Neurobiological Consequences of Early Life Stress

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Contents

7.1 Early-Life Stress – 176

7.2 Clinical Consequences of ELS – 178

7.3 Long-Term Biological Consequences of ELS – 178

7.4 Molecular Consequences of ELS: Epigenetic Programming and Telomere Biology – 181

7.5 Sensitive Periods for the Effects of ELS – 182

7.6 Fetal Programming of Health and Disease – 183

7.7 Intergenerational Transmission of the Effects of Early Life Stress – 184

7.8 Gene-Environment (GxE) Interactions – 185

7.9 Implications for Intervention – 186

7.10 Conclusion – 186

References – 187

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Trailer

The foundation for the development of a broad spectrum of stress-related disorders is laid early in development. Early-life stress, including prenatal stress exposure, increases individual susceptibility for the development of mental disorders and physical diseases across the lifespan. Persistent alterations in the brain as well as in endocrine, immune, and metabolic systems underlie this developmental programming of disease susceptibility. Thus, stress exposure in early developmental stages results in neurobiological traces or "scars" in the central nervous system that render individuals susceptible to developing a broad range of diseases throughout the lifespan. Recent evidence suggests that this risk can be passed on to subsequent generations. Genetic factors and the developmental timing of adverse exposures moderate the clinical and biological consequences of early-life stress as well as individual vulnerability to disease and course of disease. A better understanding of the neurobiological mechanisms that link exposure to early life stress with disease risk will allow for the identification of measurable parameters to help identify individuals at risk of disease and susceptibility to a specific intervention. A precise understanding of the processes of biological embedding of early life stress will further enable the development of mechanism-derived targets and time windows for interventions and prevention strategies.

Learning Objectives

This chapter summarizes current findings from human clinical studies investigating the mechanisms by which early life stress affects neurobiological systems, as well as regulatory outflow systems of the brain, and influences susceptibility for psychiatric disorders and a wide range or physical diseases. The reader will be introduced to the concept of developmental programming of disease vulnerability and neurobiological changes resulting from early-life stress.

7.1 Early-Life Stress

The foundation for health and disease is laid early in development. Early life stress (ELS) is one of the most potent and pervasive risk factors for the development of psychiatric disorders and predicts a broad spectrum of physical diseases and increased mortality across the lifespan (Gilbert et al. 2009; Grummitt et al. 2021). Early life stress involves adverse experiences during childhood, such as exposure to various forms of severe stressors, including parental loss, unstable family situations, inadequate parental care due to mental or physical illness, and poverty. The most salient form of ELS may arguably be maltreatment, which encompasses neglect of care or supervision (emotional and physical neglect) and emotional, physical, and sexual abuse in childhood.

Exposure to ELS is alarmingly common in our society. Globally, prevalence estimates for maltreatment range from 13% for sexual abuse to 36% for emotional abuse (Stoltenborgh et al. 2015).When other forms of ELS are considered, prevalence estimates rise to nearly 50% of children affected and various types of ELS often coexist (for an overview, see Heim et al. 2019).

Childhood Maltreatment

The Centers for Disease Control and Prevention (CDC) define childhood maltreatment as "any act or series of acts of commission (i.e., abuse) or omission (i.e., neglect) by a parent or other caregiver that results in harm, potential for harm, or threat of harm to a child". In this definition, harm to a child may not be the intended consequence of these acts, however, the act itself has to be deliberate and intentional (Leeb et al. 2008).

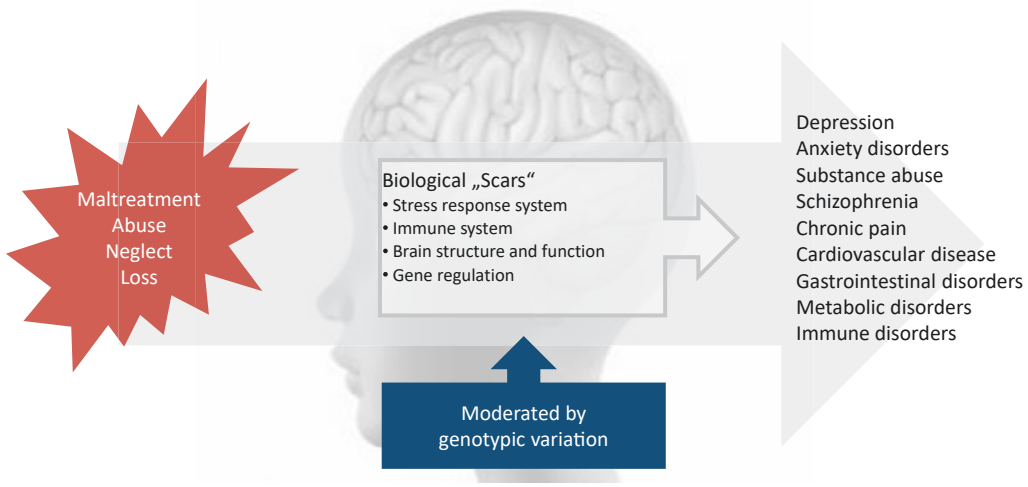


Fig. 7.1 ELS, biological effects and disease risk. (Reprinted from Heim et al. 2019)

Research demonstrates that ELS exerts pronounced effects on neural systems, as well endocrine, immune, and metabolic regulatory systems, that are fundamental to the organism's adaptation to stress. Changes in these systems that occur as a function of ELS may mediate increased risk for stress-related diseases (Fig. 7.1). The developing brain is particularly susceptible to the organizing effects of experiences. According to the concept of developmental programming, neural plasticity is particularly pronounced during early developmental periods (Lupien et al. 2009): During such times of heightened plasticity, positive and nurturing social-emotional experiences may be required for an optimal development of neural circuits that mediate adaptation to stress and emotional regulation, whereas any type of ELS occurring within such developmental periods may promote disruptions in the development of these circuits, leading to long-term "scars", which may result in maladaptive regulation upon further stress exposure an increased susceptibility for stress-related diseases across the lifespan.

Disease Vulnerability

An individual's susceptibility for developing disease across the lifespan. The extent of disease vulnerability may be dependent on whether the exposure occurs during critical periods of development during which ELS has a particularly strong and specific effect on the brain and its regulatory outflow systems. Vulnerability is dependent on interactions of ELS and genetic factors and such gene-environment interactions may be mediated by epigenetic programming (see Heim and Binder 2012).

The well-established link between ELS and increased risk for disease across the lifespan raises several questions: How does ELS exposure get "under the skin"? Which mechanisms mediate the increased long-term susceptibility to various stress-related diseases? Will each individual with a history of ELS develop some form of stress-related disease over the life course or do some individuals demonstrate resilience to the lasting conse-

quences of ELS? Advances from neuroscience and molecular biology research have provided compelling answers to these questions, which are summarized in the following sections.

7.2 Clinical Consequences of ELS

Clinical and epidemiological research demonstrates a robust and substantial increase in the risk for both psychiatric disorders and physical diseases following ELS exposure (for an overview see Heim and Binder 2012). A particularly strong association can be found for affective and anxiety disorders, including post-traumatic stress disorder (PTSD). Further, there are established dose-response relationships between childhood adversity and psychiatric disorders in adulthood (Edwards et al. 2003). Early life stress is not only associated with increased prevalence rates of these disorders, but also predicts earlier onset, chronic course, and greater severity of disease as well as poor treatment response (see Heim and Nemeroff 2001; Nanni et al. 2012). Moreover, ELS is a consistent risk factor for suicidality across disorders (see Heim and Binder 2012). In addition to its adverse effects on mental health, ELS is associated with markedly increased risk for chronic physical diseases, including cardiovascular, immune-related and respiratory diseases, diabetes and obesity, chronic pain, and reduced longevity (Felitti et al. 1998; Norman et al. 2012; Shonkoff et al. 2012). Individuals with a history of ELS often exhibit multiple comorbid psychiatric and physical disorders, suggesting the existence of an ELS-related core "lesion" across neural and peripheral regulatory systems that promotes maladaptation and disease.

7.3 Long-Term Biological Consequences of ELS

The precise mechanisms that mediate the detrimental effects of ELS on disease risk have been subject to basic and clinical investigation over the past decades. Lasting effects of ELS on the brain and its regulatory outflow systems, including the autonomic, endocrine, immune, and metabolic systems, may lead to increased sensitivity to stress and risk for a range of psychiatric and physical diseases. Studies in animal models involving maternal separation or natural variation of the quality of maternal care provide causal evidence that ELS leads to structural and functional changes in neural circuits that are involved in the mediation of stress responses, autonomic and neuroendocrine control, emotion regulation, and fear conditioning. These neurobiological changes promote exaggerated behavioral and physiological reactivity to stressors later in life (stress sensitization). For instance, adult rodents exposed to maternal separation or naturally occurring low maternal care in early life exhibit hyperactivity of the central stress-mediating neuropeptide corticotrophin releasing hormone (CRH) system and sensitization of the hypothalamic-pituitary-adrenal (HPA) axis as well as behavioral responses reminiscent of symptoms of depression and anxiety (see Heim and Binder 2012; Heim et al. 2019).

In accordance with findings from animal models, adult women with a history of ELS exhibit markedly increased pituitary-adrenal and autonomic responses to psychosocial laboratory stress, induced by the Trier Social Stress Test (TSST). This effect was particularly pronounced in abused women with concurrent major depression. Neuroendocrine alterations following ELS were demonstrated at multiple levels of stress regulation, including reduced

adrenal capacity and dysregulated negative feedback of the HPA axis due to relative glucocorticoid receptor resistance as measured with the dexamethasone/CRH challenge test. Furthermore, increased cerebrospinal fluid (CSF) concentrations of CRH and decreased CSF levels of the neuropeptide oxytocin were reported as a function of severity of ELS, suggesting that stress-mediating systems are upregulated as a consequence of ELS whereas stress-buffering neuropeptide systems are downregulated. Taken together, these findings suggest a sensitization of the endocrine and autonomic stress responses and a disturbed balance between stress-mediating and stress-protective neural systems after ELS exposure, converging into increased stress vulnerability (see Heim et al. 2008).

The neuroendocrine system is tightly linked to the immune system and systemic inflammation is one of the most replicated biological correlates of ELS. Adults exposed to ELS exhibit significantly increased plasma levels of interleukin-6 (IL-6) and C-reactive protein (CRP), particularly those with depression (Baumeister et al. 2016). Notably, studies in 12 year-old and 3- to 5-year-old children suggest that the effect of ELS on inflammation emerges already in childhood and in the immediate aftermath of exposure (Danese et al. 2011; Entringer et al. 2020). One potential pathway through which ELS can induce an increased release of these inflammatory mediators may involve the above-described dysfunction of the glucocorticoid receptor (GR), a key regulator of the immune response (see Raison et al. 2006). In addition, ELS is associated with metabolic dysregulation. Elevated inflammatory levels and cortisol secretion following ELS may lead to decreased sensitivity to insulin contributing to the development of metabolic disorders, such as type 2 diabetes or metabolic syndrome. Inflammatory processes and metabolic abnormalities may also promote atherosclerosis progression contributing to the development of cardiovascular disease (see Danese and McEwen 2012).

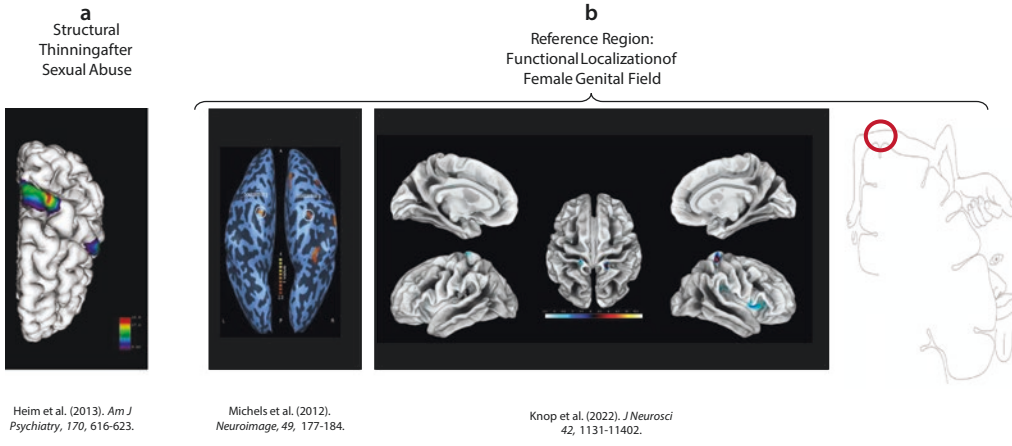
At the central nervous system level, exaggerated concentrations of cortisol or inflammatory cytokines may exert neurotoxic effects on brain structures that are implicated in stress and emotion regulation. During early developmental periods of pronounced plasticity, ELS may shape the development of these brain regions (Table 7.1). Volumetric alterations as a function of ELS have been shown specifically in cortical and subcortical regions that are particularly sensitive to glucocorticoid exposure and hence vulnerable the detrimental effects of stress, including the hippocampus (see Teicher et al. 2016). The hippocampus is critically involved in contextual aspects of fear conditioning and one of the most plastic central regions, exhibiting a high degree of synaptic reorganization and neurogenesis across the lifespan. With a high density of GRs, the hippocampus exerts an inhibitory control of hypothalamic CRH neurons. Several magnetic resonance imaging (MRI) studies in adults have demonstrated a small hippocampal volume in

Table 7.1 Brain changes in relation to early life stress experience

Structural Changes
• Smaller hippocampus
• Altered amygdala volume
• Smaller prefrontal cortex and anterior cingulate cortex
• Smaller cerebellum
• Reduced cortical thickness or volume in sensory processing areas (visual cortex, auditory cortex, somatosensory cortex)
• Reduced structural connectivity (corpus callosum, cingulum, fornix, fasciculus arcuatus, fasciculus uncinatus, fasciculus longitudinalis superior)
Functional Changes
• Increased reactivity of the amygdala to emotional stimuli (especially threat)
• Reduced activation in the striatum during the expectation of reward
• Reduced functional frontal-limbic connectivity

association with ELS (hippocampal atrophy), suggesting a dysfunctional inhibition of the stress response. Region-specific investigations of the hippocampus with high-resolution imaging demonstrate a pronounced decrease in volume in the CA3 region, the dentate gyrus and the left subiculum in ELS-exposed individuals (Teicher et al. 2012). Furthermore, structural and functional changes in cortico-limbic circuits have been reported as a function of ELS. The prefrontal cortex (PFC) is critically involved in executive functioning, regulation of goal-directed behavior, and impulse inhibition. The medial PFC is particularly relevant for emotion regulation via structural connections to the anterior cingulate cortex (ACC) and the amygdala. ELS has consistently been associated with volume loss in the PFC, including the medial PFC and ACC (see Heim et al. 2019). In addition, neuroimaging studies suggest structural and functional changes of the amygdala following ELS. The amygdala plays a key role in fear conditioning, emotion processing, as well as evaluating potentially threatening stimuli and eliciting an appropriate stress response. Whereas findings on volumetric alterations of the amygdala are inconsistent, functional MRI studies consistently demonstrate a sustained hyperactivity of the amygdala in response to emotionally threatening stimuli following ELS (Dannlowski et al. 2013). With the PFC exerting inhibitory and the amygdala exerting excitatory regulation of hypothalamic CRH neurons (Ulrich-Lai and Herman 2009), these findings may reflect a dysfunctional "top down" control of emotion regulation, fear conditioning, and stress responses that promotes disease risk.

Several studies suggest a specific impact of ELS on sensory representation areas implicated in the perception of the very nature of the abusive experience. Using whole mantle cortical thickness analysis in adults, we observed pronounced cortical thinning of the somatosensory genital field as a function of childhood sexual abuse. Emotional abuse was specifically associated with cortical thinning in the precuneus, a region that is relevant for self-awareness and self-evaluation, as well as thinning in the anterior cingulate cortex, which is relevant for emotional regulation (Heim et al. 2013; see ◘ Fig. 7.2). These findings suggest that experience-dependent plasticity leads to effects of ELS on sensory and associative



◘ **Fig. 7.2** Specific thinning of somatosensory genital field in adult women with childhood sexual abuse (**a**; Heim et al. 2013) and reference regions from sensory tactile functional imaging studies to localize the genital representation field (**b**; Michels et al. 2010; Knop et al. 2022)

processing areas in a highly region-specific manner. This specific cortical thinning in sensory processing areas may represent the most adaptive and protective response of the developing brain that may "shield" the child living under these conditions from the abusive experience, similar to sensory gating. In later life, these neurostructural changes may represent a direct biological substrate for behavioral disorders, such as sexual dysfunction. Of note, Teicher and colleagues report similar findings for other sensory modalities, including thinning of the visual cortex after witnessing domestic violence and thinning of the auditory cortex after verbal abuse (see Teicher et al. 2016).

7.4 Molecular Consequences of ELS: Epigenetic Programming and Telomere Biology

A major research question in the field of ELS research concerns the molecular effects by which early environmental exposures interact with genetic factors to produce a neurobiological phenotype with elevated vulnerability for stress and disease. In this context, epigenetic alterations as a mechanism underlying the biological embedding of the above-described stable physiologic and behavioral changes that result from ELS exposure have received much attention (Box: Epigenetic Programming, see Anacker et al. 2014).

Epigenetic Programming

The process by which the environment regulates DNA transcriptional activity without altering DNA sequence. Epigenetic changes are produced by DNA (de-) methylation, histone modifications, and non-coding RNAs (for an overview, see Jaenisch and Bird 2003).

Over the past decade, numerous studies have investigated whether exposure to ELS can leave persistent epigenetic marks in the genome, thereby altering gene expression and ultimately neurobiological substrates (Parade et al. 2021; Provençal and Binder 2015). Initial studies have typically employed a candidate gene approach, focusing on epigenetic variation in specific stress-relevant genes, including the GR gene, *NR3C1*, and *FKBP5*, a key modulator of glucocorticoid signaling. For instance, ELS has been associated with increased DNA methylation of the promoter region of *NR3C1* in the human postmortem hippocampus. This hypermethylation was associated with decreased NGFI-A transcription factor binding and reduced gene transcription (McGowan et al. 2009; Perroud et al. 2011). ELS has also been linked with DNA demethylation in functional glucocorticoid response elements of *FKBP5* in carriers of the "risk"-allele of a functional polymorphism within the *FKBP5* gene, resulting in an increased risk of developing affective disorders in adulthood (Klengel et al. 2013). More recently, research interest has shifted away from candidate gene approaches toward investigating epigenetic variation across the entire epigenome in a hypothesis-free design (Epigenome-Wide Association Studies, EWAS). EWAS have consistently demonstrated presence of methylation changes in individuals exposed to ELS (e.g., Cicchetti et al. 2016; O'Donnell et al. 2018), however, to date no clear patterns of functional enrichment within the epigenome-wide methylation profiles associated with ELS have emerged (Cecil et al. 2020; Parade et al. 2021). A recent study from our group suggests that epigenetic modifications associated with ELS may, in part, also reflect co-occurring concurrent adversities and prenatal exposures (Martins et al. 2021). Epigenetic marks can also be used to estimate a form of biological ageing that takes into account time-dependent changes in DNA methylation at specific sites in the genome. The difference between this epigenetic age and the chronological age can be interpreted as accelerated or decelerated biological

ageing. Our group recently observed accelerated epigenetic ageing in children with internalizing problems, but only if they had been exposed to ELS, whereas no acceleration of ageing was observed in children with internalizing disorder who had no history of ELS, suggesting that these molecular alterations may already be present shortly after the exposure and are associated with health status (Dammering et al. 2021).

Cellular ageing is another molecular process and form of biological ageing that has the potential to mediate the ELS-associated increased risk of developing both physical and mental health problems across the lifespan. Cellular ageing is a function of the integrity of telomeres, DNA-protein complexes at the end of chromosomes promoting chromosomal stability (Box: Telomere Biology). Telomeres shorten with each cell replication cycle until a critical limit is reached and the cell enters a state of senescence or undergoes apoptosis. Telomere length can be maintained by the enzyme telomerase, however, in most somatic tissues, telomerase levels and activity are very low so that telomeres cannot be maintained indefinitely. Thus, telomere length can serve as a biomarker for biological ageing and time until senescence and research suggests that it may also be a risk marker for a variety of age-related diseases (e.g., cancer, hypertension) as well as shorter lifespan (Price et al. 2013).

Telomere Biology

A system that plays a central role in maintaining the integrity of the genome and the cell. Telomere biology refers to the structure and function of two related entities: telomeres, a complex of non-coding double-stranded repeats of guanine-rich DNA sequences and the shelterin protein structures that serve to protect the ends of chromosomes, as well as the enzyme telomerase, a ribonucleoprotein that adds telomeric DNA to the ends of chromosomes and thus elongates and maintains telomeres (for an overview, see Entringer et al. 2018).

In addition to chronological age, telomere length is also influenced by a wide range of environmental and behavioral factors, including stress. Chronic psychological stress, such as ELS, may shape the biochemical milieu of the cellular environment, promoting conditions of inflammation and oxidative stress which can lead to telomere damage (Barnes et al. 2019). The telomere system has been shown to play an important role in the development of depression and other psychiatric disorders (Ridout et al. 2016). As such, reduced telomere length and/or telomerase activity may be underlying, in part, the association between ELS and adverse mental and physical health outcomes (see Entringer et al. 2018).

In the last decade, numerous studies have provided evidence linking ELS with reduced telomere length (see meta-analysis by Ridout et al. 2018). The developmental timing of ELS exposure appears to influence the size of the effect, with adversity earlier in development showing greater negative associations with telomere length (Ridout et al. 2018). These findings are consistent with the neurobiological findings in that they suggest that early childhood seems to be a particularly sensitive period in which stress exposure can exert long-lasting effects on various systems, including the telomere system.

7.5 Sensitive Periods for the Effects of ELS

The above-referenced findings give rise to the question as to whether or not there are sensitive periods during human childhood, where the brain is particularly sensitive to the environment, including the effects of ELS. Of note, one important factor that max contribute to variability of the outcomes of ELS between individuals may depend on the developmental timing of the ELS exposure within childhood. In other words, there may exist discrete sensitive peri-

ods during development, during which adverse exposures may be specifically detrimental, leading to longterm change. Little is known to date about such circumscribed time windows for the effects of ELS. Teicher and colleagues have conducted statistical analyses to identify sensitive periods for the effects of ELS on brain regional development. They report that the amygdala is particularly sensitive to the effects of abuse at the age of around 10 years, whereas the hippocampus has heightened sensitivity at an earlier age and the prefrontal cortex seems to be particularly amenable around puberty (see Teicher et al. 2016). Whether or not such temporally differential effects of ELS on brain regions are associated with specific symptom constellations remains poorly understood. A precise identification of sensitive periods for the effects of ELS may enable the development of timing-specific interventions that make use of sensitive periods to induce positive change with lasting effects. Further, a precise understanding of the mechanisms that determine the opening and closing of sensitive time windows of developmental plasticity may have therapeutic benefit, enabling the development of novel pharmacological targets for augmenting effects of psychotherapy by increasing plasticity. Of note, rodent models of maternal separation or naturally occurring low care typically focus on the first 2 weeks of life, which developmentally corresponds to fetal life in humans. Hence, it is conceivable that prenatal stress has profound impact on adult health and adaptation in humans, as discussed next.

7.6 Fetal Programming of Health and Disease

While most research has been conducted on ELS occurring postnatally, the intrauterine period of life represents another sensitive developmental window during which stress exposure can have long-term or even permanent consequences for health and disease susceptibility (Box: Fetal Programming; for an overview see Entringer et al. 2015).

Fetal Programming

The concept of fetal programming describes the process by which the embryo/fetus seeks, receives, and responds to signals from the gestational environment to incorporate this information into its development. The concept is based on the assumption that the rapid and foundational nature of developmental processes occurring during intrauterine life render them particularly vulnerable to environmental perturbations with lifelong consequences for disease susceptibility (see Entringer et al. 2015; Gluckman and Hanson 2004). The research field has its origins in a set of epidemiological studies, demonstrating that a person's birth weight is associated with the risk for cardiovascular disease, as well as a variety of other conditions, including depression, obesity, and diabetes, later in life (see Wadhwa et al. 2009). In this context, birth weight is assumed to reflect the developmental environment in the womb, which, in interaction with the genetic make-up, elicits context-dependent and long-term adaptations in cells, tissues, organ systems and homeostatic set points of the developing embryo/fetus.

In recent years, an impressive body of research has collected evidence suggesting that maternal psychosocial stress and emotional state during pregnancy may affect child neurodevelopment as well as social-emotional and cognitive development and thus may increase risk for a variety of adverse physical and mental health outcomes, including mood disorders, attention problems, asthma, and obesity (Entringer et al. 2015; Lautarescu et al. 2020; Madigan et al. 2018). Since there are no direct vascular or neural connections between the maternal and fetal compartments all exchange of signals and communication is mediated by biological processes via the placenta. Stress-related biological processes appear to play a role as key sensors, transducers and effectors of maternal stress on the developing fetus. It is important to note that these stress-related biological mediators participate directly or indirectly in the process of phenotypic specification of the brain and other organ sys-

tems and should not be considered as developmental disruptors.

Several studies characterize alterations in brain structure and function in association with exposure to maternal stress-related biological mediators. For instance, elevated maternal cortisol concentrations have been associated with amygdala volume, microstructure and connectivity in newborns and children, with consequences for internalizing and affective problems (Buss et al. 2012; Graham et al. 2019). The pro-inflammatory cytokine interleukin-6 (IL-6) is another potential stress-related biological mediator of environmental conditions with an important role in fetal brain development. Several studies support a link between maternal IL-6 concentrations and offspring amygdala volume, structural and functional connectivity as well as connectivity within and between networks involved in sensory processing and higher order cognition (see Heim et al. 2019).

Maternal cortisol concentrations during pregnancy have also been repeatedly associated with offspring body composition and adiposity (Entringer et al. 2017; Van Dijk et al. 2012), suggesting that cortisol may also be involved in the prenatal programming of metabolism. Alterations in metabolic function appear to be present very early in postnatal life as demonstrated by one study showing that cortisol production particularly during the third trimester of pregnancy was associated with a greater change in infant percent body fat from 1 to 6 months assessed with Dual-energy X-ray absorptiometry imaging (Entringer et al. 2017).

Furthermore, prenatal stress exposure seems to have an effect on the child's telomere length. Maternal psychosocial stress during pregnancy has been associated with shortened offspring telomeres in young adulthood and in the newborn period, whereas maternal psychological resiliency during pregnancy has been linked to increased newborn telomere length (for an overview, see Heim et al. 2019; Verner et al. 2021). The effects of maternal stress on fetal telomere biology may be mediated by alterations in gestational biology, including increased cortisol concentrations and a higher pro-inflammatory milieu (Bosquet Enlow et al. 2019; Lazarides et al. 2019). The initial telomere length at birth may have lifelong implications for telomere biology and health, the precise relationship of which remains to be explored.

Taken together, this evidence suggests that in utero exposure to maternal psychosocial stress may confer increased long-term risk of a range of negative health outcomes mediated by adaptations in organ systems during intrauterine development in response to stress-related biological signals. The presence of alterations in brain structure and function and in body composition in association with maternal biological mediators of stress so close to birth provides compelling evidence for a programming effect of the gestational environment that is independent of postnatal environmental influences.

7.7 Intergenerational Transmission of the Effects of Early Life Stress

Over the last decade, the notion that the deleterious consequences of ELS may be transmitted across generations has received increasing attention. A steadily growing body of studies have explored the effects of ELS exposure in the parental generation on neurodevelopmental outcomes in the offspring generation and observed many of the same sequelae that are well-established consequences of ELS in exposed individuals (Box: Intergenerational Transmission, Buss et al. 2017; Moog et al. 2022).

Empirical evidence points to an increased risk for a range of behavioral and emotional problems, including internalizing and externalizing problems, conduct disorder, self-

regulation difficulties, and anxiety disorders as well as neurodevelopmental disorders, including autism and attention-deficit hyperactivity disorder in children of mothers who experienced ELS. In addition, maternal ELS is associated with an increased offspring risk of developing physical health problems and risk factors, including asthma, allergy and obesity (see Moog et al. 2022). As in the directly exposed generation, structural and functional alterations in the brain as well as dysregulations in autonomic, endocrine and immune system may be underlying these mental and physical health problems. We showed that infants of mothers with experiences of ELS had less cortical gray matter, which contributed to an overall lower brain volume compared to infants of mothers without ELS (Moog et al. 2018).

Intergenerational Transmission

The contribution of parental experiences and exposures (e.g., of early life stress) in shaping the development and phenotype of the offspring.

The mechanisms underlying the intergenerational transmission of ELS effects have not been fully clarified. One potential mechanism that has been investigated mainly in animal models is epigenetic inheritance. The term epigenetic inheritance refers to germline transmission of epigenetic information between generations independent of the DNA sequence, either through direct transfer of epigenetic marks or through reconstruction and reestablishment of germline epigenetic alterations in the zygote. As reviewed in ▶ Sect. 7.4, ELS exposure has been associated with persistent epigenetic alterations in certain tissues, including the germline in humans (Provençal and Binder 2015; Roberts et al. 2018). However, while epigenetic transmission of paternal ELS has been demonstrated in animal models (Gapp et al. 2020), conclusive evidence for the existence of epigenetic inheritance in humans is still lacking. Another pathway that has been debated is based on the observation that ELS-related physiological dysregulations in the stress, immune and metabolic systems may be carried forward into pregnancy and thus affect child health outcomes via a fetal programming mechanism (see ▶ Sect. 7.6; for an overview see Moog et al. 2022). Lastly, a caregiving environment characterized by maternal psychopathology or difficulty providing high-quality parenting due to ELS-related personal, social and socio-economic constraints is another important potential mediator of the intergenerational transmission of ELS (Plant et al. 2018).

7.8 Gene-Environment (GxE) Interactions

While the increase in disease risk in association with ELS is substantial and alarming, not all children exposed to ELS go on to develop stress-related disorders, even if additional stressors occur later in life. Genetic factors likely play a moderating role in the extent to which environmental conditions, such as ELS exposure, may program neurobiological structures and functions as well as in the individual susceptibility versus resilience to developing stress-related disorders. A variety of studies have identified candidate genes in stress-regulatory systems that moderate the link between ELS and risk for depression and other disorders, including the CRH receptor 1 (*CRHR1*), GR (*NR3C1*), the GR-regulating FK506 binding protein 5 (*FKBP5*), serotonin transporter (*SLC6A4*), brain-derived neurotrophic factor (*BDNF*), and oxytocin receptor (*OXTR*) genes (for an overview, see Heim and Binder 2012). Notably, most functional polymorphisms in these genes that confer risk for depression in combination with ELS are associated with GR resistance

or enhanced stress hormone system activity. However, there has been increasing awareness that multiple gene variants likely work together to shape disease risk, such that in recent years the field has moved towards employing polygenic approaches. Polygenic risk scores incorporate the contributions of many common genetic variants and are derived from genome-wide association studies (for an overview, see Halldorsdottir and Binder 2017). For instance, a polygenic risk factor for major depressive disorder has been demonstrated to moderate the association between ELS and depression (Peyrot et al. 2014). In the future, a deeper and comprehensive understanding of GxE interactions is critically important to identify cases that are vulnerable to the pathogenic effects of ELS and require preventive intervention. Genetic markers may also be used to develop more targeted treatments, which will be discussed in the following section.

7.9 Implications for Intervention

Research findings on ELS as a risk factor for a wide range of diseases, as reviewed in this chapter, have the potential to inform the development of novel intervention strategies that target different aspects of biological embedding, disease manifestation and transmission of disease risk across generations (see Heim et al. 2019). Results from our studies demonstrating neurobiological differences and differential responses to drug or psychotherapy as a function of ELS suggest that developmental factors should be included in individual treatment decisions for patients with affective disorders. The development of algorithms based on biomarkers, genetic factors and symptom constellations could lead to personalized interventions as a form of precision medicine in the field of psychiatry. However, we propose that it is even more efficient to take advantage of the high levels of plasticity during early development and intervene before the clinical manifestation of disease to counteract, reverse or compensate biological "scars" of ELS. These interventions target the underlying mechanisms rather than symptoms and may involve "top down" compensatory regulation of the altered neural and physiological systems (e.g., via psychotherapeutic interventions starting as soon as possible after the exposure) or "bottom up" approaches directly counteracting biological embedding effects of ELS (e.g., FKBP51 antagonists). Furthermore, a better understanding of the molecular mechanisms that determine sensitive periods of brain development may enable the development of entirely novel treatment approaches that restore such a state of increased plasticity in order to reverse the programming effects of ELS (Bavelier et al. 2010). It is important to note, however, that biological alterations may not be detrimental per se but can represent adaptations that confer short-term benefits to help the system function under conditions characterized by ELS. Our research on the intergenerational transmission of ELS-related risk suggest that interventions during pregnancy that target gestational physiology, stress reduction, trauma coping and different forms of social and personal constraints that can be consequences of ELS-exposure could minimize the intergenerational effects on the offspring.

7.10 Conclusion

In sum, ELS is a profound and nonspecific risk factor for a wide range of diseases. Exposure to ELS during sensitive developmental periods, including the prenatal period, appears to lead to immediate processes of biological embedding. This biological embedding of ELS may involve epigenetic modifications in stress-regulatory genes, with subsequent dysregulation of

endocrine and immune stress response systems, metabolic dysregulation, structural and functional changes in brain regions regulating stress and emotion, as well as accelerated biological ageing. These physiological alterations may lead to manifestation of adverse mental and physical health outcomes, depending also on the presence of additional stressors later in life as well as genetic factors. The phenotypic consequences of ELS may be transmitted into the next generation, thereby multiplying the number of affected individuals. Existing and future research will inform novel approaches that make use of developmental plasticity in order to promote optimal development, health, and longevity in all children.

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