressants, methylphenidate, antipsychotics, medications associated with inflammatory diseases.

Table 2
Clinical diagnoses according to the Mini-International Neuropsychiatric Interview for Children and Adolescents (M.I.N.I. KID; DSM-IV) in patients engaging in NSSI (*n* = 35).

Psychopathology	n (%)
Diagnostic criteria fulfilled for at least one psychiatric disorder	34 (97%)
Diagnostic criteria fulfilled for at least two psychiatric disorders	27 (77%)
F1 - Mental and behavioral disorders due to psychoactive substance abuse	8 (23%)
F2 - Schizophrenia, schizotypal and delusional disorders	4 (11%)
F3 - Affective disorders	29 (83%)
F4 - Neurotic, stress-related and somatoform disorders	22 (63%)
Posttraumatic Stress Disorder	3 (9%)
F5 - Behavioral syndromes associated with physiological disturbances and physical factors	7 (20%)
F9 - Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	10 (29%)

Note. NSSI = non-suicidal self-injury; *n* = sample size.

3.2. Primary aim: prediction of PGV by group membership (confirmatory) and the potential moderating role of participant's age (exploratory)

As mentioned before, NSSI patients and healthy control participants did not differ in terms of total brain volume (NSSI: 1165.82 ± 100.50 cm^3; Controls: 1187.58 ± 88.79 cm^3, $t_{(60)} = 0.90$, $p = 0.37$), and total brain volume was not associated with PGV ($r = -0.08$, $p = 0.53$).

Results of the hierarchical linear regression model with PGV as dependent variable are presented in Table 3. The final model (step 3) was significant and explained 30.9% of variance in PGV ($F_{(58,7)} = 3.71$, $p < 0.01$). There was no main effect of group membership, meaning that there was no overall difference in PGV between healthy control participants and NSSI patients, but group membership significantly interacted with age in predicting PGV. As shown in Fig. 1, while age was a significant predictor for PGV in control participants (with higher age being associated with enlarged PGVs; $B = 61.39$, $SE = 14.94$, $p < 0.01$), no corresponding age effect was found in NSSI patients ($B = 16.83$, $SE = 12.20$, $p = 0.17$). To further illustrate these results, two multiple regression models were calculated separately for healthy control participants and NSSI patients (post-hoc analyses, see also Supplementary Material Table 1). While age, physical activity, smoking, contraceptive use and medication intake explained 53.9% of variance in PGV in the control group, these same variables only accounted for 13.3% of variance in the NSSI patient group. Neither age nor physical activity significantly predicted PGV in adolescents engaging in NSSI ($p > 0.05$). Similar results were obtained if analyses were repeated with female participants only (step 3: $R^2 = 31.2\%$, $F_{(56,7)} = 3.63$, $p < 0.01$).

Table 3
Results of hierarchical linear regression analyses predicting PGV by group membership.

	B	SE	t	p	R^2 (Change)	F-statistic *(p)*
Step 1					0.216	3.30 *(0.01)*
Age	61.39	14.94	4.11	<0.01		
Physical activity	68.61	26.18	2.62	0.01		
Smoking	-10.33	32.85	-0.31	0.75		
Contraceptives	-35.65	29.25	-1.22	0.23		
Medication intake	-28.99	40.61	-0.71	0.48		
Step 2					0.028	2.19 *(0.14)*
Group	40.15	27.05	1.48	0.14		
Step 3					0.065	5.49 *(0.02)*
Group x Age	-44.57	19.02	-2.34	0.02		

Note. PGV = pituitary gland volume; B = regression coefficients; SE = standard error; t = t-value; p = p-value; R^2 - Change = explained variance respectively additional explained variance; F-statistic (p) = F-test of explained variance respectively additional explained variance. B-, SE-, t- and p-values are reported for step 3 (model 3).
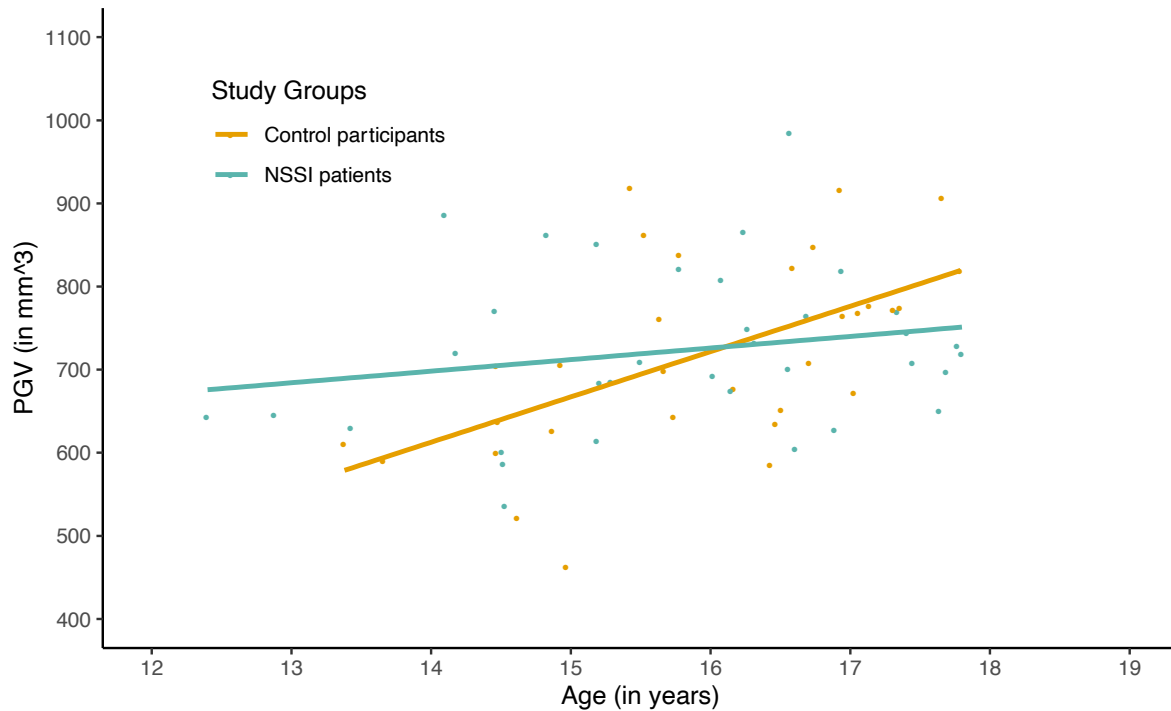
Fig. 1. Association between pituitary gland volume (PGV) and age, separated for healthy control participants and adolescents engaging in non-suicidal self-injury (NSSI).

3.3. Second aim: prediction of PGV by childhood adversity (confirmatory) and the potential moderating role of participant's age (exploratory)

The presence or absence of childhood adversity did not explain significant variance in PGV and childhood adversity did not interact with age in predicting PGV (see Supplementary Material Table 2). Similar results were obtained if using the CECA severity scores instead of the dichotomized score (see Supplementary Material Table 3).

3.4. Third aim: dimensional associations between PGV and clinical characteristics of NSSI (exploratory)

The number of BPD criteria fulfilled significantly correlated with the CECA severity score, the BDI-II total score and the number of lifetime suicide attempts, but, although positively related, did not significantly correlate with the frequency of NSSI during the past year and the frequency of NSSI during the past month. In line with previous findings, the frequency of NSSI during the past year was significantly related with the number of lifetime suicide attempts, but none of these clinical characteristics were significantly correlated to PGV (see Supplementary Material Fig. 1).

4. Discussion

The main objective of the present study was to test for group differences in PGV between adolescents engaging in NSSI and healthy control participants. Based on the literature linking the experience of

prolonged stress to NSSI and HPA axis hyperactivity (at least before a corresponding attenuation may follow over time), as well as findings relating stress, particularly chronic stress, to PGV enlargement, we hypothesized that patients engaging in NSSI would show lager PGVs compared to healthy control participants. However, we did not find evidence for overall volumetric differences between the two groups. Importantly, our study was only powered to detect effects of $f^2 \geq 0.13$ (see also Supplementary Material for corresponding power-analysis); thus, it cannot be ruled out that we have missed smaller effects in the present study. Interestingly, group membership significantly interacted with age in predicting PGV. Specifically, while PGV increased linearly with age in control participants, no corresponding association was found in the patient group. In addition, in healthy controls, age, use of hormonal contraceptives, medication intake and physical activity accounted for a substantial proportion of the variance in PGV, whereas these same variables explained considerably less variance among patients. Neither the frequency of NSSI in the past year or past month, the number of BPD criteria met, the severity of depressive symptoms, nor the number of suicide attempts explained variance in PGV among adolescents engaging in NSSI. In addition, there was no evidence that the experience of childhood adversity could account for variance in PGV better than psychopathology. These results and potential implications are discussed below.

Our findings contrast with studies that observed volumetric changes in various stress-related mental disorders including, for instance, post-traumatic stress disorder, obsessive-compulsive disorder or panic disorder (for an overview see Anastassiadis et al., 2019), as well as studies that observed greater baseline PGV and accelerated PGV growth in adolescents with early life adversity (Farrow et al., 2020; Ganella et al., 2015). However, as mentioned before, although differences in PGV have been described across studies, inconsistencies – particularly in terms of the direction of changes (i.e., PGV enlarged in the patient sample, PGV reduced in the patient sample, or no differences observed) – exist among findings. One potential reason that might explain some of the observed variability relates to the timing at which the association between PGV and psychopathology is examined (Anastassiadis et al., 2019). For instance, while larger PGVs have been found in individuals at risk that later transitioned to psychosis compared to those who did not develop the disorder (Garner et al., 2005; Shah et al., 2015), smaller volumes have been observed among chronically ill schizophrenic patients (Upadhyaya et al., 2007). As suggested by Garner et al. (2005) and Upadhyaya et al. (2007), HPA axis hyperactivity in the early phase of psychotic illness (including the prodromal phase) may contribute to PGV enlargement, which might be then followed – in line with the "attenuation hypothesis" (Kaess et al., 2018) – by a gradual decrease of HPA axis activity (i.e., blunted cortisol stress reactivity; Zorn et al., 2017) as the disorder progresses, resulting eventually in an overall reduction of PGV over time. Accordingly, rather than group differences per se, pituitary gland development trajectories might be particularly relevant. At the same time, group differences may actually become invisible – especially in case of cross-sectional data – if these developmental trajectories differ between patients. Interestingly, similar to the literature on psychosis, patients in the presumably still relatively "early phase" of NSSI disorder – i.e., at ages 12–

14.5 years – showed a tendency for larger PGVs compared to their healthy peers. Although we did not find evidence for an overall group effect – keeping in mind the restrictions related to the statistical power to detect small effect size differences – we observed an age-dependent effect. Based on findings from various MRI studies, the volume of the pituitary gland seems to increase gradually in young children, shows a growth spurt during puberty, peaks in the mid-20 s to early 30 s, and starts to decrease thereafter (Anastassiadis et al., 2019; Castillo, 2005; Lurie et al., 1990; Wong et al., 2014). Consistent with these findings (taking into account that our data are cross-sectional) a gradual increase in PGV with age was observed in our healthy control sample. In contrast, no corresponding association was found in patients engaging in NSSI, suggesting that pituitary maturation (i.e., the developmental trajectory of the pituitary gland) may be altered in this group. In this context, it's worth noting that although we did not find evidence that PGV was related to adverse experiences during childhood and/ or adolescence, NSSI patients were much more likely to have experienced various types of stressors – such as coming from families with separated or divorced parents and having experienced various forms of child maltreatment – compared to healthy control participants. In fact, when bullying, loss experiences, and witnessing domestic violence (also assessed by means of the CECA interview) were included in addition to the other forms of adversity (i.e., physical, sexual, psychological abuse, antipathy and neglect), as many as 89% of NSSI patients had faced at least one of these types of stressors. Comparable to the importance of timing between PGV assessment and psychopathology, the timing between PGV assessment and these types of experiences may be as important.

Interestingly, supported by a recent longitudinal cohort study (Sandini et al., 2020), the developmental trajectory of the pituitary gland may be indeed particularly important when it comes to psychopathology. In this longitudinal study, healthy control participants and patients with a specific genetic deletion syndrome (22q11DS) that confers a strongly increased risk for multiple psychiatric disorders and that has been linked to HPA axis hyperactivity in children (Sanders et al., 2017) and attenuated cortisol stress reactivity in adult patients (van Duin et al., 2019) were followed over a total of five visits with follow-up intervals of approximately three years in-between. The authors were able to show that patients with the deletion syndrome reached peak maturation earlier and showed a sharper volumetric decline by young-adulthood compared to healthy control participants. Interestingly, volumetric differences were not yet as pronounced in childhood or adolescence, but became more apparent from early adulthood. However, rather than mean PGV (i.e., high versus low), longitudinal PGV development was particularly relevant with respect to psychopathology. Patients that presented with slightly higher volumes during childhood, followed by a strong longitudinal decline resulting in PGV reductions by late-adolescence, showed significantly higher psychopathological symptoms and higher reactivity to daily stressors than patients with an increase of PGV over time (Sandini et al., 2020). In addition, aberrant pituitary development was related to atypical hippocampal and cortical maturation in patients with the deletion syndrome. Consistent with the finding of higher PGV during childhood among those presenting with psychopathological symptoms later in life, a longitudinal study conducted

in Australia was able to show that lager PGVs at baseline (around the age of 12 years) mediated the relationship between early pubertal timing – which represents an important risk factor for psychopathology in general (Roberts et al., 2020; Ullsperger & Nikolas, 2017) – and depressive symptoms over time (Whittle et al., 2012). Taken together, these findings provide preliminary evidence that atypical pituitary development may reflect a common biological mechanism underlying various stress-related mental disorders, including NSSI disorder. Longitudinal studies, however, are urgently needed to clarify the role of HPA axis activity, including changes in HPA axis activity thought to be caused by chronic stress experiences, in mediating pituitary maturation and how pituitary maturation is in turn related to changes in the HPA axis functioning and the development of NSSI. In addition, considering that adolescence represents a time period of major hormonal changes, including changes in the secretion patterns of pituitary gonadotropin-releasing hormones, growth hormones and thyroid hormones (Rogol, 2010; Sisk & Zehr, 2005), hormones closely associated with pituitary gland maturation and pubertal timing (e.g., Wong et al., 2014), future studies interested in PGV alterations thought to be related with changes in HPA axis activity, should also carefully investigate the role of these other important pituitary hormones.

5. Conclusion

This study provides some preliminary evidence for potentially altered pituitary maturation in patients engaging in NSSI compared to healthy controls, although no overall volumetric differences – at least in the range of medium and large effect sizes – were found between the two groups. Several suggestions for future studies emerge from our research. Future studies should (1) replicate our finding incorporating larger samples in longitudinal designs (2) with a diverse population to also examine potential sex differences, (3) try to relate PGV development to stress, including chronic stress experienced early in life (4) aim to link PGV maturation with various HPA axis activity measures (i.e., various cortisol measures), (5) carefully assess and control for other pituitary hormones such as gonadotropin-releasing, growth and thyroid hormones as well as measures of pubertal development, and (6) aim to relate PGV maturation to psychopathological symptoms.

Declarations of interest

None.

Appendix A. Supplementary material

Supplementary material related to this article can be found in the online version, at doi: https://doi.org/10.1016/j.psyneuen.2022.105662.

3. Discussion

To briefly review: The *biological embedding model* posits that environmental experiences, such as chronic stress experienced early in life, can lead to changes in biological functioning through mechanisms such as epigenetic programming, with potentially lasting consequences for development, behavior, and health. Among the various types of adverse environmental stressors that can be distinguished, the experience of child maltreatment is thought to have a particularly high potential to cause such "biological scars" because this type of experience has been most readily associated with a toxic stress response, defined as a strong, frequent, or prolonged activation of the body's stress response system; or more specifically, as a strong, frequent, or prolonged activation of the HPA axis. The HPA axis, in turn, is a neuroendocrine system whose activity is triggered not only by environmental stressors but also by circadian signals and is known to be involved in the regulation of a variety of essential physiological processes in the human body. A growing body of evidence suggests that cortisol – the main effector hormone of the HPA axis – is indeed involved in mediating the biological embedding of child maltreatment and, importantly, that HPA axis activity, and thus cortisol secretion itself, may be altered by this process in the long term. Altered functioning of the HPA axis – given its involvement in the regulation of various physiological processes, including immune function, metabolism, cardiovascular activity, and cognition – may in turn increase the risk of developing a wide range of chronic diseases later in life.

3.1. Meta-Analysis: Child maltreatment and hypothalamic-pituitary-adrenal axis functioning

As part of the present thesis, in a first step, the relationship between child maltreatment experiences and HPA axis functioning including various measures of cortisol secretion – i.e., cortisol assessed in the context of the circadian rhythm (DC), cortisol assessed in response to awakening (CAR), in response to the perception of a stressor (cortisol stress reactivity), in response to pharmacological challenges (DST, Dex-CRH test, CRH test), and cumulative measures of cortisol secretion, namely 24-hour UFC and HCC – was thoroughly investigated by means of a comprehensive systematic review and series of meta-analyses. In this context, particular attention was paid to the potential influence of psychopathology in confounding or moderating the effect of child maltreatment on cortisol metabolism.

Consistent with the *biological embedding model* (i.e., the assumption of long-term changes in biological functioning through life experiences), results of the present series of meta-analyses revealed a blunted cortisol stress reactivity in individuals exposed to child maltreatment compared with those without such experiences. However, no overall differences were found in any of the other measures of HPA axis activity (with the exception of evening cortisol). Importantly, the majority of studies were conducted with predominantly young, female adults who belonged to an ethnic majority group, and in whom child maltreatment experiences were mainly assessed by self-report. In addition, a considerable number of studies did not report on psychopathology, with studies involving clinical samples being quite

heterogeneous in terms of the predominant mental disorder (see also Section 3.3. Methodological considerations and limitations). Accordingly, the overall power to find a relevant moderator including psychopathology may have been limited. Taking this into account, for the majority of cortisol outcome indices, psychopathology did not account for heterogeneity in the relationship between child maltreatment and cortisol, with the exception of a tendency for greater blunting found in clinical samples for indices related to the cortisol stress reactivity. However, this finding should be interpreted with caution because very few studies included a purely clinical sample, and these few studies reported relatively strong negative effects compared to other studies with clinical samples. Although less pronounced, participants with a history of child maltreatment who did not report a mental disorder at the time of measurement likewise showed an attenuated cortisol stress response. Thus, these findings suggest that alterations in the cortisol stress reactivity, more specifically, a blunted cortisol stress response, may be present prior to or independent of psychopathology, a finding that will be explored in greater detail in the following sections.

It is generally accepted that cortisol, when secreted in excess, such as during prolonged stress exposure, as is likely to be the case when experiencing child maltreatment, can have various deleterious effects, particularly on the brain (e.g., McEwen et al., 2016; Sapolsky, 1999). Thus, a corresponding downregulation – i.e., the transition from an initial hypercortisolemic phase under chronic/prolonged stress to a secondary, compensatory downregulation of the HPA axis over time (e.g., Agorastos & Chrousos, 2022; G. E. Miller et al., 2007; also known under the so-called "attenuation hypothesis": e.g., Kaess et al., 2018) may indeed serve an adaptive function – especially under repeated uncontrollable homotypic stressors – protecting the body from the negative long-term effects of cortisol excess. At the same time, however, a blunted cortisol stress response, if biologically embedded during sensitive developmental periods, may interfere with the reestablishment of allostasis following the perception of future stressors and may thus reflect difficulties in the ability to cope with emotionally negative situations (e.g., Marques-Feixa et al., 2023). Given that most of the effects of cortisol in the body are genomic and thus do not occur until about an hour after the onset of a stressor, cortisol – in addition to exerting several important stimulatory effects (in support of the other stress mediators) during a stress response – actually plays a critical role in helping to restrain and thus protect the body from an overshooting stress response (Sapolsky et al., 2000). Interestingly, consistent with the notion that an adequate cortisol response to the perception of a stressor may be critical for returning the system back to baseline after the stressor had ceased, several studies have now shown that an attenuated cortisol stress reactivity is associated with a stronger proinflammatory immune response (considering that cortisol typically exerts important anti-inflammatory and immunosuppressive functions that are widely used in medicine; e.g., Buske-Kirschbaum et al., 2010; Schwaiger et al., 2016), with other studies suggesting that inflammatory processes may precede or be involved in the development of mental disorders (Kivimäki et al., 2014).

Ultimately, regardless of the exact biological mechanisms involved, an increasing number of studies suggest that a blunted cortisol stress response may indeed represent an important transdiagnostic risk factor for the development of various mental disorders. In rats, for example, a blunted HPA axis response to predator stress was found to influence susceptibility to the development of PTSD-like symptoms, whereas administration of corticosterone one hour prior to exposure to the respective stressor significantly reduced the development of such symptoms (Cohen et al., 2006). Similarly, a blunted cortisol stress response to psychosocial stress was found in women with PTSD (Metz et al., 2020). Supporting the notion that a dysregulation in HPA axis functioning – i.e., a blunted cortisol stress response – may reflect a risk factor rather than a consequence of psychopathology, in male soldiers deployed to Afghanistan, an attenuated cortisol stress response at baseline was predictive of the development of PTSD symptomatology following new-onset traumatic events during deployment (Steudte-Schmiedgen et al., 2015). In addition, a study conducted with veterans showed that greater improvement of PTSD symptoms to a novel motion-assisted virtual reality exposure therapy was associated with higher average cortisol levels at pre- and post-treatment sessions (van Gelderen et al., 2020). Finally, consistent with the finding that corticosterone administration reduced the development of PTSD symptoms in rats, a pilot study with patients presenting at the emergency department showed that a single intravenous bolus of high-dose hydrocortisone within 6 hours of a traumatic event (mostly motor vehicle accidents) significantly reduced the risk of subsequent PTSD development (Zohar et al., 2011). In addition to these findings from the PTSD literature, a blunted cortisol stress response has also been found to be associated with the development of other adverse health outcomes, such as addiction, obesity, and depressive symptoms (e.g., de Rooij, 2013; Turner et al., 2020).

The following two longitudinal studies provide compelling evidence of the potential impact of facing additional (or future) life challenges (i.e., stressors) in the case of a blunted cortisol stress response on subsequent mental health: In a study conducted by Eisenlohr-Moul et al. (2018), similar to the above findings, a blunted HPA axis stress response was overall predictive of suicidal behavior. However, developmentally higher-than-usual peer stress predicted suicide attempts only among those female adolescents who exhibited the aforementioned blunting of HPA axis activity at the baseline laboratory visit. Thus, these findings suggest that a blunted cortisol stress response constitutes a risk factor for stress-related suicidal behaviors. In the study from Galatzer-Levy et al. (2014), salivary cortisol response to a laboratory stressor was examined as a predictor of distress trajectories in urban police officers routinely exposed to life stressors and traumatic events. In this study, trajectories of resilience and recovery over a four-year-period of active duty were associated with a significant increase in cortisol response to the experimental stressor during training, whereas those who exhibited a trajectory of chronically increasing distress did not show the expected increase in cortisol in response to the challenge. Thus, again, an attenuated cortisol stress response at baseline was a risk factor for subsequent vulnerability to distress secondary to significant life stressors.

Taken together, these findings suggest that a blunted cortisol stress response (specifically to psychosocial stressors), ultimately independent of the actual etiological cause, may reflect a nonspecific risk factor for the development of psychopathology, probably by reflecting difficulties in reestablishing allostasis when faced with a stressor, with the results of the present series of meta-analyses suggesting that child maltreatment experiences, likely by a process known as biological embedding, may be considered as one plausible etiological pathway to an aberrant cortisol stress response.

However, as just suggested, other etiological causes may also be associated with a blunted cortisol stress reactivity. To further complicate matters, a heighted cortisol stress reactivity – considering the profound effects of cortisol in the brain – may likewise confer risk for psychopathology. In keeping with this theme, mental disorders, as historically defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD), have repeatedly been found to exhibit a considerable degree of heterogeneity, in part because these symptom-based categories are multidetermined. In other words, the same symptoms may result from heterogeneous underlying disease mechanisms or, conversely, syndromes that appear to be clinically distinct may actually result from the same etiology (e.g., Insel et al., 2010). Accordingly, these symptom-based categories typically lack biological validity, which in turn has complicated the identification of biomarkers in psychiatry (e.g., Insel, 2014). The role of different etiological pathways ultimately leading to similar PTSD symptom trajectories, for example, can be illustrated by the study of Galatzer-Levy et al. (2017), who reanalyzed data from a longitudinal study of participants presenting to the general emergency room following trauma exposure. In their respective analyses, the research team first identified two distinct longitudinal trajectories of PTSD symptoms, remitting and non-remitting PTSD, with subsequent network analyses revealing that decreased cortisol levels (i.e., urinary cortisol assessed over 4 hours after trauma exposure) at the time of presenting at the emergency room were associated with an increased risk for the non-remitting PTSD trajectory. Interestingly, reduced urinary cortisol, which likely represents a blunted cortisol stress response to trauma rather than lower diurnal levels, was in turn related to early childhood trauma exposure. However, the authors also identified another pathway to PTSD non-remission that was less likely to be associated with childhood adversity. The participants identified in this other pathway exhibited heightened arousal and danger in response to the trauma, which in turn was associated with elevated salivary cortisol levels. Accordingly, these findings suggest that both low and high cortisol levels may confer an increased risk for developing PTSD, depending on the respective background risk (i.e., childhood adversity versus no childhood adversity). In this vein, using data from the birth cohort Dunedin Multidisciplinary Health and Development Study, Breslau et al. (2014) showed that severe maltreatment in the first decade of life, as well as juvenile disorders, were both independently and significantly associated with the risk of developing PTSD among those exposed to trauma in adulthood, again pointing to likely differing disease pathways for the same presentation of symptoms.

Taken together, these findings clearly highlight the complexity of finding biomarkers in groups of patients who present with similar symptoms but may differ in etiological disease pathways. In addition, these results underscore the importance of conducting longitudinal studies that assess the interrelations between genetic variability, environmental factors, changes in biological functioning (i.e., HPA axis activity, immune system; including their mutual interactions), and resulting interindividual differences in vulnerability and resilience over the later life course.

In this context, it seems important to note that facing adversity during childhood does not necessarily lead to psychopathology (Collishaw et al., 2007). Overall, as noted above, findings suggest a dose-dependent relationship between the experience of child maltreatment (or early life adversity in general) and the risk of health impairments, with those reporting increasing numbers of different types of child maltreatment (or increasing numbers of different childhood adversities) or those reporting more severe experiences generally showing stronger associations (e.g., Clemens et al., 2018; Dube et al., 2001). In keeping with these findings, a recent meta-analysis (Bunea et al., 2017) found a stronger blunting of the cortisol stress response in individuals reporting maltreatment experiences – which, as has now been repeatedly suggested, may be perceived as a particularly adverse environmental stressor – compared to those exposed to other adversities during childhood. Unfortunately, in the present series of meta-analyses, the severity of child maltreatment experiences on cortisol secretion could not be investigated. Importantly, of the various factors that have been associated with resilience, a stable family environment and supportive interpersonal relationships appear to be particularly important (Afifi & MacMillan, 2011; Collishaw et al., 2007; Fritz et al., 2018). Relatedly, and in line with the assumption that stressors that elicit toxic stress responses in early childhood typically lack the presence of supportive adult relationships, studies on stress-buffering effects have shown that parental support can indeed buffer the cortisol response to psychosocial stressors in children (Bosquet Enlow et al., 2014; Doom et al., 2015; Hostinar et al., 2014, 2015). Accordingly, the risk that child maltreatment may lead to cortisol excess, likely resulting in an attenuated cortisol stress response over time, may vary depending on whether at least one stable caregiver was present during childhood. Unfortunately, this could not be examined in the present meta-analysis because there were few studies that assessed parental support in the respective primary studies.

In addition to environmental conditions – such as the presence of a stable caregiver – that may moderate the association between adverse experiences and physiological disruptions (as suggested earlier), genetic predispositions (e.g., specific polymorphisms) may also influence vulnerability or resilience to adversity (e.g., Buchmann et al., 2014; Sumner et al., 2014). The study by Sumner et al. (2014), for example, showed that adolescents with one or more G alleles of rs110402 – a polymorphism of the corticotropin-releasing hormone receptor type I (CRHR1) gene – relative to A allele homozygotes, exhibited a blunted cortisol stress response to a psychosocial stressor. Interestingly, the authors also found a trend for a stronger relationship between child maltreatment and cortisol hypo-reactivity among

G allele carriers, suggesting that variation in the CRHR1 gene may moderate the effects of child maltreatment on HPA axis functioning.

Finally, some comments or plausible interpretations of the null findings with respect to the other HPA axis activity measures (i.e., measures of daily activity, cortisol assessed in the context of pharmacological challenges and cumulative measures of cortisol secretion) seem appropriate, though keeping in mind methodological shortcomings as a potential explanation (see also Section 3.3. Methodological considerations and limitations). As described in detail in the introduction section, HPA axis activity in response to psychosocial stressors has been found to be regulated mainly by brain structures including the hippocampus, the amygdala, and the prefrontal cortex (Herman et al., 2003), with findings showing long-term changes in the limbic input of these structures to neurons controlling stress responsiveness following severe stress exposure (e.g., Herman, 2013). In contrast, the CAR, as well as the circadian release of cortisol, are not primarily regulated by the perception of stress (i.e., homeostatic challenges) and correspondingly serve quite different biological functions in the body, such as the transition from sleep to full alertness in the case of the CAR (e.g., Clow, Hucklebridge, & Thorn, 2010). Accordingly, other brain structures, such as the SCN, are majorly involved in controlling HPA axis activity in this context (Clow, Hucklebridge, Stalder, et al., 2010; Spiga et al., 2014). In addition, effects on target cells are primarily mediated by the MR, whereas the GR becomes increasingly occupied during a stress response, with these receptors differently expressed within the body (e.g., Spencer & Deak, 2017). Thus, alterations in HPA axis activity measures that are not primarily activated by stress perception (e.g., DC, CAR, HCC, UFC) may only become apparent when cortisol is measured during periods of high life stress – i.e., when stress processing actually becomes relevant for these activity measures as well. Indeed, although not primarily controlled by the perception of stress, stressful experiences do appear to influence these activity measures, as evidenced by the finding that job stress was associated with a heighted CAR (Chida & Steptoe, 2009). In support of this notion, and in line with the *biological embedding model*, results from a recently published longitudinal study revealed that independent of current life stress, individuals with adversities experienced during early or middle childhood showed a blunted cortisol response to a psychosocial stressor (Young et al., 2021). However, alterations in the circadian release of cortisol – i.e., flatter DSL profiles – were observed only in those individuals who had experienced adversity during childhood and who were exposed to concomitant high levels of stress at the time of measurement (Young et al., 2019). Thus, based on this longitudinal study, future research should focus more closely on the potential influence of current life stress if interested in HPA axis activity measures that are not primarily regulated by stress perception alone.

In summary, in support of the *biological embedding model*, the experience of child maltreatment appears to be associated with a blunted cortisol stress response, independent of current psychopathology, with accumulating evidence suggesting that a blunted cortisol stress response – likely reflecting a diminished ability to adapt to a stressor – may indeed represent a plausible etiological pathway to stress-related mental disorders. However, in order to draw causal conclusions and to investigate the precise

biological consequences associated with a blunted cortisol stress response and its temporal relationship with the emergence of psychopathology, longitudinal studies assessing the severity of child maltreatment, the role of parental support, genetic variability, and the influence of current life stress (amongst other plausible moderators) are urgently needed. In addition, given the well-known sex differences in the prevalence of stress-related disorders (S. H. Li & Graham, 2017) as well as HPA axis activity (Zänkert et al., 2019), and also relating to the finding of the present meta-analysis showing a stronger blunting of the cortisol stress response in females exposed to child maltreatment, this topic clearly warrants further research attention.

3.2. Pituitary volume in adolescents with non-suicidal self-injury

Turning now to a specific psychopathological behavior – NSSI, that is, the self-inflicted damage to body tissue without suicidal intent (Nock, 2010) – where stress processing, or difficulty to adapt to a stressor, appears to play a particularly important role with regard to etiology (e.g., Kaess et al., 2021). NSSI typically first manifests in early adolescence (Plener et al., 2015) and can be observed in the context of a wide range of mental disorders (e.g., Ghinea et al., 2020; Kaess et al., 2013). Although NSSI by definition implies the absence of lethal intent, it nonetheless represents an important risk factor for suicidality (Koenig, Brunner, et al., 2017), and although the prevalence of NSSI is much lower in adults (Swannell et al., 2014), a symptom-shift toward more socially accepted harmful behaviors, such as substance abuse, has been observed in those who engaged in NSSI during adolescence (Nakar et al., 2016). Consistent with the notion that NSSI may serve as a way to regulate affective states – e.g., to adapt to a stressor – the behavior is typically preceded by an increase in negative feelings or thoughts (e.g., tension, feelings of rejection, dissociation or anger), and accordingly, studies using ecological momentary assessments have shown that NSSI may help to induce either relief from negative feelings or aversive cognitive states, or resolution of interpersonal problems (Klonsky, 2007; Rodríguez-Blanco et al., 2018; Zetterqvist et al., 2013). An increase in negative affect, in turn, as just noted, is typically observed in response to the experience of stressors (e.g., Seddon et al., 2020), and evidence from clinical and community samples clearly supports the role of stress experiences, including early life adversity such as child maltreatment, in the etiology of NSSI (Ewing et al., 2019; R. T. Liu et al., 2016, 2018; R. C. O'Connor et al., 2012). A recent prospective study, for instance, was able to demonstrate that periods of higher-than-usual stress, compared to one's typical level, was associated with the greatest risk for engaging in NSSI (A. B. Miller et al., 2019). In another study using data from a longitudinal research project involving university students, a bidirectional relationship between stressful experiences and NSSI was observed, with increased stressful experiences predicting an increased risk to engage in NSSI through emotional dysregulation, and engaging in NSSI, in turn, similarly predicted increased stressful experiences through emotional dysregulation (Ewing et al., 2019).

Although little is yet known about the neurobiological basis of NSSI (Kaess et al., 2021), based on the evidence linking the experience of stress, especially chronic stress, with the development and

maintenance of this behavior, alterations in HPA axis functioning have been suggested. Indeed, as mentioned in the introduction section, a blunted cortisol stress response has been found in those engaging in NSSI compared to healthy controls or depressed patients without such behavior (Kaess et al., 2012; Klimes-Dougan et al., 2019; Plener et al., 2017), a finding that can also be observed in the animal literature (Tiefenbacher et al., 2005). As painful stimulation itself is known to be a potent trigger of HPA axis activity, it has been posited that NSSI may compensate for the observed inappropriate cortisol response to psychosocial stressors (Koenig, Rinnewitz, et al., 2017). Thus, cortisol released by NSSI may help to restore allostasis, which in turn may be important for mood and well-being post-stressor. Interestingly, according to the following studies, an increase in cortisol in response to a stressor may indeed be important and adaptive in the context of affect regulation, whereas a blunted cortisol stress response may indicate difficulties in stress adaptation. For example, a study conducted by Reuter (2002) found that administration of hydrocortisone prior to stress exposure ameliorated negative emotional states following stress induction (i.e., watching a film depicting violent scenes). Additionally, in a study conducted by Het et al. (2012), lower mean cortisol levels during exposure to a psychosocial stressor were associated with higher levels of negative affect after the stressor had ceased. In turn, a study of healthy participants by Krkovic et al. (2018) showed that habitual use of maladaptive emotion regulation strategies (e.g., rumination, catastrophizing) was associated with a blunted cortisol stress response to a psychosocial stressor. Taken together, these findings strongly support a plausible role for stress and, in particular, an altered HPA axis stress reactivity in the etiology of NSSI. Again, it remains unclear whether the blunted cortisol stress response observed thus far is primarily attributable to adversity experienced during childhood – as has been shown previously, NSSI is strongly associated with such experiences (e.g., Kaess et al., 2013) – or whether these alterations are generally seen among those who self-harm.

Therefore, as part of the present thesis, in the second study, we were interested in whether PGV – an alternative approach to assess HPA axis function (see introduction section for a brief overview) – differ between adolescents engaging in NSSI and healthy control participants, and whether these differences could be primarily attributed to adversity experienced during childhood. As part of an exploratory approach, based on findings demonstrating accelerated growth of the pituitary gland in the context of chronic stress (Ganella et al., 2015), and given that the volume of the pituitary gland still increases during adolescence (Anastassiadis et al., 2019), we also tested for an age-dependent group effect.

Overall, we did not find evidence for volumetric differences between patients engaging in NSSI and healthy controls, keeping in mind that due to limited power, small effect size differences could not be detected in the present study. However, group membership interacted significantly with age in predicting PGV. As would be expected under "normal" developmental conditions, PGV increased linearly with age in control participants, whereas no corresponding relationship with age was found in the patient group, providing some preliminary evidence for a potentially altered pituitary maturation in

patients engaging in NSSI, keeping in mind, however, that the analyses were based on cross-sectional data. Childhood adversity (i.e., sexual, physical and emotional abuse, neglect, and antipathy) neither explained significant variance in PGV, nor did it interact with age in predicting PGV. It is important to note, however, that when bullying, loss experiences, and witnessing domestic violence were added to the other forms of adversity, 89% of patients with NSSI had actually experienced at least one of these types of stressors, again highlighting the difficulty of disentangling psychopathology from early life adversity, especially in cross-sectional studies.

These findings, in addition to the considerations already discussed in relation to the results of the present meta-analysis (i.e., the possibility that different etiological pathways – e.g., a dysregulated HPA axis stress response (blunted or heighted) – lead to similar psychopathological symptoms depending on the respective background risk, as well as the urgent need for longitudinal studies to disentangle the effects of early life adversity from psychopathology), highlight another important aspect, namely the role of developmental changes (i.e., intra-individual changes). Indeed, intra-individual changes over time may be of particular importance in the development of psychopathological symptoms, probably to an even greater extent than inter-individual differences measured at a given point in time. According to the aforementioned "attenuation hypothesis" (e.g., Kaess et al., 2018), HPA axis hyperactivity (regardless of its actual cause) is suggested to result in HPA axis hypoactivity over time. Applied to the PGV, an initial PGV enlargement may be followed by a gradual volumetric decrease over time. Thus, it may not be group differences per se, but PGV development trajectories (or trajectories of HPA axis activity) that are of particular relevance. This seems quite reasonable considering that HPA axis responses to acute stress overall show high inter-individual variability (e.g., Zänkert et al., 2019). Interestingly, findings from a recently published cohort study (Sandini et al., 2020) that longitudinally assessed the PGV in healthy controls and patients with a specific genetic deletion syndrome that confers a highly increased risk for multiple psychiatric disorders and that has been associated with a heighted cortisol stress response in children (Sanders et al., 2017) and a blunted HPA axis stress reactivity in adults (van Duin et al., 2019) provide some support for this assumption. The authors of this longitudinal cohort study were able to show that it was not the mean PGV (high or low), but rather the longitudinal trajectory of PGV development – i.e., higher volumes during childhood followed by a strong longitudinal decline over time – that was associated with psychopathological symptoms. Interestingly, visual inspection of the figure depicting the results of the present study (see Fig. 1: Association between PGV and age, separated for healthy control participants and adolescents engaging in NSSI) reveals a similar picture, i.e., a tendency toward higher volumes in younger adolescents engaging in NSSI compared to same-aged healthy controls (keeping in mind that our data are cross-sectional). In addition, in the study by Sandini et al. (2020), aberrant pituitary development was associated with atypical hippocampal and cortical maturation. The importance of developmental changes has been repeatedly demonstrated in brain maturation studies where impaired network connectivity resulting from aberrant brain maturation trajectories has been implicated as a plausible cause of psychiatric vulnerability (e.g.,

Vanes et al., 2020; Vanes & Dolan, 2021). Thus, with respect to cross-sectional data, group differences may indeed be masked due to high inter-individual developmental variability, especially when the timing between the assessment of the biological system and the assessment of the predictor or outcome may be of particular importance, as appears to be the case for early life adversity, HPA axis functioning and the emergence of psychopathological symptoms. In fact, the possibility that group differences might be masked is even more likely when studying brain structures in children or adolescents, which in turn are known to undergo significant developmental changes from childhood to adulthood, as has been observed in the case of the pituitary gland (e.g., Anastassiadis et al., 2019). Thus, in order to investigate the temporal relationship (i.e., developmental trajectories) between the experience of early life adversity, a proposed initial HPA axis hyperactivity, structural changes in the PGV, the development of a blunted cortisol stress response, and the emergence of psychopathological symptoms such as NSSI, future studies urgently need to rely on longitudinal designs that repeatedly measure the respective variables of interest.

3.3. Methodological considerations and limitations

It is important to consider some of the methodological shortcomings of the studies that make up this thesis, not only to allow for a qualified interpretation of the results, but also to guide the conduct of future studies. Accordingly, in addition to the suggestions already mentioned earlier, this section discusses methodological considerations and provides further recommendations for future studies.

Regarding the meta-analytic study, methodological shortcomings have been addressed in detail in the corresponding publication, so only a brief summary is provided here. An important aspect that merits discussion is the finding of a high degree of between-study-heterogeneity, which raises the question of whether the conduct of the meta-analysis was appropriate in the first place. Overall, the included primary studies varied widely in their child maltreatment assessment and grouping approaches, with some studies relying on cut-off scores using validated self-reports such as the Childhood Trauma Questionnaire (CTQ; Wingenfeld et al., 2010), others applied specific definitions (e.g., repeated abuse, once a month or more for at least 1 year; Heim et al., 2000) that were sometimes based on self-developed assessment tools (e.g., Groër et al., 2016), and still others defined child maltreatment based on the presence or absence of an official child protective services (CPS) record (e.g., Bernard et al., 2010), with sometimes inadequate control if control participants were not exposed to any type of child maltreatment. Accordingly, more stringent inclusion criteria in the search and screening phase of the meta-analytic study, particularly with regard to the conceptual definition of child maltreatment, might have reduced heterogeneity among the primary studies. However, in addition to the fact that this would have resulted in a much smaller number of included studies and thus lower generalizability of the results, although there has been extensive research on the consequences of the experience of child maltreatment, there is still no overall consensus on its best operational definition. Particularly, specifying the exact boundaries of acceptable parental practices, the context and purpose of the definition (i.e., research,

legal system), and the limitations associated with the use of different assessment methods (e.g., self-reports, parental-reports, observational paradigms, or the use of official CPS records) remain challenging, and have complicated the development of a uniform definition in the past (Cicchetti & Toth, 2005; Jackson et al., 2019; Leeb et al., 2008; Manly, 2005). As suggested by Jackson et al. (2019), future research as a whole would benefit from reaching some level of consensus on the most useful and accurate methods for assessing child maltreatment. In this context, it seems nevertheless worth mentioning that neither the assessment (self-report, informant report, mixed) nor the grouping method (cut-offs, other, record) explained variance in the effect estimates, holding true for the majority of HPA axis activity outcome indices, although far fewer studies used informant as opposed to self-reports.

Aside from the difficulties related to the definition of child maltreatment and, as discussed earlier, the inability to examine the role of several presumably important moderators of the child maltreatment cortisol relationship (i.e., the severity and chronicity of maltreatment experiences, the role of age at maltreatment onset, and the potential buffering effect of having a stable caregiver), several other quality-related issues appear to be important. These include the aforementioned observation that a substantial number of the primary studies did not assess the presence of mental disorders in their respective samples, thus failing to ensure that exposed and control groups did not differ in this respect. Moreover, very few of the primary studies considered several important aspects regarding the appropriate assessment of cortisol in the context of the corresponding HPA axis activity measure, including, for instance, rescheduling the sampling when participants were ill, ensuring that participants were not under any current stress at the time of testing, assessing sampling time adherence, and addressing issues related to reliability of the corresponding activity measure. Finally, a substantial number of studies did not control for, or at least not report on, several well-established confounding variables, including menstrual cycle timing, intake of medications (including oral contraceptive use), smoking, pregnancy, night-shift work, and other types of early life adversity other than child maltreatment. There are now several best practice guidelines for the assessment of cortisol, and if reliable and valid HPA axis activity measures are to be obtained, it is strongly recommended that future studies rely on these guidelines (e.g., Allen et al., 2017; Kudielka et al., 2012; Stalder et al., 2016; Stalder & Kirschbaum, 2012; Zänkert et al., 2019). Thus, in summary, although the ability to establish a consistent relationship between the experience of child maltreatment and HPA axis functioning may have been limited by various methodological limitations, the present meta-analysis critically highlights many of the problems inherent to this research area, and in order to advance the field, future studies will need to consistently address these issues.

With regard to the second study that forms part of the present thesis, the sample size and the cross-sectional nature of the study design critically limit the interpretability of the study result. Indeed, due to limitations in statistical power (the present study was not able to reliably detect effects smaller than $f^2 = 0.13$), it cannot be ruled out that small effect size differences may have been missed. Power issues due to small samples, as can also be inferred from the review paper conducted by Anastassiadis

et al. (2019), are a common problem in the field of PGV research, which in turn may be partly explained by the fact that PGV assessments are still mainly obtained by manual tracing of MRIs rather than by automated approaches. This in turn relates to another problem, namely that differences in the segmentation style between different research groups may affect the comparability between studies, which calls for sophisticated techniques that can be applied to large datasets (Anastassiadis et al., 2019). Due to the cross-sectional nature of the data, our preliminary conclusion of an altered pituitary maturation in patients who engage in NSSI may not be justified, and accordingly, as suggested earlier, studies with larger samples with repeated measures of the pituitary gland are urgently needed. Importantly, these studies must attempt to relate pituitary maturation to cortisol secretion. Finally, it is important to note that adolescence represents a time period of major hormonal changes (e.g., Rogol, 2010; Wong et al., 2014). Thus, in order to disentangle the suggested HPA axis specific changes in PGV maturation from those mediated by other pituitary hormones such as gonadotropin-releasing hormones, growth hormones and thyroid hormones, future studies need to carefully assess and control for these other important pituitary hormones as well.

4. Outlook: Child maltreatment, hypothalamic-pituitary-adrenal axis activity, and psychopathology

To summarize, mental illnesses are increasingly viewed as complex disorders of brain circuits, with both genetic predispositions and environmental factors influencing brain development and, consequently, the developmental trajectory of psychopathological symptoms. Proceeding from this developmental perspective, it is assumed that mental disorders may have their roots relatively early in life, that is, already in childhood and/or adolescence – i.e., during windows of heightened plasticity. One of the most recognized environmental risk factors for psychopathology in general is the experience of stress, and in particular the experience of chronic stress early in life. Among the various chronic stressors that can be distinguished, experiences of abuse and neglect, collectively referred to as child maltreatment, have been found to have particularly high associations with later disease risk, including mental disorders. According to the *biological embedding model*, such adverse experiences are assumed to cause changes in biological functioning, including changes in biological systems involved in stress and emotion regulation, which are thought to be maintained through processes such as epigenetic programming. These "biological scars", by potentially affecting physiology, cognition, emotional experiences, and behavior, may in turn critically influence the vulnerability to mental disorders over time. One essential system that not only appears to be involved in mediating the biological embedding of child maltreatment, but may also be altered in its own functioning in the long run, is the HPA axis. This neuroendocrine system, triggered by both the perception of stressors and circadian signals, is involved in the regulation of a plethora of physiological processes important for maintaining and restoring homeostasis (or allostasis). Accordingly, the association between child maltreatment and cortisol secretion – the main effector hormone of this axis – including various measures of HPA axis

activity (i.e., cortisol assessed in the context of the circadian rhythm, cortisol assessed in response to awakening, in response to the perception of a stressor, in response to pharmacological challenges, as well as cumulative measures of cortisol secretion) has been extensively studied, but with mostly inconsistent results obtained in the past. In support of the *biological embedding model*, the findings derived from the present thesis provide some preliminary evidence that the experience of child maltreatment may indeed be considered as one plausible etiological pathway to aberrant HPA axis activity, namely to a blunted cortisol stress response. Importantly, this adaptation appears to occur prior to, or independent of, the onset of mental illnesses and thus may represent an important risk factor for psychopathology. According to the so-called "attenuation hypothesis", a hypercortisolemic phase, which is typically observed during chronic/prolonged stress, may lead to a secondary, compensatory HPA axis downregulation over time. This biological adaptation, while protecting the body from various deleterious effects of cortisol excess, if biologically embedded during sensitive developmental periods, may interfere with the restoration of allostasis following the perception of future stressors, thus reflecting difficulties in the ability to physiologically cope with emotionally negative situations and potentially promoting allostatic load. There is indeed growing evidence linking a corresponding aberrant HPA axis stress response (specifically to psychosocial stressors) with the development of various stress-related psychopathological symptoms over time, including dysfunctional coping strategies such as NSSI. Importantly, however, the overall effects were small and the heterogeneity large, suggesting that in addition to methodological limitations as a possible explanation (e.g., inconsistent definition of child maltreatment, failure to follow best practice guidelines for cortisol assessment, different etiological pathways leading to the presentation of similar psychopathological symptoms, and the role of high inter-individual developmental variability), several moderators may be particularly important in determining who is most likely to develop a blunted cortisol stress response following the experience of child maltreatment or early life adversity in general. These include, for instance, the severity of the respective adverse experiences, the role of parental support, genetic variability, and the influence of current life stress, moderators that have not been adequately addressed to date. Thus, in order to advance our understanding of the biological embedding of adverse early life experiences – i.e., the (intra-individual) developmental trajectory between exposure to such experiences, the subsequent development of an aberrant HPA axis stress response (including its origin and precise biological consequences) and associated heightened vulnerability to stress, and the emergence of psychopathological symptoms – large scale longitudinal studies that repeatedly measure the variables of interest including the aforementioned moderators, are urgently needed. In addition, these studies need to address the various methodological issues that currently limit the available evidence in the field. A better understanding of the biological embedding of adverse early life experiences is also particularly important in order to be able to develop appropriate interventions to prevent or reverse the development of an altered HPA axis functioning, or to treat individuals with appropriate pharmacological and psychotherapeutic

interventions (i.e., skills-based interventions as found in the Dialectical Behavior Therapy (DBT)) when appropriate physiological vulnerabilities have already occurred.

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Statement of Authorship

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I hereby certify that this doctoral thesis has been composed by myself, and describes my own work, unless otherwise acknowledged in the text. All references and verbatim extracts have been quoted, and all sources of information have been specifically acknowledged. The work has not been accepted in any previous application for a degree. I am aware that in the case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me based on the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 36, of 5 September 1996, and Art. 69, of 7 June 2011.

Place, date: Bern, 13.05.2023   **Signature:**

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