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REVIEW ARTICLE

Epigenetic Programming Effects of Early Life Stress: A Dual-Activation Hypothesis

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Abstract: Epigenetic processes during early brain development can function as 'developmental switches' that contribute to the stability of long-term effects of early environmental influences by programming central feedback mechanisms of the HPA axis and other neural networks. In this thematic review, we summarize accumulated evidence for a dual-activation of stress-related and sensory networks underlying the epigenetic programming effects of early life stress. We discuss findings indicating epigenetic programming of stress-related genes with impact on HPA axis function, the interaction of epigenetic mechanisms with neural activity in stress-related neural networks, epigenetic effects of glucocorticoid exposure, and the impact of stress on sensory development. Based on these findings, we propose that the combined activation of stress-related neural networks and stressor-specific sensory networks leads to both neural and hormonal priming of the epigenetic machinery, which sensitizes these networks for developmental programming effects. This allows stressor-specific adaptations later in life, but may also lead to functional mal-adaptations, depending on timing and intensity of the stressor. Finally, we discuss methodological and clinical implications of the dual-activation hypothesis. We emphasize that, in addition to modifications in stress-related networks, we need to account for functional modifications in sensory networks and their epigenetic underpinnings to elucidate the long-term effects of early life stress.

Keywords: Neuroepigenetics, Sensory development, HPA axis, Critical period, Bdnf, Mecp2.

1. INTRODUCTION

Epidemiological and clinical data shows that Early Life Stress (ELS) affects later stress responsivity, emotion regulation, and cognitive function as well as lifetime vulnerability to psychopathology [1-6]. Especially, severe psychosocial stress in childhood, characterized by sexual or physical abuse, neglect, or loss, is associated with increased vulnerability to major depression, anxiety disorders, and Post-Traumatic Stress Disorder (PTSD) [7-15]. The association between ELS and increased long-term vulnerability for stress-related psychopathologies is at least in part mediated by persistent changes in the endocrine response to stress [16-19] and its central regulation [14]. In addition, ELS has been repeatedly associated with morphological changes in brain regions involved in stress regulation. Findings include a smaller hippocampus (in women) [20-22], reduced medial prefrontal cortical volume [23], reduced right orbitofrontal cortical volume [24] and reduced right amygdala volume (in women with PTSD) [25]. Moreover, the effects of ELS on the hypothalamic-pituitary-adrenal (HPA) axis, the major endocrine response system to stress, and brain structure and function are well established in animal models. Research in rodents using a maternal stress and/or maternal separation paradigm showed consistently that pre- and postnatal stress results in elevated HPA axis activity as well as structural and functional changes in neural networks in the brain regions involved in neuroendocrine control, vigilance, and emotion regulation [19, 26-34].

Epigenetic modifications in neural networks likely contribute to the life-long consequences of early life stress on mental and physical health [13, 33]. Epigenetic mechanisms are able to form relatively stable molecular adaptations of the chromatin. They are sensitive to environmental factors including psychosocial stress and affect gene transcription. This makes them the ideal candidates for the observed programming effects. However, it is still unclear how stress exposure early in life interacts with the epigenetic machinery in neural networks to program developmental trajectories.

The existing reviews discussing epigenetic programming effects of early life stress clearly point towards the heterogeneity of findings, which complicates identification of molecular mechanisms [33, 35, 36]. Differences across studies have been explained by differences in stressor, time-point of exposure, the intensity of exposure and species specificity [33, 37]. These reviews focus on the mechanism through which ELS impacts the stress system and how this leads to epigenetic programming effects at stress-related genes. Here, we ask whether the observed vulnerabilities, especially those related to cognitive function and psychopathology, solely

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result from modifications in stress-related networks, or whether parallel epigenetic modifications in sensory networks may also contribute to the long-term effects of ELS. Sensory systems function as primary mediating systems between the perception of a stressor and the stress response. They also interact with the functional organization of neural networks underlying the development of higher cognitive functions [38]. Emerging evidence suggests that the effects of ELS on brain development extend to sensory systems [39]. Moreover, the stress system participates in early fine-tuning processes of sensory networks necessary for sensory and cognitive development [40, 41]. We propose that the underlying neuroepigenetic pathways established in early sensory development contribute to the long-term effects of ELS. Our 'dual-activation hypothesis' states that concerted activity in both central regulatory networks of the HPA axis and developing sensory networks leads to the establishment and consolidation of epigenetic modifications which underlie the long-lasting programming effects of environmental stressors.

This thematic review is based on a systematic search in Pubmed, PsycINFO, Psycarticles, and Psyndex plus using combinations of the following key words: 'epigenetics', 'DNA methylation', 'histone modification', 'stress', 'early life stress', 'HPA axis', 'glucocorticoids', 'cortisol', 'corticosterone', 'Gr', 'Fkbp5', 'Crf', 'Avp', 'sensory development', 'sensory networks', 'hearing', 'vision'. We discuss only those findings in the review, which concern core features of the dual-activation hypothesis. This includes ELS induced epigenetic programming of stress-related genes with impact on HPA axis function (see 3), the interaction of epigenetic mechanisms with neural activity in stress-related neural networks (see 4), epigenetic effects of glucocorticoid exposure (see 5), and the impact of stress on sensory development (see 6).

2. NEUROEPIGENETICS: DEFINITION AND FUNCTIONAL CONTEXTS

Molecular epigenetics is defined as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" [42]. However, the heritability criterion is not useful for neuroepigenetic studies concerned with epigenetic modifications in nondividing neurons [43]. Accordingly, Day & Sweatt define neuroepigenetics as a potential subfield of epigenetics that deals with the unique mechanisms and processes allowing dynamic experience-dependent regulation of the epigenome in nondividing cells of the nervous system, along with the traditionally described developmental epigenetic processes involved in neuronal differentiation and cell-fate determination [43-45].

At the same time, Iles warns that a broad understanding of epigenetic mechanisms can lead to an unrealistic 'hype' of epigenetics in the study of brain development, development of behavior, and psychopathologies [46]. A broad definition would confuse transient changes in gene expression related to neural activity with long-term epigenetic modifications. To avoid confusion, we distinguish epigenetic mechanisms in neuronal cells according to their functional context. We differentiate structural (on the maintenance of genomic structure oriented) epigenetic mechanisms, synaptic epigenetic mechanisms, and developmental epigenetic mechanisms [38] (see Box 1). The distinction between transient mechanisms involved in short-term synaptic adaptations and long-term epigenetic programming mechanisms with developmental impact is indispensable in the context of ELS.

Box 1 - Functional differentiation of neuroepigenetic mechanisms

Structural epigenetic mechanisms: Mechanisms that maintain the genomic structure in neuronal cells, *e.g.* genomic repair mechanisms, mechanisms that maintain low expression levels of pro-apoptotic genes or cell-type specific gene expression patterns.

Synaptic epigenetic mechanisms: Mechanisms that regulate the gene expression underlying acute synaptic activity as well as *short-term* adaptations of synaptic plasticity and function.

Developmental epigenetic mechanisms: Mechanisms that contribute to the establishment and consolidation of *long-term* differentiation in structure (neuronal cell type, morphology) and function (synaptic sensitivity, plasticity) of neuronal cells, *e.g.* differentiation of neural stem cells, enduring changes in dendrite growth, long-term changes in neuronal plasticity.

To identify developmental epigenetic mechanisms in contrast to synaptic epigenetic mechanisms, we need to demonstrate the relative stability of epigenetic modifications and impact on developmental trajectories. This requires longitudinal studies and experimental settings, which allow measuring epigenetic modifications at a minimum of two time-points. In addition, identified epigenetic mechanisms must be linked to structural and/or functional changes in neural networks. Here, focusing on critical/sensitive periods of neural network formation or reconsolidation is the most fruitful starting point to link epigenetic modifications with developmental trajectories. Finally, developmental epigenetic mechanisms may be the result of "Systems Heritability" (Day & Sweatt [43]), that means transient epigenetic mechanisms in one brain area may induce long-lasting epigenetic modifications in another brain area *via* neural activity. For the study of developmental epigenetic mechanisms, as in the case of ELS programming effects, we, therefore, need to analyze not only modifications in primary target systems, *e.g.* the stress system but also in interconnected neural networks, *e.g.* the sensory systems as well as those for cognitive and emotional processing.

Accordingly, with the dual-activation hypothesis, we state that epigenetic programming effects following ELS result from parallel activation and interplay of sensory and stress-related networks in critical developmental periods of neural development. This dual-activation facilitates the establishment and maintenance of epigenetic modifications constituting divergent developmental trajectories and thus functioning as developmental epigenetic mechanisms

3. EPIGENETIC PROGRAMMING OF THE HPA AXIS FOLLOWING ELS

Epigenetic modifications represent a plausible pathway by which early experiences are integrated into the molecular

regulation of adult hormonal responses and behavior. A variety of animal studies demonstrated that differences in stress responsivity and behavior following ELS are associated with epigenetic differences at stress-related genes including those coding for the glucocorticoid receptor *(Gr)*, the neuropeptide arginine vasopressin *(Avp)*, the corticotropin-releasing factor *(Crf)*, and the FK506 binding protein 5 *(Fkbp5)* [19, 47-49]. For some of the findings, corresponding results could be found in human tissue (in brain tissue: [50, 51]; in blood: [52-54]; in saliva [55]). Taken together, results point towards a combination of common, species-specific, sex-specific, and stressor-specific regulatory mechanisms, which seem to be sensitive to timing, quality, and intensity of the stressor [33, 13]. In the following, we exemplarily discuss findings, which indicate epigenetic programming effects of stress-related genes *Gr, Avp, Crf,* and *Fkbp5* in the hippocampus and the hypothalamus, two brain regions functionally involved in the central regulation of the HPA axis. These findings indicate that the epigenetic regulation of the HPA axis contributes to the long-term programming effects. However, the findings also show that epigenetic regulation of the HPA axis likely results *via* several parallel pathways.

3.1. DNA Methylation Changes at the *Gr* in Hippocampus and PVN

Several studies found differences in DNA methylation in the promoter region of the *Gr* following ELS. Pioneer studies by Meaney and colleagues in Long-Evans rats discovered an epigenetic programming effect of ELS at the *Gr* in the hippocampus stably affecting HPA axis function and behavior [26, 56-58]. Low levels of maternal licking and grooming (LG) during early life increased HPA axis responsivity to stress. This was associated with persistent DNA hypermethylation at specific CpG dinucleotides within the hippocampal *Gr* exon 1_7 promotor and increased histone acetylation facilitating binding of the transcription factor nerve growth factor-inducible protein A (Ngfia), which increased *Gr* expression [56]. In two human post-mortem studies, the same group found increased DNA methylation at the promoter of the *Gr* in hippocampus tissue of suicide completers with a history of childhood maltreatment compared to suicide completers without such a history [50, 51]. This included the exon 1_F, the human orthologue of the exon 1_7 in rats. In contrast, a study using a different maternal stress paradigm and a different species of rats did not find changes in the DNA methylation of the *Gr* exon 1_7 promoter region in the hippocampus [27].

Of note, in a later analysis, Meaney and colleagues identified that the level of 5-hydroxymethylcytosine (5hmc) of the *Gr* exon 1_7 promotor was three times higher in the hippocampus of low compared with high LG offspring [59]. The bisulfite sequencing method used in the study by Weaver *et al.* [56] to detect DNA methylation does not differentiate between 5hmc and 5-methylcytosine (5mc) [49]. While 5mc repeatedly associated with long-term repression of gene expression [60], 5hmc is the first oxidative product in active demethylation of 5mc by the ten-eleven translocation family of proteins [61]. In the CNS, the functional role of 5hmc is still unclear. First studies link 5hmC to DNA de-methylation in memory formation [62] and to the regulation of neuroplasticity genes in the hippocampus in response to acute stress [63].

Bockmühl *et al.* investigated in mice whether ELS programs DNA methylation and gene expression of the *Gr* in the paraventricular nucleus (PVN) of the hypothalamus [64]. Although they found no differences in the proximal *Gr* promotor including the mouse orthologue of the rat exon 1_7, they found hypermethylation at CpG sites in the shore region of a more distal CpG dense island in the *Gr* promotor. At one of these CpG sites, hypermethylation was robustly maintained over three months. In addition, they report an increase in overall hypermethylation and age-related increases in *Gr* mRNA transcripts in the PVN in ELS mice indicating a functional role of this more distal shore region of the *Gr* promotor in *Gr* regulation across the lifespan. In contrast, an earlier study stressing pregnant mice found increased DNA methylation at the mouse orthologue of the rat exon 1_7 in the hypothalamus of the adult male offspring associated with a heightened HPA axis response to acute stress [65].

These exemplary results support the notion that ELS has a long-lasting impact on HPA axis responsivity *via* DNA methylation of the promoter region of the *Gr* in brain regions involved in stress-regulation, especially in the hippocampus and the hypothalamic PVN. The loci of modified DNA methylation at the *Gr* and the effects on expression vary across species and brain regions. Some of the studies also found that ELS affects the overall level of DNA methylation [50, 51, 64], which represents a broad and unspecific epigenetic modification. Such general epigenetic modifications may be detectable in peripheral tissue and, thus, candidates for potential biomarkers. For example, Radtke *et al.* found that the interaction between childhood maltreatment and *Gr* methylation in lymphocytes strongly correlated with an increased vulnerability to psychopathology [66]. However, as Palma-Gudiel *et al.* point out, the heterogeneity in stressors and targets in DNA methylation analysis of the *Gr* make it difficult to integrate the existing findings in a coherent functional model [37].

3.2. DNA Methylation Changes at *Avp* and *Crf* in the Hypothalamus

Further genes involved in the regulation of the stress system showing epigenetic modifications due to ELS include *Avp* and *Crf* in the hypothalamic PVN. In mice, maternal separation induced sustained life-long expression of hypothalamic *Avp* in the parvocellular subpopulation of neurons in the PVN due to reduced levels of DNA methylation at CpG sites in the enhancer region of *Avp*. This was associated with increased corticosterone secretion, heightened endocrine responsiveness to stress and altered feedback inhibition of the HPA axis [67]. In subsequent studies, Murgatroyd *et al.* identified that the neural activation due to ELS led to phosphorylation of methyl-CpG binding protein 2 (Mecp2), and that this resulted in a reduced ability of Mecp2 to bind to the enhancer of *Avp* and recruit DNA methyltransferases. This then led to DNA hypomethylation at this particular genomic site, which further inhibits transcriptional repression and gene silencing [68]. Overall, the mechanism described by Murgatroyd *et al.* represents one example of synaptic activation of epigenetic programming effects following ELS.

A study stressing pregnant mice, which found increased DNA methylation at the GR promoter in the hypothalamus of male offspring also found hypomethylation at CpG sites of the corticotropin-releasing factor (*Crf*) promoter region in the hypothalamus [65]. Rice *et al.* observed decreased mRNA expression of *Crf* in chronically stressed immature mice [69]. McIlwrick *et al.* compared mouse lines selected for HPA axis reactivity and report decreased mRNA expression of *Crf* in the PVN and increased *Crf* expression in the dorsal hippocampus of mice with high HPA axis reactivity exposed to ELS [70]. McIlwrick *et al.* conclude that during the hypo-responsive period of the HPA axis early in development, the HPA axis is not able to downregulate the abnormally high levels of corticosterone induced by ELS in HPA axis hyper-responsive individuals. The abnormally high levels of corticosterone then set of an epigenetic programming cascade that modulates lifetime HPA axis sensitivity [70]. In contrast, Bockmühl *et al.* found no differences between neither ELS mice nor ELS mice exposed to chronic unpredictable stress and controls in hypothalamic *Crf* expression [64]. In chicken, postnatal heat conditioning led to a resilient or sensitized response of the thermo-regulation system, depending on the ambient temperature during conditioning, and this was associated with changes in the expression level of *Crf* mRNA in the PVN after a subsequent heat challenge one week later [41].

These heterogeneous findings show that, in addition to species, stressor, and timing specific variation, epigenetic modifications targeting *Crf* expression may not only generally affect the stress response but also function as stressor-specific fine-tuning mechanism. In the case of heat conditioning in chicken, the stressor-specific modifications also contain information about the stressor quality - *e.g.* low or cold ambient temperature - allowing for a highly adaptive response later in life. Here, ELS is not only associated with a general adaptation of the stress response but also with stressor-specific fine-tuning mechanisms reflecting the physical properties of the stressor.

3.3. DNA Methylation Changes at *Fkbp5* in Blood, Hippocampus, and Hypothalamus

Another target of interest in the study of epigenetic programming effects following ELS is *Fkbp5*. Fkbp5 impacts the stress response *via* an indirect regulation of Gr sensitivity [71, 72]. Genetic variation in *Fkbp5* as well as changes in *Fkbp5* mRNA expression and DNA methylation have been associated with extreme trauma [73], vulnerability to PTSD [54], and chronic stress [74]. Yehuda *et al.* even reported tentative evidence of transgenerational effects of differential DNA methylation at the *Fkbp5* intron 7 in blood cells of Holocaust survivors and their offspring compared to controls, possibly indicating a long-term programming effect across generations [73]. Also in blood cells, Klengel *et al.* found reduced DNA methylation at CpGs associated with glucocorticoid response elements in the intron 7 of *Fkbp5* in *Fkbp5 rs1360780 AG/AA* allele carriers with a history of child abuse compared to controls [54]. They validated this finding in hippocampal progenitor cells, and found that the same CpGs in intron 7 of *Fkbp5* showed strongest DNA methylation after treatment with dexamethasone [54]. In contrast, McIlwrick *et al.* observed reduced baseline mRNA expression levels of *Fkbp5* in the PVN of adult HPA hyper-responsive mice that were exposed to ELS compared to controls, but no differences in other brain areas [70].

In sum, individuals exposed to ELS show diverse patterns of DNA methylation at stress-related genes in stress-regulating brain areas (hippocampus and hypothalamus) associated with heightened HPA axis reactivity later in life. This indicates an epigenetic programming mechanism in stress-related neural networks during a critical period of stress response development (developmental window) [75, 76]. Lifetime stability of epigenetic changes, type of stress response, and behavioral patterns, together with the time-dependence of the induction - early in life - indicate an evolutionary and developmental function of the underlying mechanisms. Programming effects seem to result from several parallel pathways including synaptic activation (see 4) and hormonal activation *via* the global effects of glucocorticoids on the epigenetic machinery (see 5). Accordingly, the epigenetic programming effects seem to result from a combination of general epigenetic modifications, such as overall DNA methylation, and stressor, species, and tissue-specific modifications. Modifications even may partly contain information of the stressor's physical properties [41], pointing towards a role as stressor-specific fine-tuning mechanism. The pathways through which ELS affects epigenetic mechanisms in neural networks are still investigated. With our dual-activation hypothesis we state that such highly adaptive, stressor-specific modifications likely depend on additional activation mechanisms based on the sensorial quality of the stressor and that these interact with the stress system.

4. ACTIVITY INDUCED EPIGENETIC MODIFICATIONS IN NEURAL NETWORKS

In neurons, epigenetic mechanisms regulate the differentiation of neuronal stem cells into neurons, astrocytes, and oligodendrocytes [77-79]. However, some of the enzymatic processes, which regulate epigenetic mechanisms of neuron development, are interrelated with enzymatic mechanisms that establish and maintain synaptic function [80, 81]. This indicates a possible epigenetic fine-tuning mechanism in neurogenesis sensitive to neuronal activity. In addition, neurons undergo significant epigenetic modifications during post-natal brain development [82], and some of these can be induced by synaptic activity [83-86]. Chromatin modifications are involved in the regulation of axon and dendrite growth [87], and DNA demethylation is discussed as activity-dependent mechanism of adult neurogenesis [80]. Together these findings indicate that epigenetic mechanisms function as mediators, which coordinate neural and genetic activity in the developing brain by modifying the spatial and biochemical structure of DNA binding sites and their reactivity to transcription factors.

Epigenetic modifications also contribute to the molecular underpinnings of neural plasticity and neural network formation [88, 89]. For example, neuronal diversity, resulting from activity-dependent spatiotemporal differentiation, is associated with epigenomic differences [90]. DNA methylation and histone modifications facilitate and maintain synaptic plasticity and function [88, 91], *e.g. via* differential methylation of *Bdnf* promoter regions [92]. Initial studies point to an

additional role for RNA interference, the interaction of micro RNA molecules with DNA, messenger RNA, or enzymes regulating protein synthesis, in synaptic plasticity [93]. Furthermore, epigenetic mechanisms sensitive to synaptic signals, and especially the interplay of histone modifications and DNA de/methylation, seem to function as potential molecular underpinnings of memory formation [45, 94-96]. First studies revealed a role of DNA methylation and demethylation as well as histone modifications in memory formation by affecting several neuroplasticity genes [97-103]. Thus, synaptic activity is one pathway through which epigenetic modifications are induced in neural networks.

In the context of ELS, the best described mechanism for a synaptic induced epigenetic modification is the programming of stress-related genes and HPA axis function, most importantly *Avp* in the hypothalamic PVN and *Crf* in the hippocampus as well as the proopiomelanocortin *(Pomc)* gene in the pituitary gland, *via* the Mecp2 pathway [67, 68, 104]. Neural activity following ELS induces Mecp2 (S241) phosphorylation [68]. This specific type of phosphorylation is associated with reduced binding of Mecp2 to the DNA at the enhancer region of *Avp* in the PVN. The lack of Mecp2 facilitates DNA demethylation due to decreased recruitment of DNA methyltransferases (Dnmts) during development and subsequently increased transcriptional activity of *Avp* in the long-term. Zimmerman *et al.* report a similar mechanism for the reduced Mecp2 binding at the promoter region of *Crf* in the hippocampus [104]. Remarkably, the effect was highly specific in timing (early in life), neural circuit, and gene loci; for example, neither *Crf* in the PVN nor *Avp* in the hippocampus were similarly affected [104]. This points towards a highly specific coordination of neural activity and expression of stress-related genes on the epigenetic level. The example of the Mecp2 pathway indicates that such coordination when taking place during critical periods of neural network formation and methylome reconfiguration, can result in long-term epigenetic programming.

The stress sensitivity of Mecp2 even seems to have transgenerational effects. Franklin *et al.* report, among other epigenetic modifications, an increase of *Mecp2* DNA methylation and a decrease of mRNA expression in the cortex of the offspring of mice exposed to a maternal separation and maternal stress paradigm [28]. Mecp2 is critically involved in activity-dependent neuronal plasticity and transcription in the developing brain [60], and the loss of its ability to recognize DNA methylation and repress transcription in mutations of *Mecp2* has been identified to cause Rett syndrome [105]. Also, a role of Mecp2 phosphorylation in learning processes is discussed [104], with first results pointing in this direction [106]. Hereby, different forms of Mecp2 phosphorylation have been reported to be associated not only with demethylation and enhanced transcription but also increased binding of Mecp2 to the DNA, increased methylation, and enduring transcriptional repression [104]. Consequently, Zimmermann *et al.* discuss Mecp2 as general epigenetic programming protein linking neural activity with DNA de-/methylation and changes in gene transcription [104].

Another pathway could involve the epigenetic regulation of the brain-derived neurotrophic factor (Bdnf), since *Bdnf* gene expression seems to be affected by ELS. Rats reared in hostile postnatal environment showed hypermethylation and reduced expression of *Bdnf* in the prefrontal cortex [107]. In a prenatal stress paradigm, the offspring of stressed rat dams showed decreased *Bdnf* expression in the amygdala and hippocampus and increased DNA methylation at *Bdnf* exon IV [108]. This finding was also observed in an ELS paradigm using caregiver maltreatment during infancy. Female but not male rats showed increased levels of DNA methylation at the *Bdnf* promoter exon IV in the ventral hippocampus and amygdala [109]. A study in chicken showed that dynamic changes of DNA methylation are involved in the regulation of *Bdnf* expression during postnatal thermotolerance acquisition [110, 111]. In a follow-up study, Kisliouk and Meiri found dynamic changes in H3K27 di-methylation (me2) levels in the hypothalamus including the promoter of *Bdnf* following postnatal heat conditioning [112]. Also, chickens exposed to fasting stress at 3-days-of-age showed modified histone methylation (di- and tri-methylation) at lysine 27 of histone 3 (H3K27) in a promoter region of *Bdnf,* and these were associated with corresponding changes in *Bdnf* expression levels [113]. In general, epigenetic regulation of *Bdnf* has been linked to neuroplasticity and function [98], and has been reported to interact with neural activity [114]. In a mouse model, over-expression of *Bdnf* prevented stress-induced reductions of dendritic branching in the hippocampus [115]. In addition, Bdnf seems to reverse reduced excitability in hippocampal neurons induced by stress levels of corticosterone [116, 117], and additional activation of neuronal activity in a stressful situation increases Bdnf synthesis, probably to buffer Bdnf degradation caused by stress [118].

Moreover, epigenetic programming *via* Mecp2 and Bdnf pathways following ELS is likely interconnected. An early study by Martinowich *et al.* demonstrated that neuronal depolarization demethylates the *Bdnf* promoter *via* the release of the Mecp2 repressor complex and increases *Bdnf* expression [119]. Li *et al.* reported that activity-dependent Bdnf release is reduced in the hippocampus of Mecp2 negative mutant mice compared to controls [120], and Su *et al.* showed in a rat model of depression that Mecp2 controls Bdnf expression in the hippocampus *via* interactions with micro RNA-132 [121].

According to our dual-activation hypothesis, these synaptic induced epigenetic modifications in stress-related neural networks contribute to the long-lasting effects of ELS. However, we suggest that the observed effects result from the interaction of synaptic induced modifications with epigenetic programming effects due to glucocorticoid exposure.

5. EPIGENETIC EFFECTS OF GLUCOCORTICOID EXPOSURE

In the case of ELS, the existing evidence indicates that activity-induced modifications act in concert with hormonal epigenetic programming. Together they function as 'developmental switch' by establishing long-lasting epigenetic modifications during critical developmental periods. For example, sex differences support a hormonal influence on epigenetic programming effects through ELS. They indicate that sex-specific hormonal signatures in the brain modulate the hormonal effect of glucocorticoids. Mueller and Bale

observed in mice that prenatal stress early in gestation increased long-term HPA axis sensitivity in male but not female offspring, and this was accompanied by decreased DNA methylation in the promoter region of *Gr* and *Crf* as well as higher *Gr* and *Crf* expression in the hypothalamus [65]. Doherty *et al.* reported an increase in global DNA methylation and decrease in genome-wide hydroxymethylation in the dorsal hippocampus and amygdala of the adolescent male, but not female rats exposed to repeated caregiver maltreatment [109]. Furthermore, the critical periods during which the stress response has been shown to be most sensitive for epigenetic programming effects - namely prenatal development, early childhood, and adolescence - are characterized by developmental relevant hormonal changes [36].

Glucocorticoids have a major effect on organ maturation during embryonic development. Especially their ability to accelerate lung development is well studied and glucocorticoids are used as ante- as well as postnatal treatment in cases of preterm labor [122]. Other organ systems, including the liver, pancreas, kidney, and heart show similar effects under glucocorticoid treatment [123]. These maturation processes mainly result in developmental changes of gene transcription and protein synthesis, *e.g.* of the synthesis of surfactant proteins in the lung. First studies show that this is accompanied by functional relevant modifications of DNA methylation [124, 125]. Thus, glucocorticoids seem to have an organizational role during organ development, probably mediated through developmental epigenetic mechanisms. The impact of ELS on epigenetic mechanisms could in part mimic such an effect of glucocorticoids during organ maturation. Possible is either a global effect of glucocorticoids with a subsequent indirect impact on the expression of stress-related (*Crf, Avp, Fkbp5*) and other genes, or a target-specific interaction. For both mechanisms, first evidence is accumulating.

5.1. Genome-wide Effects of Glucocorticoids

Some of the findings in ELS studies already point towards a global effect of glucocorticoids on epigenetic mechanisms, reporting genome-wide differential DNA hyper- and hypomethylation in human blood and brain tissue of individuals with a history of ELS [51, 126]. Mychasiuk *et al.* found global DNA hypomethylation in the hippocampus and frontal cortex of Long-Evans rats exposed to strong prenatal stress and DNA hypermethylation in the hippocampus of rats exposed to mild prenatal stress [127]. They also found sex differences in DNA methylation for the mild prenatal stress group in the frontal cortex, with males showing DNA hypermethylation and no effects in females compared to controls indicating hormonal buffering of this effect [127]. Mechanistically, Dnmt1, a methyltransferase enzyme involved in maintaining DNA methylation, could mediate a global impact of glucocorticoids. Yang *et al.* observed a dose-dependent decrease of *Dnmt1* expression in pituitary adenoma cells (cell line AtT-20) following dexamethasone treatment as well as a similar decrease in the hippocampus of corticosterone-treated mice [128]. Furthermore, ELS seems to affect histone modifiers actively involved in histone modifications. In a mouse model of ELS (maternal separation), Pusalkar *et al.* found a significant decrease of the expression of histone acetyltransferases (HAT), histone lysine methyltransferases, and histone deacetylases (Hdacs) in the medial prefrontal cortex [129]. Some of these modifications persisted over 15 months, thus indicating a relatively stable mechanism.

5.2. Target-specific Effects of Glucocorticoids

A considerable number of genes are directly affected by glucocorticoids. In the context of ELS, Bockmühl *et al.* report that corticosterone injections in ELS mice led to increased transcription of GC-responsive genes, such as *Fkbp5*, *Dusp1*, and *Sgk1* [64]. Especially *Fkbp5* seems to be involved in the differential regulation of *Gr* expression following ELS as well as chronic stress. Accordingly, Lee *et al.* showed that glucocorticoid administration persistently decreased DNA methylation and increased transcription of *Fkbp5* in brain and blood cells of mice [130, 131]. Yang *et al.* observed decreased DNA methylation of the intronic enhancer region of *Fkbp5* in the dentate gyrus compared to whole hippocampal tissue in mice treated with glucocorticoids [128].

Posttranslational interactions of glucocorticoids may also contribute to the long-term effects of ELS. For example, glucocorticoids interact in several ways with Bdnf, with interactions depending on brain area and presence of other hormones or neurotransmitters. In cortical neurons, glucocorticoids interact with Bdnf through tyrosine kinase receptor TrkB. Binding of glucocorticoids to Grs downregulates phospholipase Cγ-dependent pathways and Bdnf-mediated release of glutamate [132]. Furthermore, Jeanneteau *et al.* found that impairment of Gr function in the PVN resulted in enhanced *Crf* expression, up-regulated hypothalamic levels of Bdnf, and disinhibition of the HPA axis [133]. Their findings indicate that Bdnf induces *Crf* expression *via* the TrkB-Creb signaling pathway. The authors also demonstrated that differential regulation of *Crf* in the PVN depends on the cAMP response-element binding protein coactivator Crtc2, which interacts with Bdnf and glucocorticoids to regulate *Crf* [133].

These are first hints for genome-wide effects of glucocorticoids on DNA methylation and histone modifications in different brain areas and for additional target-specific effects within the central regulation of the stress response. Together, they demonstrate the high potential of glucocorticoids to induce epigenetic modifications as well as modulate posttranslational mechanisms affecting the stress system. In combination with the accelerating effect of glucocorticoids in organ maturation, this indicates a functional relevant effect of glucocorticoids on developmental epigenetic mechanisms as well as a heightened glucocorticoid sensitivity of these mechanisms during critical periods of brain maturation. This hormonal impact on the epigenetic machinery probably represents another pathway, which contributes to the long-lasting effects of ELS. We argue that in critical periods of brain development this hormonal activation interacts with the observed synaptic activation of epigenetic programming effects. These parallel pathways probably prime the epigenetic machinery for long-lasting modifications, which then function as developmental epigenetic mechanisms contributing to divergent developmental pathways. The combined synaptic and hormonal activation may not only contribute to programming effects of the stress system but also other neu-

ral networks. Likely candidates are the developing sensory networks.

6. STRESS AND SENSORY DEVELOPMENT

The developing brain is highly sensitive to sensory input. During critical periods, sensory input is necessary for the development of sensory systems and the underlying neural networks (for example, for visual development [134, 135]; for auditory development [136, 137]; for tactile development [138]). On a neural and physiological level, some clinical and animal studies indicate a functional role of the stress system in experience-dependent sensory network formation across different sensorial modalities. For example, in their study of somatosensory development in preterm infants, Maitre *et al.* observed that the neural response to touch depended on brain maturation and the sensorial quality of the stimulus with supportive touch inducing a stronger response compared to painful touch [139]. A possible explanation could be that the stress system buffers the neural response to negative sensations, especially pain. Moreover, this indicates that the stress response could function as supporting structure for the long-term integration of sensory experiences and their qualitative nature during early neural network formation. Bock *et al.* found that, in male White-Wistar rats, repeated maternal separation-induced decreased dendritic spine density in the anterior cingulate cortex when the ELS treatment took place prior to the hyporesponsive period of the HPA axis. In contrast, dendritic spine density increased for pups exposed to maternal separation during the hyporesponsive period of the HPA axis. In addition, spine density increased in the somatosensory cortex independent of timepoint of exposure to maternal separation [30]. These findings indicate that during the somatosensory integration of the stressor, the emotional evaluation and valence acquisition depends on the developmental period of the stress system.

Several studies by Teicher and colleagues showed stressor-specific structural and functional effects of ELS (childhood maltreatment) on developing neural networks underlying sensory processing [39]. For example, parental verbal abuse was associated with increased grey-matter density in the primary auditory cortex within the left superior temporal gyrus [140] and with alterations in fiber integrity of language processing pathways [141]. In contrast, visually witnessing repeated interparental domestic violence during childhood was associated with reduced grey matter volume in the visual cortex [142] and decreased the integrity of the left inferior longitudinal fasciculus, a visual-limbic pathway [143]. In a sample of adult women including individuals with and without a history of child abuse, Heim *et al.* found that childhood sexual abuse was associated with cortical thinning of the primary somatosensory cortex, specifically in areas of genital representation [144]. In contrast, emotional abuse during childhood was associated with cortical thinning of precuneus and left cingulate cortex, regions associated with self-awareness and self-evaluation [144]. In addition, Zimmerman *et al.* point out that the period during which they observed long-term effects of ELS on stress response and behavior in mice is a period of sensory-driven cortical network formation, and that this is compatible with a role of Mecp2 in the modulation of synaptic function in these networks [104]. This points towards a bidirectional interaction, with stress participating in the sensory development and sensory input participating in the development of the stress response, although the molecular mechanisms remain to be elucidated.

For some sensory networks, bidirectional interaction with the stress system is well established. For example, the temperature regulation system is strongly interconnected with the stress system [145]. In chicken, Tzschentke *et al.* demonstrated that mild thermo-stimulation during the last four days prior to hatching - a critical period of thermo-regulation development - improved physical performance and induced long-lasting changes in thermo-sensitivity of hypothalamic neurons [146-148]. During this critical period, established feedback mechanisms are optimized and adapted to environmental conditions [148]. The species-specific sensorial fine-tuning mechanism also interacts with the stress response. Yahav *et al.* found that 3-day-old chickens exposed to mild thermal stimulation during late embryogenesis (E16-18) exhibited significantly lower plasma corticosterone levels than controls when exposed to a thermal challenge [149]. Together with the observed dynamic changes of DNA methylation and histone modifications in the promoter of *Bdnf* during postnatal thermotolerance acquisition in chicken [110-112; see above], it is very likely that epigenetic modifications underlie these sensory and stress-related fine-tuning mechanisms. Here, Bdnf seems to contribute to the coordination of critical periods in neural networks. In a mouse model, Bdnf levels have been shown to regulate the critical periods for visual cortex plasticity sensible for deprivation [150, 151]. Changing Bdnf levels have been also associated with the onset of other critical periods including the period for sensitivity to variations in early maternal care [152, 153].

First evidence also indicates that the interaction between stress-related and sensory networks during critical periods affects basic cognitive functions. Sui *et al.* observed improved performance in a passive avoidance test in 1-day-old chicks exposed to a 12/12h light circle at the last days prior to hatching (E19-21) compared to chicks raised in complete darkness [154]. In a second study, they could show that chicks raised in darkness showed similar improvement in the test performance when they received corticosterone injections during the same developmental period [40]. The authors conclude that the effects of light exposure on memory performance are mediated by HPA axis activity. In a final follow-up study, they demonstrated that exposure (at E20) to a steroid receptor antagonist (RU486) or a protein synthesis inhibitor (anisomycin) reverses the effects of light exposure or corticosterone injections on memory performance [155]. Again, the effect falls into a critical period of sensorial and cognitive development. Johnston *et al.* demonstrated that light exposure three days prior hatching (at E19) effects the development of lateral specialization and cognitive performance, including imprinting memory formation [156]. The long-term stability of these effects as well as the molecular, probably epigenetic, underpinnings remain to be determined.

However, the contribution of the stress response to the sensor specific fine-tuning in sensory networks very likely constitutes one pathway underlying the epigenetic programming effects of ELS. In rare, species-specific cases of envi-

ronmental adaptations, such an integration *via* epigenetic programming seems also to take place in adult individuals. Dias and Ressler report a case of epigenetic programming for an olfactory receptor in mice and a fear conditioning paradigm [157]. Fear conditioning with acetophenone resulted in CpG hypomethylation at the *Olfr151* gene compared to controls and enhanced neuroanatomical representation of the *Olfr151* pathway in the olfactory epithelium [157]. Changes in DNA methylation at *Olfr151* were also found in the sperm of the F0 males exposed to acetophenone and the sperm of their naive F1 male offspring indicating an adaptive function across generations [157].

7. DUAL-ACTIVATION OF STRESS-RELATED AND SENSORY NETWORKS: AN INTEGRATIVE PERSPECTIVE

ELS afflicts the organism during a critical developmental period early in life, when the stress system undergoes adaptive changes according to the available environmental input. Epigenetic mechanisms in neural networks have the potential to establish long-lasting adaptations of these networks to environmental signals. The existing evidence, mainly from rodent models, supports the notion that such a programming mechanism contributes to the long-term effects of ELS. Among the most likely candidates for epigenetic programming of the stress response are hippocampal *Gr* and *Fkbp5* as well as hypothalamic *Avp* and *Crf*. Nevertheless, causal pathways linking epigenetic modifications of the stress response following ELS to physiology and behavior later in life remain to be established.

One difficulty in establishing definite pathways is the heterogeneity of findings. Epigenetic modifications following ELS vary across species and tissue as well as stressor type, intensity, time-point, and duration [13, 33, 37]. Several etiological models have been proposed to integrate the existing data. For example, Chattarji *et al.* emphasize that stress effects on neural activity and function differ vastly across hippocampus, prefrontal cortex, and amygdala [34]. Although they are concerned with chronic stress, their argument that the behavioral correlates likely to result from a combination of the area-specific effects also holds for ELS. Specifically for ELS, Bock *et al.* emphasize that the impact of a stressor and the molecular pathways through which the stress signal gets integrated into the epigenome depend on the respective period of species-specific neural development [33]. According to their model, the most sensitive phase is the neonatal and juvenile phase of neural differentiation and synaptogenesis. Furthermore, they point out that hormonally induced and activity-dependent epigenetic modifications interact in differentiating neurons, while in neuronal precursor cells, epigenetic modifications occur only *via* hormonal influences independent of synaptic activity [33]. Zannas and Chourous argue for cumulative effects of stress-induced epigenetic modifications over the lifespan [36]. Different stressful experiences during critical and sensitive periods result in genome-wide or target specific epigenetic modifications, which add to the overall lifetime vulnerability for stress-related diseases [36].

The broad impact of ELS on epigenetic mechanisms affecting brain development and neural network formation together with the diversity of developmental outcomes including cognitive impairment and affective disorders suggests that we must consider heterogeneous mechanisms on the molecular level. The occurrence of genome-wide and target-specific epigenetic modifications and the specificity of modifications not only in regard to brain areas but also genetic targets clearly indicates an interplay of multiple pathways at work. Some of the epigenetic modifications induced by ELS even integrate information about intensity (strong *vs*. mild, [109]) and the physical quality of the stressor (high *vs*. low ambient temperature, [41]). In addition, structural and functional alterations in stressor-specific sensorial networks depend on the sensorial quality of the stressor [39, 144], while alterations in stress and emotion processing related networks seem to depend on the developmental period of the stress response.

We can integrate these findings and existing models, when we assume a dual-activation of the epigenetic machinery underlying the observed programming effects after ELS (Fig. **1**). According to this dual-activation hypothesis, epigenetic programming is induced *via* combined synaptic and hormonal activation: In critical periods of neural network formation, stimulus-induced neural activation initiates modifications in the underlying epigenetic regulatory systems. Parallel induction of acute HPA axis activity leads to hormonal priming of the epigenetic machinery for long-term programming effects *via* the release of glucocorticoids. Thus, during critical developmental periods, hormonal, and synaptic induced epigenetic modifications act in concert to establish the observed programming effects with developmental impact. The summarized evidence suggests that ELS induces these programming effects in stress-related networks, resulting in the diverse epigenetic modifications at stress-related genes observed in ELS studies. However, it is very likely that additional programming effects occur in connected networks, and that these contribute to the life-long effects of ELS.

Here, sensory networks are the most likely candidate. Not only are they activated during stressor perception, they also partly share a critical developmental period with the stress system early in life. Furthermore, the role of glucocorticoids in organ maturation and in experience-dependent sensory development clearly indicates a distinct influence of the stress system on sensorial networks. In addition, the findings of stimulus-specific epigenetic programming effects [109, 41] and stimulus-specific variations in neural network functionality [39, 144] also point towards the participation of sensory networks. Therefore, we assume that synaptic and hormonal activation of the epigenetic machinery together result in stressor-specific epigenetic programming within the activated stress-related and sensory neural networks. Alterations may not only occur in the stress response but also in sensorial and related cognitive and emotional processing (Fig. **2**). This allows stressor-specific adaptations, but may also lead to functional mal-adaptations, depending on timing and intensity of the stressor.

Findings in clinical populations support stressor-specific outcomes and a role of sensory systems in symptomatology and functional impairment. For example, patients suffering from mental illness with a history of ELS differ in

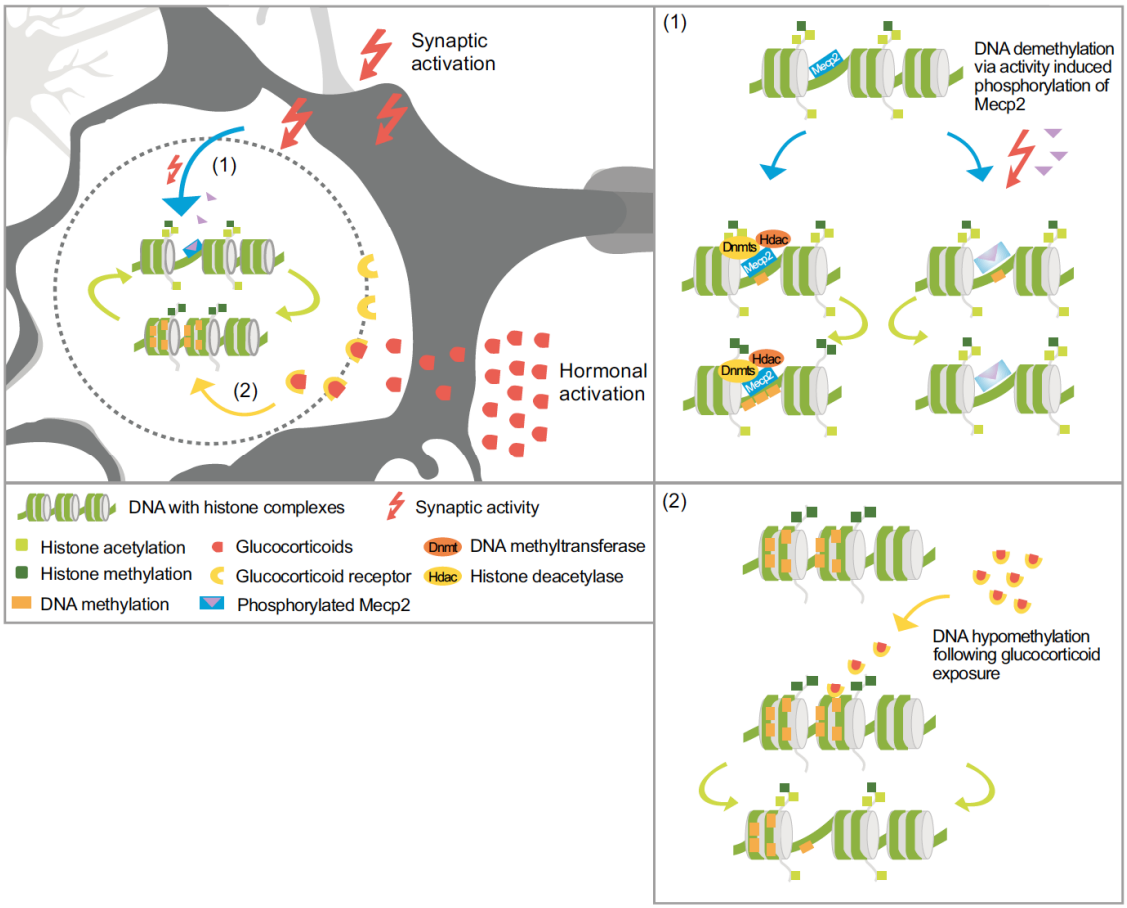

Fig. (1). During critical periods of neuronal development, early life stress leads to synaptic and hormonal activation of epigenetic programming mechanisms in stress related and sensory networks. Dual-activation sensitizes the epigenetic machinery for long-term modifications and potentially allows for stressor-specific adaptations.
Two exemplary pathways within stress-related networks are shown in detail: (**1**) Neural activity in stress related networks induces functional specific phosphorylation of Mecp2. This leads to reduced recruitment of Dnmts and Hdac and subsequently reduced DNA methylation at the specific gene site during development [68]. (**2**) Increased glucocorticoid exposure in critical periods leads to Gr induced target-specific or global hypo- or hypermethylation (only global hypomethylation depicted, [51, 126, 127]). The Gr potentially interacts *via* several pathways with epigenetic mechanisms; the exact mechanisms are still unknown.

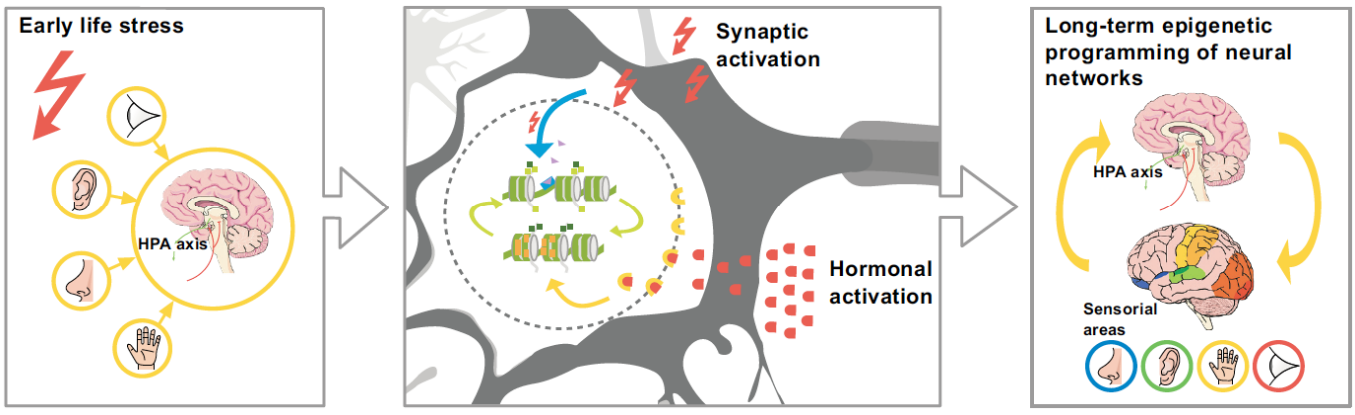

Fig. (2). In critical periods of neural network formation, early life stress activates the HPA axis *via* stressor specific sensory networks. The induced synaptic activation initiates modifications in the underlying epigenetic regulatory systems of stress-related and stressor specific sensory networks. In addition, acute HPA axis activity induces further epigenetic modifications *via* the release of glucocorticoids. Neural activity and hormonal background act in concert to maintain stimulus specific functional modifications in stress-related and sensory neural networks. Due to the bidirectional interaction of stress-related and sensory networks, long-term alterations not only occur in the stress response but also in sensorial and related cognitive and emotional processing.

symptomatology and diagnosis according to the type of ELS [7]. In addition, differences in sensory processing are associated with symptom severity, treatment outcome, and functional impairment across a wide range of affective and psychotic disorders [158, 159]. Although it is not clear, whether these sensory dysfunctions are cause or effect of the disorder, their contribution to symptomatology and course of illness indicate a potential vulnerability in the underlying neural networks. These likely do not differ much between specific diagnostic categories, but instead, underlie a symptomatic spectrum [160]. Further elucidation is needed how these differences in sensory processing relate to higher cognitive functions and emotional processing. Some indications for a bidirectional relationship can be drawn from clinical intervention studies. For example, Dale *et al.* showed that auditory training enhanced some of the cognitive dysfunction in schizophrenia patients, and that this was driven by plasticity in auditory cortical areas [161]. With our dual-activation hypothesis, we assume that the interplay between epigenetic programming effects in stress-related and sensory networks during critical developmental periods of these networks contributes to the diverse symptomatology following ELS and should be included in bottom-up characterizations of clinical diagnoses.

The dual-activation hypothesis has clinical implications for the treatment of mental disorders following ELS, stress-related sensory dysfunction, and in the treatment of preterm neonates. Assuming an interplay between ELS and the sensorial quality of the stressor, treatment of mental disorders following a history of ELS should not focus on the stress system alone. Instead, stressor-specific treatment could enhance therapeutic outcomes. Of note, Weaver *et al.* reported that cross-fostering to high LG rat dams reversed the epigenetic effects of ELS in the offspring of low LG dams [56]. Although in humans, the sensorial quality of ELS might be a little more complex, clinicians should assess cognitive and sensory dysfunctions and eventually address them in therapy. The functionality and relevance of such an approach have already been demonstrated for deficits in auditory perception in schizophrenia patients [162]. The cognitive training targeting auditory and verbal learning improved sensory responses in the auditory cortex and engagement of prefrontal regions, and the improvement was associated with better executive functions [161]. Furthermore, linking stress-related and sensorial networks during early brain development can lead to the discovery of pathways and mechanisms underlying stress-induced sensorial dysfunction, such as tinnitus, hearing loss, loss of sight, and psychosomatic pain. A growing body of evidence shows that chronic pain is a common symptomatology in individuals with a history of early life stress [163]. Finally, the dual-activation hypothesis supports therapeutic approaches in the treatment of preterm neonates, which include positive sensorial stimulation such as skin contact as part of the postnatal parent-child interaction.

Experimental approaches further elucidating the mechanisms underlying the dual-activation hypothesis need to combine animal studies, longitudinal studies following children exposed to early life stress, and clinical intervention studies. Longitudinal studies following children exposed to early life stress, which register sensory deficits in addition to cognitive and behavioral development, emotional processing, and potential psychiatric symptoms later in life, would be highly informative. Also, intervention studies addressing potential deficits in sensory perception and processing in clinical populations would further elucidate the role of sensory systems in mental illness. One example is the mentioned auditory training in schizophrenia patients. Both types of human studies could include neuroimaging studies addressing functional differences in ELS populations [39]. However, the identification of underlying epigenetic mechanisms depends on appropriate animal studies.

Such animal studies would need to differentiate between different sensorial qualities of potential stressors. The currently most frequently used stress paradigm in rodent models - maternal separation with or without additional maternal stress - represents a multi-sensory stressor including at least temperature changes, lack of tacit stimulation, and stress vocalization. In contrast, studies should also focus on stressors with only one sensory modality, *e.g.* temperature, (predator) odor, acoustic stressors (stress vocalizations by other individuals or predator sounds), *etc*. Differences in behavioral outcomes would indicate stressor-specific developmental pathways, and thus modulation *via* sensory networks. Furthermore, potential epigenetic modifications need to be analyzed not only in stress-related networks but also in the respective sensory networks. It might be even more likely to identify adaptive changes in sensory networks as their adaptation is specific to the stressor. For example, Dias & Ressler [157] could demonstrate such an epigenetic modification in the olfactory system using a fear conditioning paradigm, which is known for its interaction with the HPA axis [164]. In addition, studies would be of strong interest, which contrast stress exposure during critical periods of the stress system and of the targeted sensory systems as well as during an overlapping developmental window. This is in accordance with the suggestion of Bock *et al.* that the pathways, through which epigenetic modifications are induced, depend on the developmental period [33].

CONCLUSION

Overall, the observed epigenetic programming effects of ELS are very likely not limited to the modulation of the stress response. Parallel programming effects probably occur in sensory networks activated by the stressor and depending on its sensorial quality. In addition, sensory and stress-related networks both participate in cognitive and emotional processing and in memory formation. Neural projections from sensory and stress-related networks to prefrontal and limbic areas may initiate epigenetic programming in the respective system and aligns with the notion of 'systems heritability' (see above) likely adding to the long-term effects of ELS. Future research needs to further elucidate these potentially bidirectional epigenetic programming effects in stress-related and other neural networks using experimental models able to differentiate between stressors of different sensorial modalities.

LIST OF ABBREVIATIONS

5hmc	=	5-hydroxymethylcytosine
5mc	=	5-methylcytosine

Avp	=	Arginine vasopressin
Bdnf	=	Brain derived neurotrophic factor
CNS	=	Central Nervous System
Crf	=	Corticotropin-releasing factor
Dnmts	=	DNA methyltransferases
ELS	=	Early Life Stress
Fkbp5	=	FK506 binding protein 5
Gr	=	Glucocorticoid receptor
HAT	=	Histone acetyl transferases
Hdacs	=	Histone deacetylases
HPA axis	=	Hypothalamic-pituitary-adrenal axis
LG	=	Liking and Grooming
Mecp2	=	Methyl-CpG binding protein 2
Ngfia	=	Nerve growth factor-inducible protein A
Pomc	=	Proopiomelanocortin
PTSD	=	Post-traumatic Stress Disorder
PVN	=	Paraventricular nucleus

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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