Chapter 7
Consequences of Developmental Stress in Humans: Adversity Experienced During Childhood and Adolescence

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Abstract Early life stress is a term used to describe adversities which may occur during childhood and adolescence. The majority of human studies focus on negative outcomes resulting from early life stress. There is an emerging research field which aims to investigate possible positive outcomes of early life stress. In this chapter, human studies are reviewed with regard to both maladaptive and adaptive consequences of early life stress. Recent findings suggest that early life stress is associated with central nervous alterations, altered physiological stress responses, impaired cognitive functioning as well as an increased risk of developing behavior problems, and somatic and psychiatric illnesses. Early life stress may also result in posttraumatic growth (PTG) which describes changes in self-perception, interpersonal relationships, and worldview. A psychobiological stress model is proposed to integrate the findings.

7.1 Introduction

There is a growing body of literature reporting that early life stress during childhood and adolescence appear to have a negative impact on development and numerous health outcomes later in life. Periods of heightened brain plasticity mark developmental phases during which the brain is most vulnerable to stress. It is well known that exposure to adverse conditions during these critical sensitive phases in development may lead to long-term alterations in brain structures, various bodily functions (e.g., immunological or endocrinological), and behavior, which may facilitate the manifestation of disease.

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There is sufficient evidence that stress-responsive systems[1] play a mediating role in the association between stress exposure and various developmental or health consequences. Stress processing originates in specific brain regions that are responsible for the early perception and evaluation of potentially threatening or stressful features of the current situation. The outcome of such an evaluation may lead to the activation of the stress axes, the sympatho-adrenal-medullary (SAM) system and the hypothalamus–pituitary–adrenal (HPA) axis (for details, see Sect. 2 of Chap. 6). Briefly, the SAM system elicits the release of norepinephrine and epinephrine, both of which are involved in the "flight-or-fight" response. The HPA axis includes the paraventricular nucleus (PVN) in the hypothalamus which releases the corticotrophin-releasing hormone or factor (CRH or CRF, respectively) which in turn induces the secretion of the adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary gland into the blood stream. Finally, cortisol is secreted from the adrenal cortex, exerting its effects throughout the body (e.g., on metabolism, immune system, behavior, or cognition). Cortisol has counter-regulating effects on the HPA axis by inhibiting the further release of CRH and ACTH and thus acts as a negative feedback factor. The pulsatile secretion of cortisol follows a diurnal rhythm characterized by high morning levels and a decrease of cortisol levels during the course of the day. The cortisol awakening response (CAR), an important marker for cortisol regulation, describes the morning peak of cortisol levels measured 30 min after awakening and has been related to a number of negative health outcomes (Kudielka and Wust 2010). Thus, studying cortisol release during the morning and/or during the day constitutes a well-researched approach to study HPA axis *activity*. In human research, the most prominent and effective stressors to study HPA axis *reactivity* are (a) performing a cognitive task (e.g., giving a speech and/or solving a difficult arithmetic task) in the presence of an evaluating audience or (b) administration of pharmacological substances (pharmacological challenge test). The latter is used to study HPA axis regulation, particularly via activating the system's inherent feedback mechanisms (Ditzen et al. 2013). Pharmacological challenge tests are used to investigate how HPA axis activity is affected by temporary suppression due to administration of synthetic glucocorticoids (e.g., dexamethasone suppression test, DST), by stimulation due to administration of CRH or ACTH (CRH stimulation test, $ACTH_{1-24}$ stimulation test), or by a time-lagged combination of suppressing and stimulating substances (e.g., dexamethasone/corticotrophin-releasing hormone test, Dex/CRH test).

[1] *Stress-responsive systems* refer to various physiological systems that are activated in response to stress. The most prominent systems are the hypothalamus-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), particularly the sympatho-adrenal-medullary (SAM) system, the central nervous system, and the immune system. We introduce the term *stress axes*, which refer to the HPA axis and the ANS, since these well-studied stress-responsive systems are known to interact and partly regulate the other aforementioned stress-responsive systems.

Considering the amount of literature and the limited space of a book chapter, a selective overview of the literature on stress experienced during childhood and adolescence will be presented.[2] The overall goal of this chapter is to review the literature and give an overview of the current state of knowledge about possible short- and long-term consequences of stress occurring in childhood and adolescence (early life stress).

7.2 Stress During Childhood and Adolescence: Early Life Stress

We introduce the term *early life stress* which refers to stress that occurs during childhood and adolescence. Early life stress describes here a relatively heterogeneous concept which encompasses various adverse events that most people perceive as stressful and thus possibly lead to the activation of the above-mentioned stress-responsive systems. One source of early life stress constitutes childhood maltreatment which in turn can be divided into emotional abuse, physical abuse, sexual abuse, emotional neglect, or physical neglect. Growing up in an orphanage or institutional care provides a setting with possibly increased risk for neglect. One of the most extreme cases of neglect became public after the fall of the Ceausescu regime in Romania. Living conditions in institutional care during that time were characterized by deprivation of basic needs as well as emotional and physical neglect (most of the cited studies in this chapter have been conducted in Romanian orphans). These adverse living circumstances in institutions seem to be more likely under conditions of social poverty or under strict political regimes. Another source of early life stress may be the separation or loss of a parent or someone close. Finally, traumatic events such as natural disasters or war experiences are considered here as early life stress.

Children and adolescents might be particularly prone to stress since certain developmental stages (e.g., puberty) are characterized by various biological and hormonal changes. Early life stress during such sensitive periods may have consequences for biological outcomes, temperament and behavior, mental development, or general health later in life.

[2] A systematic literature search was conducted on databases PubMed and Google Scholar using a combination of the following keywords: stress brain, child(hood) maltreatment (outcome), maltreatment infant, early stress, child adversity health outcome(s), parental loss, and posttraumatic growth. The list of abstracts was reviewed with regard to the type of stress and outcome (neuroendocrine, behavioral, psychological, or health-related consequences). Only English-language, peer-reviewed original research papers were included. Additionally, the references of the papers and those of published review articles have been checked for further articles meeting our search criteria. Although we have tried to consider as many publications as possible, we are aware that the presented literature is not comprehensive.

In this chapter we present findings organized along the following outcomes:

- *Effects on the central nervous system (CNS)*. This includes alterations in brain structure or brain functions (indicated by volume or activity of certain brain regions) using neuroimaging methods. Since recent research has revealed important central nervous effects of the neuropeptide oxytocin in humans (e.g., interpersonal bonding, affiliation behavior, and stress reduction), we present preliminary findings for this hormone here.
- *Effects on the HPA axis.* Findings are separately presented for basal HPA axis activity (e.g., cortisol diurnal profile or CAR) and HPA axis reactivity in response to a psychological stressor or a pharmacological challenge test.
- *Effects on temperament and behavior*. Measurement of personality or temperament is often achieved through assessing the infant's attachment style, which describes how secure the bonding between infant and primary caregiver is. Negative behavior is usually operationalized as internalizing problems (withdrawal, somatic complaints, anxiety/depression) or externalizing problems (aggressive, delinquent behavior) which are thought to be disadvantageous manifestations of behavior.
- *Effects on cognitive functioning and academic performance.* Developmental tests and intelligent tests are used to measure executive functions (e.g., decision making, response control), attention, memory, verbal skills, reasoning, and general intellectual/academic performance.
- *Effects on somatic health*. Somatic health is measured either as perceived general health or as the occurrence of specific somatic illnesses (e.g., infectious disease).
- *Effects on psychological health*. Psychological health may be measured via assessing symptoms such as depression, anxiety, or suicidal thoughts, and via diagnosing clinical disorders, such as personality disorders, major depressive disorder, anxiety disorders, and substance abuse.

In general, the traditional research focus in this field lies on negative outcomes of stress. Therefore, the majority of findings present maladaptive consequences in this chapter. In the next paragraphs we will present a selection of findings related to these effects, with maladaptive outcomes measured during childhood and adolescence (2.1.), maladaptive outcomes measured during adulthood (2.2.), and adaptive outcomes in children, adolescents, and adults (2.3.).

7.2.1 Maladaptive Outcomes Measured During Childhood and Adolescence

Studying outcomes of early life stress in children and adolescents may provide valuable information about short-term effects, since adverse events may have taken place only recently. In the following, possible effects on the CNS, the HPA axis,

temperament and behavior, cognitive functioning and academic performance, somatic health, and psychological health are discussed.

Effects on the CNS. Several neuroimaging studies suggest that maltreated children and adolescents have small volumes of selected temporal regions (De Bellis et al. 2002) and the orbitofrontal cortex (Hanson et al. 2010), both of which are involved in executive and cognitive functions (e.g., reasoning, memory) and emotion regulation, as well as a small corpus callosum (Teicher et al. 2004), which connects both hemispheres. In another study, adopted orphans showed decreased activity in some of the aforementioned brain regions (specifically in the orbitofrontal cortex, temporal cortex, and brain stem) compared to same-aged children (7-11 years) with medically intractable partial epilepsy or to healthy adults (Chugani et al. 2001). De Bellis and colleagues, using both a cross-sectional (De Bellis et al. 2002) and a longitudinal approach (De Bellis et al. 2001), failed to show that childhood maltreatment was related to altered hippocampus or amygdala volumes, i.e., brain regions which are thought to be associated with emotion regulation and memory. In summary, there are some findings suggesting that early life stress may be associated with structural and functional alterations of brain regions that are related to cognitive and emotional functioning.

Effects on the HPA axis. There are numerous studies that investigated HPA axis activity (using basal cortisol levels) with regard to early life stress. One study showed that adoptees who spent more than 9 months in an orphanage displayed augmented daily cortisol levels, suggesting a generally enhanced HPA axis activity, compared to early adopted children and non-adopted children (Gunnar et al. 2001). Other studies focused on cortisol levels at a specific time of the day, mostly morning cortisol levels. One study found that neglected children (aged 3–31 months), still living with their birth parents, showed lower waking cortisol levels and significantly higher cortisol levels at bedtime compared to maltreated children who had been placed in foster care and compared to non-maltreated children (Bernard et al. 2010). In line with this finding, another study has found that sexually abused 5–7-year-old girls with posttraumatic stress disorder (PTSD) showed lower morning cortisol levels than control girls (King et al. 2001). In contrast to the aforementioned findings, sexually and physically abused children (mean age, 9.25 years) displayed higher morning cortisol levels than non-maltreated, emotionally maltreated, neglected, or physically abused subgroups who were studied during a day camp research program (Cicchetti and Rogosch 2001). A possible explanation for the inconsistent results in morning cortisol levels may be differences in age (range, 3 months–9 years) and time of morning sampling (range, 5–12 am) among these studies.

In addition to basal measurement, studying HPA axis reactivity specifically contributes to the understanding of underlying mechanisms of HPA axis (dys-)regulation. Healthy non-abused adolescents, aged 12–16 years, showed increased cortisol levels and a gradual flattening over time following an acute stress test, while nondepressed maltreated adolescents did not show such a pattern in cortisol levels (MacMillan et al. 2009). Another study found that the presence of any anxiety disorder, early life stress, or chronic stress during adolescence predicted peak cortisol

response to a psychological stress test, whereby the interaction of early life stress and chronic stress during adolescence was the best predictor of this stress response (Rao et al. 2008). Another study reported that intravenous CRH administration led to greater ACTH peaks in depressed abused children (age range, 7–13 years) than in depressed, non-abused children or children with no history of either depression or abuse, whereas no group differences were apparent for cortisol responses (Kaufman et al. 1997). These studies hint at an altered HPA axis response under challenge; however, the direction of this response appears to be unclear. It is conceivable that anxious or depressive symptoms partly determine the direction and extent of the stress response, leading to either hyper- or hyporeactivity of the HPA axis.

Effects on temperament and behavior. In institutions such as orphanages, caregivers have to provide care and supervise several children at the same time, which may make it difficult to meet the child's individual needs and to form selective interpersonal bonding between a primary caregiver and the child (Drury et al. 2011). As forming a child-caregiver bond may thus be limited in such an environment, several studies have examined attachment styles in children with a history of institutional care. One study in adoptees found insecure attachment styles and high occurrence of indiscriminately friendly behavior, as determined by parents' reports (Chisholm 1998). In another study, adoptees showed barely any attachment behavior in a strange situation procedure, which often serves as a tool to assess an infant's attachment style to a primary caregiver (Zeanah et al. 2005). These findings suggest that experiences of institutional care may be a risk factor for maladaptive temperament, as measured via attachment styles.

There is also some evidence that early life stress may be related to behavioral problems. For example, one study found that adolescents, who had been physically abused in early childhood, were more likely to have been arrested for violent and nonviolent offenses than non-abused adolescents (Lansford et al. 2007). Another study found gender differences among sexually abused adolescents, with boys showing more sexual risk behavior and delinquent behavior than girls (Chandy et al. 1996). A summer camp study, using a longitudinal design, found that maltreated children exhibited significantly greater externalizing behavior problems and more impaired affect and behavior regulation (lower levels of ego-resiliency and higher levels of ego-undercontrol[3]) than non-maltreated children (Kim et al. 2009). In another study, children with a history of institutional care were more likely to show externalized or internalized disorders than never-institutionalized children (Zeanah et al. 2009). Similarly, sexually abused children and adolescents had more externalizing and internalizing symptoms than those without a history of abuse in another study (Maikovich-Fong and Jaffee 2010). In line with these findings,

[3]Ego-control describes to the degree to which individuals express or inhibit their impulses. Individuals with ego-undercontrol are characterized by spontaneous, emotionally expressive behavior, and pursuit of immediate gratification of desires. Ego-resiliency refers to the individuals' ability to modulate these impulses adaptively in response to situational demands and affordances (Huey and Weisz 1997; Letzring et al. 2005).

maltreatment-related PTSD was associated with internalizing and externalizing symptoms in children and adolescents (De Bellis et al. 2002). Finally, parent–child aggression was found to be associated with conduct problems, attention problems, anxiety-withdrawal, and motor excess in boys, whereas girls only showed increased anxiety-withdrawal (Jouriles et al. 1987). Considering the available literature, early life stress seems to raise the risk for attachment disturbance and behavioral problems.

Effects on cognitive functioning and academic performance. Evidence for possible cognitive alterations in affective children or adolescents comes from studies examining academic performance or performance in standardized tests. One study found that physically abused adolescents were less likely to have graduated from high school than non-abused peers (Lansford et al. 2007). Studying gender differences in maltreated adolescents revealed that male adolescents with a history of sexual abuse tended to report performing below average and had a higher dropout risk than sexually abused female adolescents (Chandy et al. 1996). In another study, maltreated adolescents were found to score lower on tests assessing reading performance and reasoning compared to non-maltreated adolescents (14 years) (Mills et al. 2011). A longitudinal study found that children living in an orphanage (measured at the age of 42 and 54 months) showed more cognitive impairment (e.g., verbal abilities) than orphans who were placed in a foster family before the age of 31 months (Nelson et al. 2007). This same study suggested an age-associated beneficial effect of foster care, i.e., the younger the child at the time of entry in foster care, the more cognitive improvement due to foster care was found. In another study, 8-year-old children with any orphanage experiences in early life were found to perform worse on tests requiring visual memory and executive function (e.g., decision making or response control) compared to peers without a history of institutional care (Bos et al. 2009). Another study partly confirmed these findings, i.e., adoptees at the age of 8 years showed deficits in visual memory, attention, and associative learning measures but not in executive functions (Pollak et al. 2010). Mild impairment in verbal skills, impulsivity, and attention were reported for adoptees compared to never-institutionalized children with medically intractable partial epilepsy (Chugani et al. 2001). In a longitudinal study, non-maltreated children showed a pronounced decline in attention problems over the course of time, while in maltreated children attention problems slightly increased between age 4 and age 6 and then remained consistently on a high level until age 10 (Thompson and Tabone 2010). These findings clearly indicate that early life stress has negative effects on a child's cognitive development, as indicated by early school leaving and poor academic performance, as well as poor results in tests assessing memory, verbal skills, or attention.

Effects on somatic health. Several findings suggest that early life stress may negatively affect a child's health. One study showed that parents of maltreated 4–6-year-old children rated their child's health as poor more often and reported more serious illness when the child suffered from repeated adverse events than children without such adversities (Flaherty et al. 2006). In another study, childhood maltreatment

occurring before the age of 11 years was found to increase the risk of asthma by 73% and even double the risk of non-asthma cardiorespiratory and nonsexually transmitted infectious diseases in adolescents (Lanier et al. 2010). These studies indicate a heightened risk for diseases later in life due to early life stress.

Effects on psychological health. Apart from detrimental effects of early life stress on somatic health, the psyche may be affected as well. One study found that single and multiple negative early life events (e.g., loss of someone close, parental separation, serious conflicts) were associated with depression disorder in adolescents (Patton et al. 2003). In another study, the report of repeated childhood sexual abuse was associated with personality disorder in a dose–response manner, going together with higher scores on neuroticism and lower agreeableness (Moran et al. 2011). In a longitudinal study of children at the age between 4 and 10 years, maltreated children were found to show a steeper increase of anxiety/depression over time (Thompson and Tabone 2010). Other studies have confirmed this finding for high levels of depressive symptoms (Schilling et al. 2007), whereby girls seemed to be more affected (Chandy et al. 1996). High depression scores have been found in female adolescents who experienced a relatively mild life event in the past year (i.e., new stepbrother or stepsister; (step)brother or (step)sister leaving home and father losing his job) and who had at least one parent having a history of depression or anxiety (Silberg et al. 2001). These studies suggest that early life stress may enhance the risk for showing high levels of depression and personality disorders.

To summarize these findings, early life stress appears to be associated with decreased volumes of certain brain regions which are known to regulate memory and emotion (e.g., corpus callosum, orbitofrontal cortex, and temporal regions). Inconsistent results were reported for HPA axis activity and reactivity, a finding that may be partly explained by different study designs. Externalizing and internalizing problems, as well as antisocial behavior were predominately present in children and adolescents with early life stress. Also, early life stress was associated with early school leaving and impaired cognitive performance (e.g., memory, verbal skills, or attention). Children or adolescents, who experienced early life stress, seem to be at high risk for somatic and psychiatric conditions.

7.2.2 Maladaptive Outcomes Measured During Adulthood

Numerous studies investigated adults who retrospectively reported having experienced early life stress. These studies provide valuable information whether early life stress may have long-lasting effects on health later in life. In the following paragraphs, a selection of findings for the effect on the CNS, the HPA axis, temperament and behavior, cognitive functioning and academic performance, somatic health, and psychological health are presented.

Effects on CNS. Several neurocognitive studies have found small left hippocampus volumes, a brain structure which is associated with memory, in abused females with

depression (Vythilingam et al. 2002) or anxiety disorder (Stein et al. 1997). Adults with a history of early life stress were found to have small anterior cingulated cortex and caudate nuclei (located within basal ganglia), brain regions that are associated with attention and motor control, respectively (Cohen et al. 2006). In another study, PTSD women with childhood abuse showed increased affective responses to a trauma script as well as decreased activity in the anterior cingulated cortex and right hippocampus, both of which are related to memory (Bremner et al. 1999). These studies suggest that childhood maltreatment seems to be associated with decreased volume and activation of memory-related brain regions. Oxytocin is suggested to play an important role in bonding and attachment and thus may influence interpersonal relationships and interactions. One study found that early life stress was related to reduced plasma oxytocin levels (Opacka-Juffry and Mohiyeddini 2011). Similarly, another study found that reduced cerebrospinal fluid oxytocin levels were associated with childhood maltreatment, especially in females with severe childhood maltreatment (Heim et al. 2009). These two studies indicate that early life stress is related to decreased oxytocin levels later in life, which may be associated with maladaptive bonding and attachment in personal relationships.

Effects on the HPA axis. Measuring basal cortisol levels enables to study alterations in HPA axis activity in adults who have experienced early life stress. One study found that adults with a current anxiety disorder, who also had been severely maltreated before being adopted, demonstrated lower morning cortisol levels and a flattened diurnal cortisol secretion (van der Vegt et al. 2010). Another study found positive associations between severe childhood maltreatment and elevated cortisol levels throughout the day in women with either fibromyalgia or osteoarthritis (Nicolson et al. 2010). However, physically and psychologically healthy women, who experienced childhood maltreatment, did not differ in their diurnal cortisol pattern from those without such adverse experiences (Klaassens et al. 2009). The inconsistency in these findings for diurnal cortisol levels might be partly ascribed to the different samples (i.e., patient sample with an anxiety disorder, pain patients, and healthy subjects without a current somatic or psychiatric disorder). In contrast, a relatively consistent picture appears for the effect of early life stress on the CAR, which describes a rapid increase of cortisol concentrations within 30 min after awakening and is usually considered a valid index of an intact HPA axis regulation. A decreased CAR has been found in adults with chronic fatigue who have been maltreated during childhood (Heim et al. 2009), in adults who were severely maltreated before adoption (van der Vegt et al. 2009), or in adults who lost a parent before the age of 14 (Meinlschmidt and Heim 2005). Based on these findings, a preliminary conclusion can be drawn in that adults with childhood maltreatment experiences may show attenuated basal morning cortisol levels.

In addition, there is a variety of studies which investigated the impact of early life stress on HPA axis reactivity using various approaches. Studying the HPA axis response to psychological stress, females with a history of childhood abuse and current PTSD showed higher cortisol levels before, during, and immediately after exposure to a trauma script than abused women without current PTSD (Elzinga et al. 2003). Giving a speech about a controversial topic was used as a stressor in

another study, with the finding that adults with parental loss experiences before the age 16 showed increases of cortisol concentrations in response to a stress test in contrast to a control group (Luecken 1998). In another study, both abused women with and without current major depression showed increased ACTH responses to a psychological stress test compared to non-abused women (Heim et al. 2000). In the same study, only depressed women with a history of childhood abuse showed higher cortisol responses to the stressor than depressed women without childhood abuse and nondepressed women with or without childhood abuse experiences. In the same sample both the maximum ACTH and cortisol responses to a psychological stress test were predicted by the history of childhood abuse and the number of distinct types of abuse events (Heim et al. 2002). Another study found that adults, who retrospectively reported multiple adverse events, exhibited a smaller cortisol response to a psychological stress test than control subject; interestingly, this effect was more pronounced in male subjects (Elzinga et al. 2008). Lovallo et al. (2012) investigated whether early adverse life events (e.g., being mugged, threatened with a weapon, experiencing a robbery, sexual assault, or parental separation before age 15) have an impact on endocrine stress reactivity in adults without a psychiatric disorder. Adults who retrospectively reported more such adversities showed smaller cortisol responses to a psychological stressor. These findings provide some evidence that early life stress may be associated with altered HPA axis responses to psychological stressors.

Another approach to study HPA axis reactivity is using pharmacological challenge tests. Using the low-dose dexamethasone suppression test (DST), a test which is used to examine HPA axis negative feedback sensitivity, depressed women with childhood trauma were found to have lower cortisol and ACTH afternoon levels (super-suppression) compared to abused nondepressed women or non-abused healthy controls, whereas no difference was found when the test was conducted using the standard dose (Newport et al. 2004). The administration of CRH or ACTH stimulates the HPA axis with results in secretion of subsequent hormones of the HPA axis and thus is used to study the integrity of top-down HPA axis regulation. In one study, abused nondepressed women showed higher mean stimulated ACTH concentrations 5 and 30 min after the CRH stimulation test compared to healthy non-abused controls; in contrast, depressed women (regardless of the presence of history of childhood) showed lower CRH-stimulated ACTH levels than controls. In the same study both abused women with and without major depression demonstrated lower baseline and stimulated cortisol levels than control subjects (Heim et al. 2001). Further, the same sample underwent an $ACTH_{1–24}$ stimulation test, with the finding that abused females without depressive symptoms demonstrated decreased basal and stimulated cortisol concentrations, whereas abused depressed females had only lower baseline cortisol values compared to controls (Heim et al. 2001). The combined dexamethasone/corticotrophin-releasing hormone (Dex/CRH) test is a useful tool to study HPA axis sensitivity. One study found that abused men with current major depression demonstrated augmented ACTH and cortisol responses to the Dex/CRH test (Heim et al. 2008). Another study corroborated these increased cortisol levels in response to the Dex/CRH test in adults who

had lost a parent before the age of 18 years. However, no effect of parental loss was present for ACTH responses (Tyrka et al. 2008). In another study, adults with a history of childhood maltreatment exhibited nonsignificant decreased ACTH and cortisol responses to a Dex/CRH test after adjusting for potential confounders (age, menopausal stage, body mass index, use of contraceptives) (Klaassens et al. 2009). In contrast to the aforementioned findings for cortisol levels, Carpenter et al. (2009) found attenuated cortisol responses to the Dex/CRH test in adults who had been emotionally abused as a child. These contradicting results might be partly explained by the type or severity of early life stress, as well as by specific genetic factors. As for the latter, a protective CRHR1 receptor polymorphism in males has been found, i.e., maltreated men with this polymorphism showed low cortisol responses to the Dex/CRH test (Heim et al. 2009). These preliminary findings indicate generally low basal HPA axis activity, accompanied by altered HPA axis reactivity. Whether hyper- or hyporeactivity is predominant appears to be partly determined by the type of HPA axis stimulation, genetic factors, or comorbidity with a psychological disorder.

Effects on temperament and behavior. Using a longitudinal design, childhood maltreatment was found to be associated with internal and external problems in early adulthood (Silverman et al. 1996). One cross-sectional study found that adults, who were maltreated as child, were at high risk of showing antisocial behavior and conduct disorders (Nelson et al. 2002). This was corroborated in two longitudinal studies which found that young adults reporting early life stress, such as parental separation or childhood maltreatment, had an increased rate of antisocial behavior (Schilling et al. 2007; Thornberry et al. 2010). There is some evidence for genetic contributions that seem to moderate the association between childhood maltreatment and antisocial behavior. In particular, several studies found a moderating role of the polymorphism in the monoamine oxidase (MAO)-A gene, which encodes the activity of the enzyme MAO-A, which in turn metabolizes monoamines, i.e., neurotransmitters such as norepinephrine, serotonin, and dopamine. It was found that men who had a history of childhood maltreatment and a polymorphism associated with low MAO-A activity showed an increased risk for antisocial behavior compared to maltreated men with high MAO-A activity (Beach et al. 2010a, b; Caspi et al. 2002). These studies suggest that early life stress may increase the risk for behavioral problems in adulthood.

Effects on cognitive functioning and academic performance. One study showed that adults with a history of childhood abuse had greater verbal short-term memory deficits than controls but no difference was present in intelligence scores (Bremner et al. 1995). In accordance to this finding, two other studies found impaired memory, particularly affecting the verbal domain, in adults who reported childhood maltreatment, whereas no negative effect on attention or executive function (e.g., reasoning or planning abilities) was observed (Majer et al. 2010; Navalta et al. 2006). These studies indicate memory impairment in adults who experienced early life stress.

Effects on somatic health. Emotional abuse was found to be related to obesity in men but not in women (Gunstad et al. 2006). A representative survey found that

adults, who retrospectively reported childhood physical abuse, showed a higher risk for having a heart disease than non-abused adults (Fuller-Thomson et al. 2010). In another study, adults with a history of multiple adverse childhood experiences (such as abuse, domestic violence, criminal familial environment) were more likely to be hospitalized due to autoimmune disease compared to adults without such a history (Dube et al. 2009). One study found that women with a history of childhood sexual abuse were more likely to experience chronic fatigue, asthma, or cardiovascular problems than female controls, whereas physically abused women suffered more from chronic pain compared to controls (Romans et al. 2002). In accordance with the aforementioned finding, physically abused women were found to suffer more from chronic pelvic pain and chronic low-back pain, and women with severe sexual abuse during childhood reported chronic pelvic pain more often compared to controls (Lampe et al. 2003). Two studies provide some evidence for positive associations between childhood maltreatment experiences and heightened risk of chronic fatigue syndrome (Heim et al. 2009; Heim et al. 2006). Another study reported that emotional abuse or physical neglect raised the risk for chronic fatigue syndrome, irritable bowel syndrome, fibromyalgia, and arthritis (Tietjen et al. 2010). In summary, early life stress appears to increase the risk for negative health outcomes later in life.

Effects on psychological health. There are several studies which investigated the association between early life stress and the occurrence of psychological disorders based on clinical diagnoses according to international classification systems, such as the ICD-10 (WHO 2004) or the DSM-IV (APA 2000). For example, one epidemiological survey found that early life stress increased the risk for psychological disorders in adulthood, including affective, anxiety, or substance disorders (Fujiwara et al. 2011). Another study found that both childhood sexual or physical abuse was related to an increased risk for depression, PTSD, alcohol, or drug dependence (Silverman et al. 1996). Another study reported similar findings, with self-reported childhood sexual abuse being associated with depression, general anxiety disorder, panic disorder, alcohol, or drug dependence (Kendler et al. 2000). Children and adolescents (age range, 6–18 years) who had lost their father during the Kosovo War were more likely to show major depression, posttraumatic disorder, or panic disorder 10 years later compared to peers with similar war experiences but no father loss (Morina et al. 2011). Two other studies found more symptoms of personality disorders in adults who retrospectively reported childhood maltreatment compared to non-maltreated adults (Johnson et al. 1999; Tyrka et al. 2009). One study found that adults, who retrospectively reported childhood sexual abuse, were at high risk to develop depression (Kendler et al. 2004). Another study showed that depressive patients reported the loss of the mother before the age of 17 years more often than controls; this negative effect was not found for the loss of the father (Kunugi et al. 1995). Another study found that men with alcohol dependence did not differ from controls with regard to parental loss before the age of 16 (Furukawa et al. 1998).

Numerous studies operationalized psychological health by assessing psychological symptoms (e.g., depression or anxiety levels measured by questionnaires) or high-risk behavior (e.g., regular use of drugs), which do not meet fully the criteria

of psychological disorders. However, these psychological symptoms and risk behavior may give indications for psychological well-being or risk to develop a psychological disorder in the future. One cross-sectional study (Nelson et al. 2002) and two longitudinal studies (Schilling et al. 2007; Thornberry et al. 2010) found an increased rate of drug use in young adults when they had experienced early life stress. Thoughts and attempts of suicide can be seen as indicators for depression. Several studies found that the risk for suicide thoughts or attempts was dramatically increased in adults with a history of early life stress (Dube et al. 2001; Thornberry et al. 2010). A great number of studies give evidence that early life stress, in particular childhood maltreatment or parental loss, may be associated with increased levels of depression (Kiecolt-Glaser et al. 2011; Lampe et al. 2003; Nelson et al. 2002; Wingo et al. 2010), or both anxiety and depression (Handa et al. 2008; Heim et al. 2009; Heim et al. 2006; Nicolson et al. 2010; Tyrka et al. 2008). Summarizing these findings, early life stress seems to be associated with an increased risk for psychiatric disorders in adulthood.

To summarize the findings, early life stress may be associated with reduced volumes of memory-related brain regions (e.g., hippocampus). Adults, who retrospectively reported early life stress, appear to have decreased levels of oxytocin, which is known to be related to bonding. Low morning cortisol levels seem to be characteristic for adults with a history of early life stress. Early life stress may be associated with altered HPA axis responses to psychological stressors and to pharmacological challenge tests. Further, early life stress may be related to behavioral problems, such as antisocial behavior. The findings suggest that early life stress may influence negatively memory, particularly of verbal material. Adults with a history of early life stress may be more likely to suffer from negative somatic health outcomes (e.g., pain disorder, chronic fatigue) or negative psychological health outcomes (e.g., depression, anxiety, drug abuse, personality disorders) later in life.

7.2.3 Adaptive Outcomes Measured in Children, Adolescents, and Adults

The previous sections have delineated maladaptive outcomes of early life stress, which is the traditional focus in human research. Adaptive consequences of early life stress are often disregarded in human research. In the last years, however, researchers have started to investigate adaptive outcomes of developmental stress, which will be briefly summarized in the next paragraphs.

There are three concepts that may provide approaches to study adaptive consequences of early life stress: (a) resilience, (b) compensating factors to reduce negative effects of stress, and (c) posttraumatic growth (PTG); we present findings particularly for the latter concept, since PTG comes most closely to the idea of adaptive consequences.

Resilience in this context describes the individual's ability to develop in a normal range despite experienced early life stress (see also review, Feder et al. 2009). A resilient individual may have genetic dispositions (protective polymorphism; see

also conclusion) which protect the individual from negative consequences of adverse conditions. Also adaptive coping styles (e.g., cognitive reappraisal) and resilient personality factors (e.g., dispositional optimism) may characterize resilience in an individual.

Individuals who are vulnerable to stress and consequently are at high risk for maladaptive consequences due to early life stress may benefit from compensating factors. These include various types of social support (e.g., instrumental, emotional support) and a supportive social network which may buffer the stress impact (Ozbay et al. 2007). Interventions such as educational support, assistance in academic performance (tutoring, coaching), and public health programs may diminish developmental deficits and enable a "normal development" of the infant.

Finally, the concept of PTG proposes possible positive effects resulting from experiencing and overcoming an adverse event (see review, Meyerson et al. 2011). According to the theory of PTG, an adverse event (trauma) may change the individuals' concept of themselves, relationship to others, and life in general. The Posttraumatic Growth Inventory (PTGI) has been developed to assess PTG; there are separate versions for both children and adults (Kilmer et al. 2009; Tedeschi and Calhoun 1996). This scale comprises 5 domains, which may be changed due to trauma experience: (1) perception of self/personal strength (e.g., being stronger than individual thought), (2) relationship to others (e.g., closer relationship to family and friends), (3) appreciation of life (e.g., changing priorities), (4) new possibilities (e.g., new interests and goals), and (5) spiritual change (e.g., strengthening faith). There is some evidence that children who have experienced a traumatic event (e.g., injury or death of a loved one, natural disaster, or accident) report higher PTG scores than children without such trauma experiences (Alisic et al. 2008). The PTGI has been successfully administered in children and adults of various types of early life stress: cancer during childhood or adolescence (Barakat et al. 2006; Kamibeppu et al. 2010; Turner-Sack et al. 2012), serious or chronic illness in childhood (Devine et al. 2010), death of a close one (Ho et al. 2008; Wolchik et al. 2008), traffic accidents (Salter and Stallard 2004), childhood sexual abuse (Shakespeare-Finch and de Dassel 2009), terror exposure (Laufer et al. 2010; Levine et al. 2008; Levine et al. 2009), or exposure to natural disasters (Cryder et al. 2006; Hafstad et al. 2010; Kilmer and Gil-Rivas 2010; Yu et al. 2010).

This research trend contributes to the understanding of a comprehensive picture of early life stress and its consequences on the individual and may further provide applicable interventions and treatments for individuals who suffered from early life stress.

7.3 Integration and Interpretation of the Findings

The findings presented in this book chapter suggest that stress experienced during childhood or adolescence may have long-lasting consequences long after exposure to adversity has stopped. We propose a psychobiological stress model that is used to integrate and interpret some of these findings (Fig. 7.1).

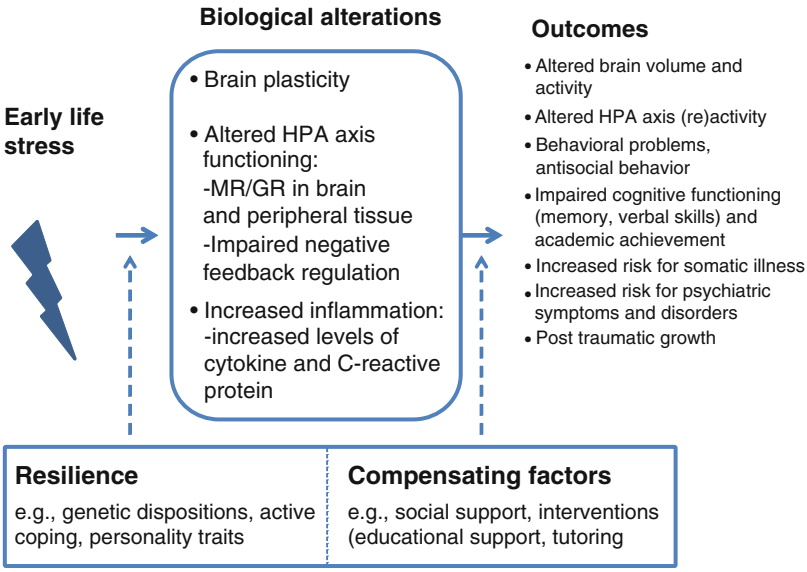

Fig. 7.1 Psychobiological model

It is established that the human brain is particularly sensitive to stress in early life due to the heightened brain plasticity during this vulnerable period. The HPA axis appears to be involved in such functional and structural brain alterations. Specifically, there are several brain regions with a particularly high density of glucocorticoid receptors (GR), e.g., hippocampus and prefrontal cortex, both of which regulate HPA axis activity by negative feedback mechanisms. Consequently, excessive cortisol secretion due to early life stress may result in persistent altered GR sensitivity in these brain regions. This in turn may lead to functional impairments, particularly when the individual is exposed to stress and thus to glucocorticoids. Impaired memory, which was found in both children and adults with a history of early life stress, may be related to such altered GR sensitivity of the memory-associated brain regions (e.g., hippocampus and prefrontal cortex). Animal models showed that glucocorticoid overexposure may have neurotoxic effects, particularly in the CA3 region of the hippocampus, which may explain decreased hippocampal volumes as the result of excessive stress.

Specifically, the findings summarized above suggest that early life stress may negatively affect HPA axis activity and reactivity. Heim and colleagues (Heim et al. 2008) hypothesized that early life stress may lead to the development of highly sensitive stress-responsive systems which is indicated by increased psychological and biological responses to adulthood stress, accompanied by alterations in HPA axis regulation. In particular, the authors suggest that increased ACTH secretion, as it has been observed in the literature, may be mediated by downregulation of pituitary CRH receptors and impaired negative feedback regulation of the HPA axis under stimulation.

Early life stress was found to negatively affect both somatic and psychological health which has been also largely demonstrated in studies using animal model (Cirulli et al. 2009; O'Mahony et al. 2009; Schmidt et al. 2011). There is sufficient evidence that diseases or psychological disorders are related to hypo- or hyperactivity of the HPA axis as a result of stress (Chrousos 2009). Since the stress axes and the immune system interact (e.g., cortisol has suppressive or stimulating effects on immune processes), dysregulation of the HPA axis may contribute to the development and maintenance of conditions in which the immune system plays an important pathophysiological role. There are a handful of studies which investigated the association between early life stress and inflammation, which is an approach to study immune activity. These studies found increased levels of inflammatory markers. For example, adults who had been maltreated as child showed higher basal interleukin-6 levels and higher tumor necrosis factor (TNF)-alpha levels than controls (Kiecolt-Glaser et al. 2011) as well as increased IL-6 responses to a psychological stressor (Carpenter et al. 2010), indicating increased inflammation. A longitudinal study found that childhood maltreatment was associated with increased C-reactive protein (CRP) levels in adults, indicating systemic inflammation (Danese et al. 2009). A persistent inflammation may increase the risk for developing diseases later in life; for example, high CRP levels appear to be related to cardiovascular diseases and high TNF-alpha levels to rheumatoid arthritis.

Besides the aforementioned negative outcomes of early life stress, there is also some evidence for adaptive consequences of stress. Some individuals report that the evaluation of themselves, relationships to others, and life in general has changed in a positive direction after the exposure of a traumatic event, which in essence describes the idea of PTG. Early life stress may thus force individuals to reappraise and reorganize general concept of themselves, their world, and the future. There is some evidence that expected maladaptive consequences of early life stress may be alleviated or even inhibited by an individual's protective factors (resilience) or compensating factors (e.g., social support), which have biological correlates and pathways (Feder et al. 2009). These protective and compensating factors may act as a moderating role in the association between early life stress and (mal)adaptive outcomes.

This psychobiological stress model proposes a biological link between stress and (mal)adaptive consequences. The brain plays a central role in this model. Both maladaptive and adaptive consequences may result from brain plasticity and active cognitive reappraisals.

7.4 Conclusion

This book chapter summarized the main findings of the last few decades of research on the impact of early life stress in humans. However, despite the relative abundance of studies, some questions which should be addressed in future studies remain. In the following, we want to give an outlook on current research and future directions by addressing still insufficiently studied research questions.

7.4.1 Underlying Biological Mechanisms for Associations Between Early Life Stress and Negative Outcomes

There is great evidence that early life stress has extensive negative effects on mind and body. These negative effects are probably partly mediated by alterations of the HPA axis, one of the most prominent and most studied stress-responsive systems. However, this mediation cannot explain all findings; thus, other stress-responsive systems and factors should be taken into account in order to understand the underlying mechanisms of how early life stress may lead to negative outcomes. To the best of our knowledge, the association between early life stress and the SAM system has been scarcely investigated. However, it is known that alteration of both the HPA axis and the SAM system may increase the risk for diseases (McEwen and Seeman 1999). Thus, further research is needed incorporating assessment of both the HPA axis and the SAM system. Another stress-responsive system, which is scarcely investigated with regard to early life stress, is the above-mentioned immune system. First studies, however, suggest that early life stress may be associated with enhanced inflammation, indicating an enhanced activity of the immune system. Clearly, the intricate relationships between stress axis and the immune system should be considered in future studies in order to further elucidate the detrimental effects of early life stress on both psychological and somatic health.

7.4.2 Risk and Protective Factors (Vulnerability and Resilience)

In general, the presented studies in this chapter suggest that early life stress may increase the likelihood or *risk* for negative outcomes, but not that early life stress per se inevitably leads to negative outcomes. It is conceivable that stress may play a triggering role, and that stress and other potential risk factors (vulnerability), but also protective factors (resilience) may be relevant in whether negative health outcomes manifest or not. There is some evidence from the literature for polymorphisms that might act as risk or protective factors. However, these alone cannot explain the variance of stress-related morbidity. We should not neglect the role of environmental risk and protective factors, e.g., social support may have a buffering effect and can be used as basis for intervention programs. Future studies are required to investigate interindividual differences by considering possible risk and protective factors. These vulnerability factors may help to identify high-risk individuals, who may benefit from prevention and intervention programs.

7.4.3 Epigenetics

There is some evidence that early life stress may interact with genetic predispositions for psychological conditions. For example, one study found that certain glucocorticoid receptor gene polymorphisms in interaction with occurrence of early life

stress may increase the risk of (recurrent) depression symptoms (Bet et al. 2009). The severity of depression was found to be influenced by an interaction of childhood maltreatment with a CRHR1 polymorphism (Bradley et al. 2008; Heim et al. 2009) or with a polymorphism associated with high MAO-A activity (Beach et al. 2010). A similar gene x environment interaction was found for PTSD symptoms, with the severity of PTSD symptoms being predicted by the FKBP5 polymorphism and childhood maltreatment (Binder et al. 2008). These polymorphisms are related to monoamine metabolism (e.g., catecholamine, serotonin) or glucocorticoid receptors. There is some evidence that these neurotransmitters (e.g., serotonin) and hormones (e.g., cortisol) may be at least partly involved in the development and manifestation of psychological conditions.

It is well established that the environment can alter gene activity; this can be seen by the extent of DNA methylation. The extent of DNA methylation in the promoter regions of genes regulates gene expression and thus the transcription activity of genes, i.e., the synthesis of gene products, mostly proteins. Protein synthesis is fundamental and essential for body functioning. Studies have shown that childhood abuse was associated with overall methylation at the SLC6A4 region (Beach et al. 2010) and methylation at the 5HTT promoter region (Beach et al. 2011); in these studies, the extent of methylation was suggested to influence the synthesis of the serotonin transporter, which in turn plays an important role in the pathophysiology of depression.

Another genetic marker, which appears to be influenced by environmental conditions, is the shortening of telomere length. As a marker of cellular aging, shortening of telomere length is suggested to be indicative for biological aging, and to be a risk factor for early onset of a variety of age-related diseases. Telomeres, i.e., repetitive DNA sequences at the end of chromosomes, shorten with age due to repetitive cell divisions. The shortening of telomeres appears to be promoted by unhealthy lifestyle (e.g., smoking) or stress and thus may constitute a possible stress-sensitive marker (Tyrka et al. 2010). One study found that the time reared in institutional care before adoption was associated with shorter telomere length in children aged 4–10 years, indicating telomere length shortening due to early life stress (Drury et al. 2011). Further evidence for telomere shortening due to early life stress was provided by several cross-sectional studies which were conducted in adult samples (Kananen et al. 2010; Kiecolt-Glaser et al. 2011; O'Donovan et al. 2011; Tyrka et al. 2010).

Clearly, these studies, still small in number, hold great promise of elucidating mechanisms that translate early life stress into negative outcomes later in life by studying biological systems on a molecular level.

7.4.4 The Type of Early Life Stress

In this book chapter we introduced early life stress as a concept that encompasses various stressful events, such as childhood maltreatment (i.e., forms of abuse and neglect), parental loss, and traumatic events (e.g., war). Thus, we cannot give any

differentiated conclusion about the impact of a single type of early life stress. It seems plausible that the type of early life stress may be a determining factor. To our knowledge, there is a lack of comparison studies, e.g., comparison among the type of childhood maltreatment (emotional neglect, physical neglect, emotional abuse, physical abuse, and sexual abuse). One reason for this lack of such studies might be that individuals often experienced several types (physical and sexual abuse); thus, a more precise analysis may not be possible. Other factors, such as the number, severity, and duration of such adverse events, possibly have additional effects and thus should be assessed in future studies.

In summary, stress throughout the entire life span seems to be associated with negative consequences for health and well-being. Future research is needed to explore possible risk factors, protective factors, and the underlying biological mechanisms between the association of stress and health. This research will hopefully advance the development of appropriate interventions.

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