Opinion

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Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics

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Early-life stress lastingly affects adult cognition and increases vulnerability to psychopathology, but the underlying mechanisms remain elusive. In this Opinion article, we propose that early nutritional input together with stress hormones and sensory stimuli from the mother during the perinatal period act synergistically to program the adult brain, possibly via epigenetic mechanisms. We hypothesize that stress during gestation or lactation affects the intake of macro- and micronutrients, including dietary methyl donors, and/or impairs the dam's metabolism, thereby altering nutrient composition and intake by the offspring. In turn, this may persistently modulate gene expression via epigenetic programming, thus altering hippocampal structure and cognition. Understanding how the combination of stress, nutrition, and epigenetics shapes the adult brain is essential for effective therapies.

Early-life environment programs the brain structure and function

Early-life (EL) is a period of unique sensitivity. It is well known that perinatal environmental conditions exert lasting effects on adult brain structure and function, and on the susceptibility to developing psychopathology [1,2]. Most EL experiences are embedded in the parent–offspring relationship [3], and alterations in maternal care [4], including sensory stimulation, warmth, and nutrition [5], can affect the development and function of the offspring's brain (Figure 1). Furthermore, clinical data suggest a direct association between early-life stress (ELS) (e.g., maternal depression [2], the 9/11 attacks [6] and abuse [7–9]), and the incidence of psychiatric disorders and cognitive impairments.

Interestingly, similar impairments to those observed following ELS are found in children exposed to perinatal

Glossary

Adult neurogenesis: a unique form of adult brain plasticity consisting of a multi-step process in which neuronal progenitor cells proliferate, differentiate, migrate, and integrate into the existing circuit. This occurs primarily in the subventricular zone and in the subgranular zone of the dentate gyrus in the hippocampus. Adult hippocampal neurogenesis is upregulated by several environmental factors, such as physical exercise and hippocampus-dependent learning, and is downregulated by ageing and stress.
DNA methyl transferases (DNMTs): enzymes regulating cytosine methylation. Three DNMTs have been identified in mammals: DNMT1, DNMT3a, and DNMT3b. DNMT1 is considered to be a maintenance methyltransferase, whereas DNMT3a and DNMT3b are considered to be involved in *de novo* DNA methylation. DNMT3b expression peaks during embryonic development, but DNMT1 and DNMT3a are also expressed in mature neurons.
DNA methylation: the covalent modification of DNA by the attachment of a methyl (CH_3) group to a cytosine, usually in the context of cytosine–guanine (CpG) dinucleotide sequences. This generally results in gene silencing.
Epigenetic modifications: epigenetic modifications alter patterns of gene expression without changing the primary DNA sequence. Epigenetic modifications include DNA methylation and post-translational modifications of histone proteins, and regulation by non-coding RNAs. These control accessibility of the DNA transcription machinery and thus determine whether a region of DNA is open and transcriptionally active (euchromatin), or condensed and largely transcriptionally inactive (heterochromatin).
Folate (folic acid or vitamin B9): this is an essential micronutrient because most mammals cannot endogenously synthesize folate and it must be obtained from the diet. As folate can carry and chemically activate methyl groups, it is essential for methylation of DNA and for nucleotide synthesis. It is an essential B vitamin that plays a critical part in brain development; folate supplementation during early pregnancy protects against neural tube defects.
Histone modifications: modifications on the N-terminal tails of histone proteins (e.g., methylation, phosphorylation, acetylation, and uibiquitination). These modifications largely define the state of the chromatin (euochromatin or heterocromatin).
One-carbon metabolism (homocysteine metabolism): the essential mirconutrients folate, vitamin B6, and vitamin B12 are critically involved in homocysteine metabolism, and a lack in any of these micronutrients may result in excess homocysteine and/or deficiency in S-adenosyl-methionine (SAM), a universal donor of methyl groups that is required for DNA methylation and the synthesis of DNA, RNA, hormones, proteins, and neurotransmitters. Folate and vitamin B12 are required to re-methylate homocysteine into methionine (essential for the formation of SAM), whereas vitamin B6-dependent enzymes can metabolize homocysteine to form cysteine.
Programming: the process whereby a stimulus or insult, given or occurring during a critical period, has irreversible long-term effects on the organism.

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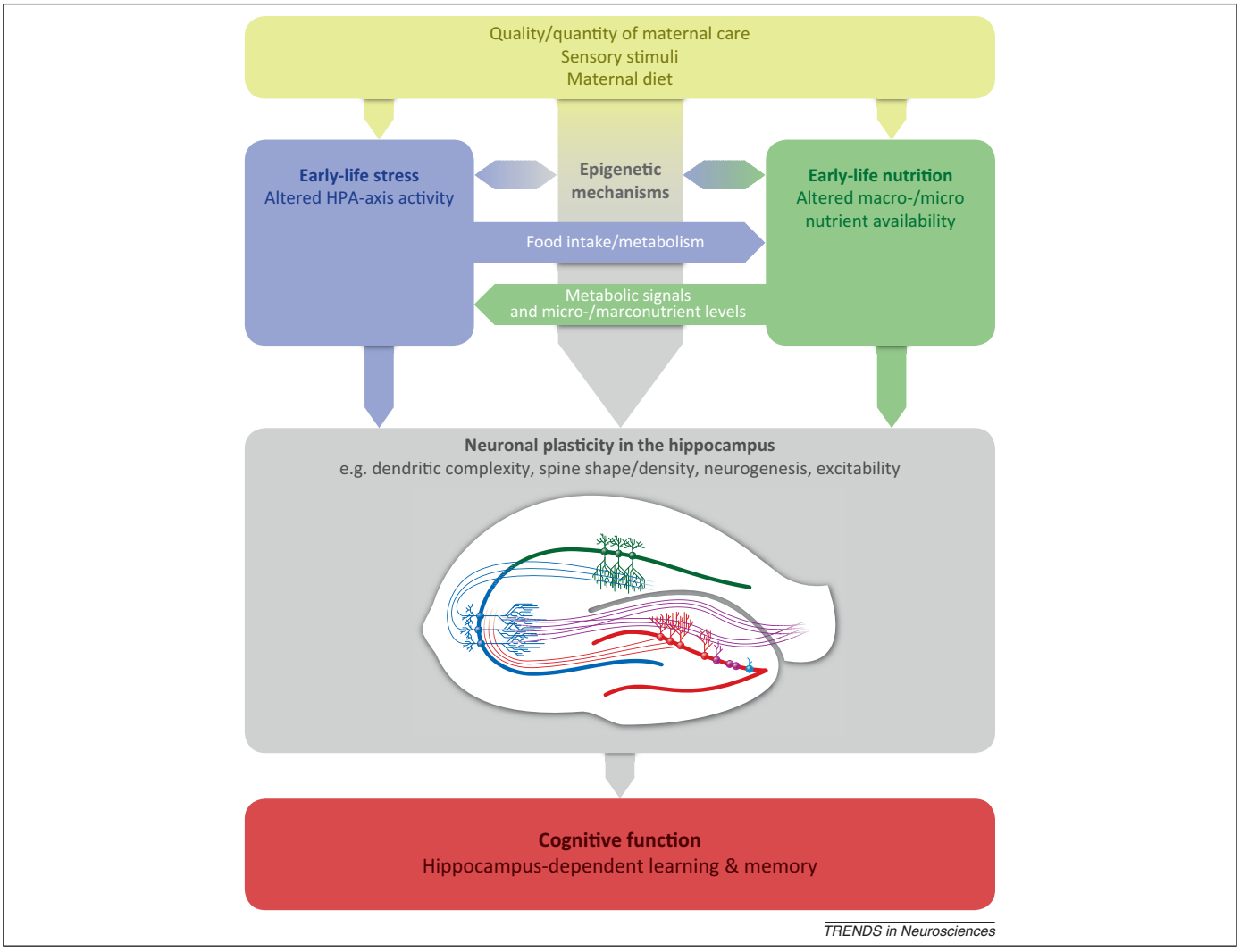

Figure 1. Schematic representation of the pathways via which alterations in the quality and/or quantity of maternal care, sensory stimuli, and maternal diet during early life influence both hypothalamic–pituitary–adrenal (HPA)-axis activity and micro-/macronutrient availability. Although early-life stress and early-life nutrition are often studied as independent factors, they can be modulated by the same environmental conditions, and they strongly influence each other. Both factors can lastingly affect (possibly via epigenetic mechanisms) neuronal plasticity in the hippocampus, which in turn results in permanent alterations in hippocampus-dependent cognitive function.

malnutrition [5,10–12] or famine [13] (but see [14]). The quality of early nutrition has major effects on adult cognitive function [15], suggesting that dietary elements are possibly instrumental in mediating the ELS and EL malnutrition induced impairments. To develop appropriate interventions, it is important to understand the mechanisms by which ELS and EL malnutrition exert their long-lasting effects on the brain and disease susceptibility. As evident from the above-mentioned examples, stress and malnutrition often occur simultaneously, and are interrelated. Feeding behavior and metabolism are closely regulated by neuroendocrine mechanisms that are influenced by stressful events, and malnutrition affects the stress system as well (Figure 1). Up to now, most research directed at understanding the processes underlying programming (see Glossary) by the EL environment viewed stress hormones and nutritional elements as independent factors [16–18]. Here, we propose that to fully understand the processes underlying the programming of the brain by ELS, it is key to study the interplay of these elements and how they mediate the programming of the brain: for example, possibly via epigenetic mechanisms.

In the following sections we review some of the evidence that ELS as well as EL nutrition affect hippocampal structure, plasticity, and function (Box 1). After addressing the role of maternal sensory stimuli, circulating stress hormones/neuropeptides, and nutrient availability in mediating these effects, we introduce the importance of examining the coordinated interaction of these elements and discuss how these effects could be mediated by epigenetic mechanisms.

The hippocampus, highly susceptible to early-life experiences

To understand how EL experiences affect mental health and cognition, numerous studies have focused on the hippocampus, as this brain region is implicated in both cognition [19] and regulation of the stress response [20]. In fact, the hippocampus is particularly sensitive to the EL environment because it mostly develops postnatally, is highly plastic, and is rich in stress-hormone receptors.

The human hippocampus develops between the last trimester of gestation and 16 years of age [21], whereas the rodent hippocampus develops between embryonic

Box 1. The hippocampus: a brain structure with a high degree of plasticity

The hippocampal formation (Figure I) includes: the hippocampus proper, including cornu ammonis 1 (CA1) and CA3, dentate gyrus (DG), subiculum, and entorhinal cortex (EC). The trisynaptic circuit — the main hippocampal information-processing unit — connects EC–DG–CA3–CA1–EC (see arrows). The DG receives input from the EC via perforant path axons. From the DG, mossy fibers connect to CA3 pyramidal cells, which connect to CA1 pyramidal cells via Schaffer collaterals. The hippocampus has a high degree of plasticity throughout life. Dynamic changes in dendritic arborization and synapse formation/elimination continuously alter neuronal connectivity. These changes can be assessed morphologically (e.g., by characterization of dendritic arborization and spine shape/density) or functionally (e.g., by electrophysiological recordings). Additionally, within the subgranular zone (SGZ) of the DG, adult neurogenesis occurs. This process comprises the proliferation of neuronal progenitor cells (NPCs), their migration into the granular cell layer (GCL), and their differentiation into functional mature granule cells.

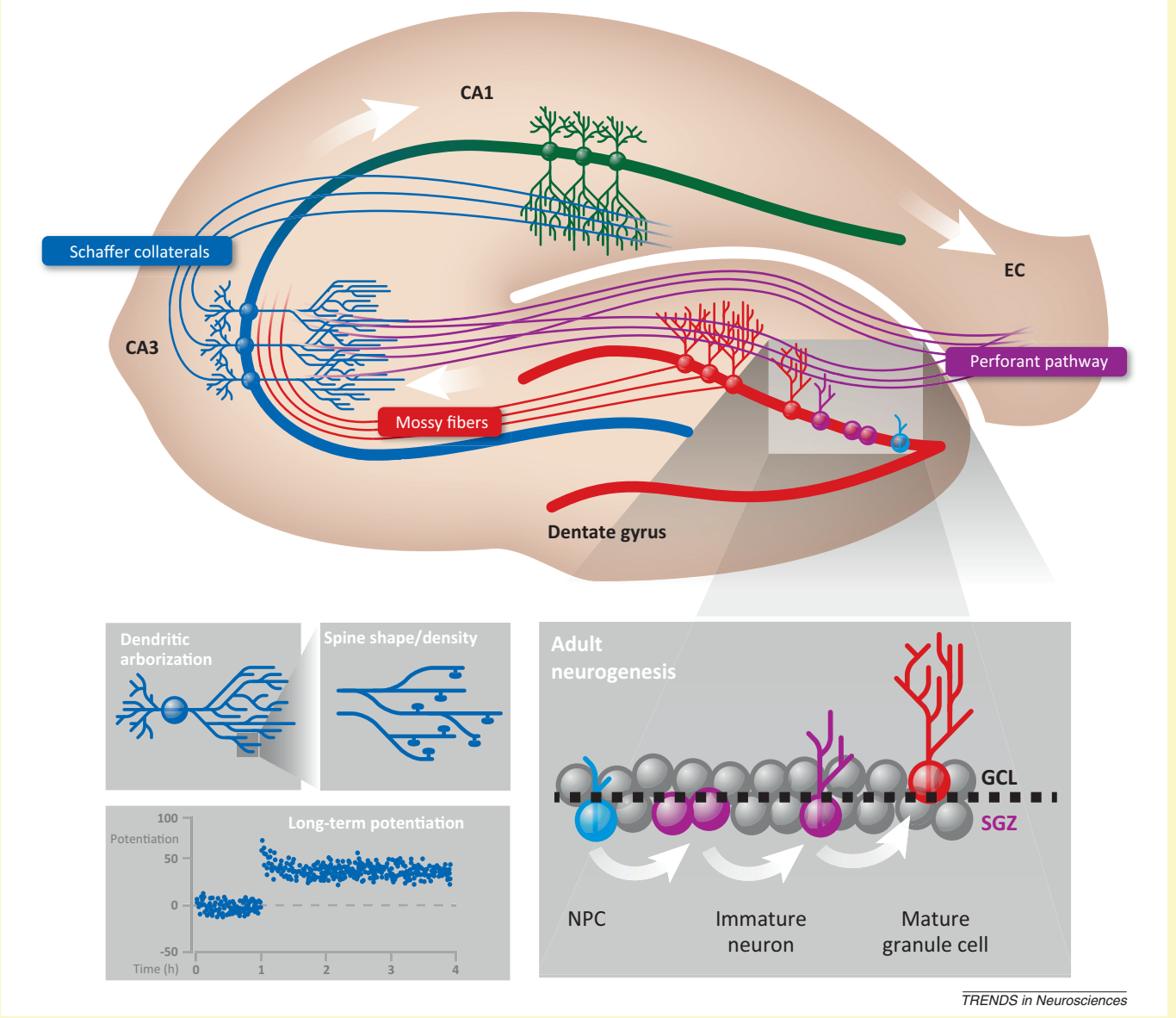

Figure I. The hippocampal formation and its forms of neuronal and synaptic plasticity.

day 18 and postnatal weeks 2–3 [22]. The hippocampus exhibits a high degree of structural and synaptic plasticity and undergoes dynamic changes in neuronal connectivity that can be assessed morphologically or functionally (Box 1).

Furthermore, the dentate gyrus of the hippocampus is one of the few brain regions that exhibits the ability to generate new neurons during adulthood [23]. This fundamental form of structural plasticity is termed adult neurogenesis and is regulated by various factors (e.g., it is inhibited by stress and stimulated by exercise or enrichment [24]). Dysregulation of neurogenesis [25] and impairments in long-term potentiation (LTP) [26] or dendritic complexity [27] have been implicated in reduced hippocampus-dependent cognition (e.g., spatial memory, declarative memory, and pattern separation [19]).

In the following sections, we discuss the evidence that alterations in hippocampal structure and plasticity might underlie the lasting effects of EL stress and malnutrition.

Programming effects of perinatal stress

Stressful experiences occurring during critical developmental time windows impair cognitive function. Considering the vulnerability of the developing hippocampus, exposure to stress during this period is expected to interfere with its structural and functional maturation in a permanent manner. Indeed, adverse EL experiences in humans (e.g., childhood abuse or maltreatment) [9] and perinatal stress in rodents [28–30] (Box 2) correlate with cognitive impairments and are associated with affected hippocampal structure. For instance, in rats, exposure to stress during gestation impaired spatial learning in adult offspring, suppressed LTP [31,32], altered spine density and dendritic length [33], and reduced levels of proliferation and newborn cell survival [29,34]. These effects were already evident at postnatal day 1 (P1) [35,36] and lasted up to 22 months of age [29]. Similarly, postnatal stressors in rodents, such as maternal deprivation [30], repeated maternal separation [37,38], or chronic ELS [26,39], impair the acquisition of spatial information and are associated with impaired LTP, aberrant mossy fiber growth, dendritic atrophy [26,40,41], and changes in levels of adult neurogenesis [30,42–46]. Importantly, whereas stress effects during adulthood are often reversible [47,48], ELS-induced hippocampal structural changes and cognitive deficits persist throughout life [49]. Interestingly, whereas adult rat offspring from maternally deprived or from low-caring mothers show impaired learning and reduced synaptic plasticity under basal conditions, they exhibit improved contextual learning and enhanced LTP under stressful conditions [30,41]. This suggests that ELS, rather than exerting 'deleterious effects' in general, prepares the organism to respond optimally under comparable situations encountered later in life, a concept known as the match–mismatch theory [50].

In conclusion, perinatal stress alters cognition into and throughout adulthood. Although alterations in hippocampal plasticity and synaptic integrity are likely to be instrumental, the specific elements in the early environment (e.g., sensory stimuli and nutrition), and the molecules and molecular mechanisms mediating these long-term effects are only partly resolved.

Programming effects of perinatal nutrition

Given the high metabolic activity and energy demand of the brain, its functioning requires adequate supply of micro- and macronutrients. Even minor dietary insufficiencies can have adverse effects, especially during critical stages of development, when they can permanently change brain structure and cognitive functioning. For instance, children exposed to perinatal malnutrition exhibit cognitive deficits and increased risks for psychopathology in adulthood [5,10–12,14]. Preclinical studies also demonstrate that offspring of malnourished dams exhibit cognitive deficits [51–53] (but see [54]). Many nutrients are essential for neuronal growth and brain development, but during the perinatal period, the intake of iron, zinc, selenium, iodine, folate, vitamin A, vitamin B6, vitamin B12, choline, long-chain polyunsaturated fatty acids, and proteins overall is of particular importance. For example, fetal and neonatal iron and protein deficiency results in long-term deficits in memory functions [12].

Although it is unclear whether alterations in hippocampal structure and synaptic plasticity are instrumental in mediating these cognitive deficits, there is evidence that perinatal manipulations in nutritional status induce alterations in hippocampal neurogenesis [55,56], as well as reduce granular cell size, dendritic complexity, and synaptic spine density [57]. These structural changes are associated with enhanced interneuron-mediated inhibition [58] and deficits in LTP in malnourished animals [59]. Furthermore, vitamin B6 and B12 deficiencies during gestation and lactation persistently impair hippocampal structure and function [12,60]. Finally, protein malnutrition results in reduced neuronal DNA and RNA content and an altered fatty acid profile that, in turn, could change neuronal function, synapse number, and/or dendritic arborization [61,62].

These data indicate that synapses in the malnourished hippocampus might be less capable of supporting plasticity and that alterations in the hippocampal circuitry during development could account for cognitive deficits induced by perinatal malnutrition. However, further research is needed to understand which nutrients are most relevant and how exactly nutritional deficiencies affect hippocampal structure and function.

The role of sensory stimulation from the mother and stress hormones

Alterations in tactile stimulation from the mother (potentially induced by maternal stress exposure as well as malnutrition; see next section) are instrumental in mediating the consequences of EL experiences. The key role of these sensory stimuli has been established by studies demonstrating that both artificial manipulation of maternal care (via maternal separation or deprivation, chronic ELS, and handling; Box 2) [40,63,64] and the natural variation in maternal care between [41,65] and within litters [66] programs the brain and behavior of the adult offspring. In line with this, stroking (simulating maternal tactile stimuli) reversed the effects of maternal separation in rats [67]; and in (pre)term human neonates, moderate touch (e.g., massage) reduces reactivity to stress at adult ages [68]. In the next section we examine how these sensory stimuli can be affected by other elements of the EL environment (stress and nutrition).

Next to maternal sensory stimulation, EL experience-induced alterations in circulating levels of stress hormones and stress-related peptides are considered to be instrumental in mediating the lasting effects of EL experience on the brain and behavior. This includes lasting changes in the hippocampus and cognitive functions. EL experience programs the neuroendocrine system (the hypothalamic–pituitary–adrenal (HPA) axis), which is activated on stress exposure. When the HPA axis is activated, corticotrophin-releasing hormone [CRH; also known as corticotrophin-releasing factor (CRF)] is released from the hypothalamic paraventricular nucleus. In turn, CRH stimulates the pituitary to release adrenocorticotrophic hormone (ACTH), resulting in the synthesis and release of glucocorticoids (corticosterone (CORT)) from the adrenal glands. There is ample evidence that EL experience affects CRH [69], glucocorticoid receptors (GRs), and mineralocorticoid

Box 2. Animal models to study the programming effects of early-life stress and nutrition

The 'developmental origins of health and disease' hypothesis proposes that the early-life (EL) environment, from gestation till puberty, can set the stage for adult pathology. During this developmental period, quality of the EL environment critically depends on the mother providing the prenatal environment and forming the primary source of nutrition, warmth, and tactile stimulation during postnatal EL. These critical components are often manipulated in animal models used to study the long-term effects of EL experiences.

Commonly used manipulations to induce prenatal stress in rodents include exposure of the pregnant dam to single or repeated stress (Figure IA). Postnatal ELS can be induced by single prolonged separation of dam and pups for 24 hours, for example, at postnatal day 3 (P3) (maternal deprivation; Figure IB), or by repeated daily separations for 2–5 hours (maternal separation; Figure IC). Furthermore, a powerful method to induce chronic EL stress consists of reducing the amount of nesting and bedding material during the first postnatal week (Figure ID). This induces fragmented maternal care, thereby mimicking aspects of a human chronic ELS situation in which the mother is present but unable to provide appropriate care. Besides experimentally induced alterations in maternal care, selection based on natural variation is used to compare offspring that received low versus high levels of maternal care (Figure IE). For the above-described models, the effects on the level of maternal sensory stimuli are well characterized. Indeed, the lasting effects of these manipulations on brain structure and function have been mostly attributed to altered maternal sensory input, although other key components of the dam–pup interaction (e.g., nutrition and warmth) also have a role.

EL malnutrition is usually induced by altering maternal diet during pregnancy and/or lactation [e.g., overnutrition with a high-fat diet (Figure IIA), protein intake restriction (Figure IIB), or global dietary restriction (Figure IIC)]. Again, in most of these studies, only the manipulated element is considered as the main player, ignoring the fact that nutritional manipulation itself might affect maternal care and stress hormones. However, when addressing the mechanisms underlying EL programming of the brain, it is key to consider which environmental elements are involved and how these components interact.

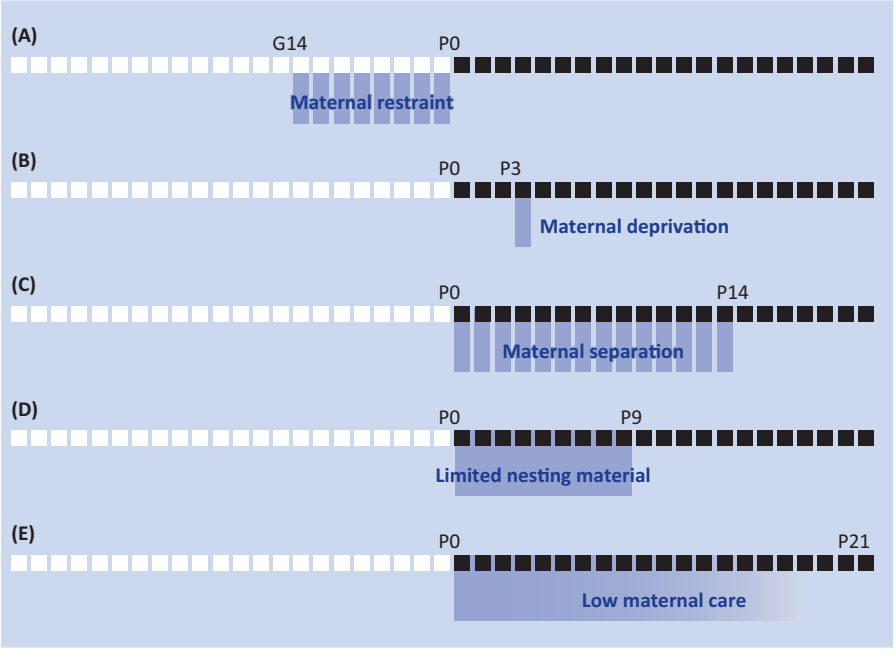

Figure I. Frequently used experimental manipulations to induce early-life stress in rodents.

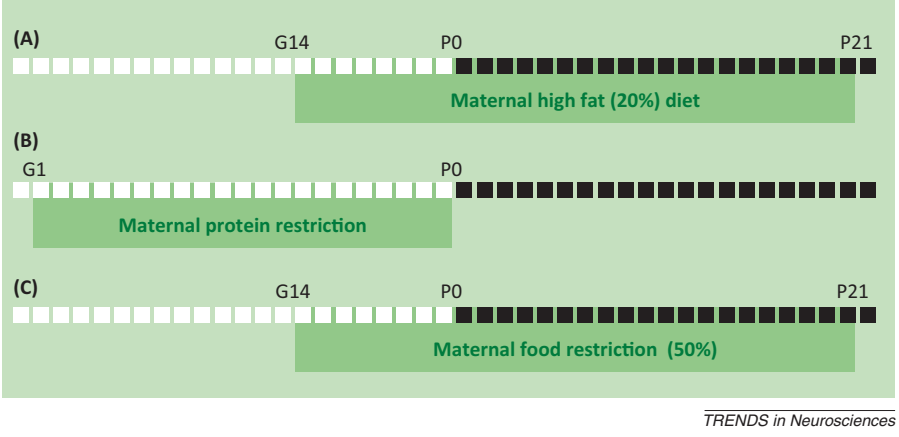

Figure II. Frequently used experimental manipulations to alter early-life nutrition in rodents.

receptors (MRs) [70], as well as arginine vasopressin (AVP) [71] and brain-derived neurotrophic factor (BDNF) [72]. If these persistently altered factors are responsible for the functional consequences, then modulating these changes pharmacologically should prevent or reverse the functional consequences. Because CORT–GR/MR and CRH–CRF receptor type 1 ($CRFR_1$) have received the most attention so far, we will discuss these in detail.

EL experience has lasting consequences on CORT levels [39,73,74] and affects GR and MR expression [70,75]. An elegant series of experiments highlighted the relevance of GR exon I_7 for later life consequences and its potential as a target for reversal of EL effects [70]. However, it is not clear whether these alterations are directly responsible for mediating the lasting effects of ELS. In fact, even though CORT is a logical candidate, there is some controversy in the literature because CORT alteration following ELS is not consistent across animal models [40,45,76]. Neonatal treatment with the synthetic glucocorticoid dexamethasone lastingly impairs spatial learning and reduces hippocampal synaptic plasticity [77,78], and reducing CORT levels by adrenalectomy of adult mice exposed to ELS restores neurogenesis to control levels [45]. However, permanently reducing CORT levels by adrenalectomy at P10 does not alter subsequent levels of adult neurogenesis [79], and suppressing the rise of CORT induced by maternal deprivation does not prevent the HPA-axis alterations discussed above [80]. Thus, the complexity of corticosteroid regulation by ELS points to the need for further research in this area.

CRH expression is persistently altered by EL experience in the hypothalamic paraventricular nucleus (PVN) [39,40,63,69,81] and in the hippocampus [26]. Several lines of evidence indicate a critical role for CRH in mediating lasting EL effects. For example, chronic exposure to CRH and chronic ELS have similar effects on hippocampal structure [40]. Moreover, CRH repression is the first alteration in the HPA axis that occurs after handling [82]. Blocking $CRFR_1$ in control rats (P10–P17) improves cognitive functions [75], and blocking $CRFR_1$ after chronic ELS prevents ELS-induced LTP impairment and dendritic atrophy, and preserves hippocampal cognition [26]. Finally, in conditional $CRFR_1$-knockout mice subjected to chronic ELS, cognition, LTP, and spine density are restored [83].

In line with these preclinical data, single-nucleotide polymorphisms in the *Crhr1* gene protect against depression in childhood-maltreated individuals [84]. Therefore, pharmacological targeting of GR and CRFR signaling may enhance resilience to ELS-related cognitive impairment and affective disorders [40].

Interaction among maternal care, stress system, and nutrient availability

Based on the studies discussed so far, it is clear that maternal tactile stimulation and nutrient availability are key factors in the early environment, and that stress hormones and neuropeptides are instrumental in mediating the lasting effects of these EL experiences. Most studies consider these elements individually, but for optimal intervention it is fundamental to understand how these environmental elements and molecules interact and influence each other. We therefore next examine the available evidence supporting a coordinated interaction of these elements in the lasting effects of EL experience.

Food intake and HPA-axis activity are closely interrelated with overlaying neuronal pathways that respond to (and integrate) both nutritional and stressful stimuli. Indeed, basal HPA-axis activity and stress responsiveness are altered in genetically obese rats [85] and in rodents fed a high-fat diet [86] or subjected to perinatal food restriction [87]. Conversely, chronic stress conditions have been correlated with changes in food intake [16]. The HPA axis is sensitive to modulation by metabolic signals, including leptin, insulin, glucose, and ghrelin [88,89]. This is also true early in life [90,91], when food intake and nutrition of the progeny depend on maternal care and diet. Indeed, next to quality and quantity of maternal care and circulating stress hormones, metabolic signals are crucial in programming the HPA axis [90]. For instance, only combined food administration and sensory stimulation of pups during maternal deprivation prevents the deleterious effects of this EL stressor on the HPA axis and on hippocampal GR expression, whereas stroking alone is not sufficient to achieve this recovery [80]. In addition to changes in HPA-axis tone, maternal separation reduces plasma glucose and leptin levels, and increases ghrelin levels in the offspring [90]. Pharmacologically blocking this reduction in glucose, or the increase in ghrelin, attenuates the HPA-axis response to maternal separation [90]. This suggests that metabolic signals play an important part in triggering the HPA-axis response of the neonate to maternal separation.

Furthermore, plasma leptin levels in the offspring are modified by the availability and composition of the maternal milk. Maternal milk is rich in fat and is required for growth and brain development [91–93]. Feeding mothers a high-fat diet from gestational day 14 and throughout lactation increased maternal milk fatty acid and leptin content and persistently increased the offspring's plasma fat and leptin levels [92]. These metabolic changes are associated with a blunted hormonal stress response [94], and increased GR expression and anxiety [95]. Although this effect on the HPA axis could be directly due to the increases in leptin levels [91], differences in maternal diet might have affected maternal behavior as well [17], thereby contributing indirectly to the observed effects.

In a similar way to fat content, protein restriction [96] and general undernutrition during gestation and/or lactation [97] affect the HPA axis of the progeny. In addition to the direct effects of protein restriction on the quality of maternal milk, these nutritional restrictions increased expression of the genes encoding CORT and decreased expression of the gene encoding placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). Protein restriction also possibly led to fetal overexposure to maternal CORT, which could be partly responsible for some of the alterations in the HPA axis of the progeny. This exemplifies again the tight relationship among stress, nutrition, and metabolic signals.

Interestingly, the effects of perinatal malnutrition on adult stress responsiveness and cognitive function resemble several of the long-term deficits induced by perinatal

stress. Both insults result in cognitive deficits and an increased susceptibility to psychiatric disorders [98,99]. One possibility is that impairments in adult cognition and stress responsiveness observed following both perinatal stress and malnutrition depend on the combined effects of lack of key nutrients, affected maternal behavior, and altered HPA-axis activity (Figure 1). In line with this hypothesis, maternal undernutrition results in altered maternal behavior [17] and in high plasma CORT levels in the adult offspring along with reduced GR expression [100]. This suggests that the deleterious effects of maternal nutrient restriction could also result from differential sensory input from the mother and enhanced HPA-axis activity.

Certainly, the opposite possibility should be considered as well. During (EL) stress, regulation of appetite and metabolism are altered, thereby affecting the intake of essential macro- and micronutrients [101]. For instance, exposure to perinatal stress increased the risk of developing obesity later in life and affected feeding regulation in both clinical [102,103] and preclinical studies [104–106]. These effects of stress on appetite regulation and metabolism are in large part mediated by glucocorticoids and stress-related peptides such as CRH and urocortins [107], which affect the neural circuits and hormones involved in the regulation of feeding behavior. A detailed analysis of how these systems interact has been conducted [18].

In conclusion, there is some evidence that, in addition to maternal sensory stimulation and stress hormones, the lack of key nutrients affects the brain directly in the case of both restricted nutrition and perinatal stress. The next question then is which molecular mechanisms mediate the programming effects of EL experience. Thus, below we explore the role of epigenetic modifications.

Early-life stress and epigenetic mechanisms

Various reports have implicated epigenetic mechanisms in mediating persistent effects of EL experience [69–72] (Table 1). Epigenetic modifications determine whether a gene is transcribed or repressed without changing the DNA sequence. In contrast to the genome, the epigenome is dynamic, thereby allowing the organism to adapt to the environment, and therefore it is an excellent candidate for mediating the effects of EL experiences on the brain. For example, increased hippocampal GR expression induced by high levels of maternal care is associated with decreased DNA methylation and increased histone acetylation binding to the GR promoter [70] (but see [108]). Similarly, translational research has found lower hippocampal GR expression and increased GR promoter DNA methylation in suicide victims with a history of childhood abuse or neglect [109]. Furthermore, ELS-induced increases in AVP levels are associated with DNA hypomethylation [71], whereas ELS-induced reduced BDNF expression in the prefrontal cortex is accompanied by increased DNA methylation [72], and maternal deprivation-induced increases in CRH expression are accompanied by decreased DNA methylation [69]. Finally, the handling-induced reduction in CRH expression is associated with persistently increased levels of neuron restrictive silencing factor [81], further indicating that environmental factors during EL can trigger the epigenetic machinery and persistently change transcription of important regulatory genes.

There is evidence that the epigenome is also affected more globally, as the epigenetic response to maternal care is coordinated in clusters across broad genomic areas [110], and maternal separation in mice changed global levels of histone deacetylases [111]. Accordingly, whole-genome DNA methylation is significantly different

Table 1. Examples of epigenetic modifications induced by early-life experiences

Early-life intervention	Altered gene expression	Tissue	Epigenetically regulated	Species	Refs
Low maternal care	↓ Glucocorticoid receptor	Brain (hippocampus)	↑ DNA methylation of exon I_7 of GR[a] promoter	Rats	[70]
Maternal deprivation (P1–10 for 3 hours)	↑ AVP	Brain (hypothalamus)	↓ DNA methylation ↓ MeCP2 binding	Mice	[71]
Exposure to stress-abusive dam (P1–7)	↓ BDNF	Brain (prefrontal cortex)	↑ DNA methylation IV exon promoter	Rats	[72]
Maternal deprivation	↑ CRH	Brain (hypothalamus)	↓ DNA methylation of CRH promoter CRE	Rats	[69]
Handling	↓ CRH	Brain (hypothalamus)	↑ NRSF	Rats	[81]
Maternal separation	Genome wide	Brain (forebrain)	↓ HDAC expression ↑ H4K12ac	Mice	[111]
Childhood abuse/neglect	↓ Glucocorticoid receptor	Brain (hippocampus)	↑ DNA methylation	Human	[109]
Insitutionalized children	Genome wide	Periphery (blood)	Differential patterns of DNA methylation	Human	[112]
Postnatal overfeeding	↑ Glucocorticoid receptor	Periphery (adipose tissue)	?	Rats	[134]
Protein restriction during gestation	↑ Glucocorticoid receptor	Periphery (liver)	↓ DNA methylation of exon I_{10} of GR promoter	Rats	[127]
Periconceptional maternal vitamin B/methionine restriction	Genome wide	Periphery (fetal liver)	Differential patterns of DNA methylation	Sheep	[113]
High maternal choline intake (third trimester)	↓ CRH	Periphery (placenta)	↑ DNA methylation of CRH promoter ↑ Global DNA methylation ↑ H3K9me2	Human	[115]

[a]Abbreviations: AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; CRH, corticotrophin-releasing hormone; GR, glucocorticoid receptor; H3K9me2, histone H3 lysine 9 bimethylation; H4K12ac, histone H4 lysine 12 acetylation; HDAC, histone deacetylase; MeCP2, methyl CpG-binding protein 2; NRSF, neuron restrictive silencing factor.

between institutionalized children and children raised by their biological parents [112].

Thus, epigenetic mechanisms both targeted at specific genes and genome wide seem to be good candidates for mediating the programming effects of EL.

Effects of nutrition on the epigenome

Interestingly, early nutrition modulates the epigenome in several peripheral tissues. In both humans and animals, diet is a potent modulator of epigenetic marks during the perinatal period [113–115]. EL nutrition can modulate the epigenome by alterations in: (i) the supply of methyl donors; (ii) the activities of DNA methyltransferases (DNMTs); or (iii) activities of specific transcription factors [116]. Here, we review the evidence that such mechanisms could be at work in the brain.

The dietary methyl donors folate, vitamins B6 and B12, methionine, choline, and betaine all affect DNA and histone methylation [117]. Fetal choline availability is essential for normal brain development, and maternal choline deficiency alters development and neurogenesis in the fetal mouse hippocampus [118]. Alterations in choline availability during fetal brain development induce epigenetic modifications of genes directly involved in epigenetic machinery [119], signal transduction [120], HPA-axis reactivity [115], and neuronal differentiation [121,122]. In fact, pregnant and lactating women possess a system assuring the necessary choline intake by the fetus and infant, respectively [123]. In rodents, maternal diets supplemented with choline improved the memory of the offspring and were associated with increases in neurogenesis in the embryonic brain [124,125].

Finally, perturbations in maternal diet can alter DNMT expression: for example, pregnant rats fed a protein-restricted diet showed increased blood homocysteine concentration [126], which was associated with a reduction in DNMT1 expression and inhibited binding of DNMT1 at the liver GR promoter [127]. Because DNMT1 expression is regulated by homocysteine and folic acid [127], modulation of DNMT1 expression by differences in one-carbon metabolism could provide a link between maternal diet and epigenetic regulation of the offspring's gene expression. However, whether a lack of specific nutrients during the critical developmental period affects brain structure and function, and whether this involves epigenetic mechanisms remains to be determined (Box 3).

Can dietary intervention reverse the effects of perinatal stress and/or malnutrition?

Despite the apparent stability of methylation marks, alterations in DNA methylation induced by maternal diet or differential nurturing behavior can be prevented and reversed by interventions in postnatal life [128]. Both folate and glycine supplementation to maternal diet reversed the effects of protein restriction during pregnancy on blood pressure and vascular function of the offspring [129], and prevented the aforementioned epigenetic changes [130]. In addition, the phenotype and gene expression of the offspring from protein-restricted dams were altered by folate supplementation during the juvenile–pubertal period [131]. Finally, central infusion of l-methionine at P90 reversed the maternal care-induced effects on DNA methylation [132]. Accordingly, formula fortified with protein and high energy improved neural development of children who suffered brain damage [133]. Taken together, early nutrition appears to be a promising candidate for modulating (some of) the lasting consequences of EL experience on adult brain structure and function.

Box 3. Outstanding questions

- Do the lasting alterations caused by early-life malnutrition involve the same mechanisms as the early-life-stress-induced cognitive impairments and alterations in neuronal plasticity?
- How does early-life stress affect nutrient intake during the critical developmental period? How does early-life malnutrition affect the stress system? What is the interaction between stress hormones/neuropeptides and essential nutrients?
- Are epigenetic mechanisms responsible for maintaining the lasting changes in brain structure and function after adverse early-life experiences? And what is it that actually triggers these epigenetic mechanisms? What makes these modifications specific for certain brain structures or certain genes?
- Can a lack of essential micronutrients (e.g., dietary methyl donors) be involved in the early-life-stress-induced cognitive impairments?
- Is there a critical time window during which the deleterious effects of adverse early-life experiences can be reversed by therapeutic intervention?
- Can the lasting deleterious effects of adverse early-life experiences be prevented or treated by nutrition-based intervention?

Concluding remarks

In summary, adverse experiences during critical developmental periods persistently affect gene expression, which ultimately might determine cognitive outcomes and disease susceptibility in adulthood. Hippocampal development, various forms of neuronal plasticity, and synapse formation are tightly regulated by maternal sensory stimuli, exposure to hormones and neuropeptides (e.g., CORT and CRH), the availability of macro- and micronutrients, and epigenetic mechanisms. Therefore, EL events that alter any of these components will interfere with outcome measures later in life.

It remains difficult to dissect the contributions of the EL environment and nutrition to (epigenetic) programming of hippocampal structure and function, as they influence each other and often occur simultaneously. Yet understanding the mechanisms by which nutrition and other environmental cues influence epigenetic regulation and identifying the periods of susceptibility and stability of the induced changes is critical for the identification of individuals at risk and for the development of novel intervention strategies.

Much evidence points towards a crucial role for epigenetic mechanisms in mediating the lasting effects of adverse EL experiences on hippocampal structure and function. Next to maternal care, stress hormones, and neuropeptides, early nutrition seems to play an important part in modulating these epigenetic influences on hippocampal anatomy and physiology. Therefore, non-invasive interventions targeted at maternal nutrition, which are relatively easy to implement, could have a significant effect on the brain and on the behavior of the offspring in the long term.

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References

1 Loman, M.M. and Gunnar, M.R. (2010) Early experience and the development of stress reactivity and regulation in children. *Neurosci. Biobehav. Rev.* 34, 867–876
2 O'Connor, T.G. *et al.* (2005) Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biol. Psychiatry* 58, 211–217
3 Bowlby, J. (1950) Research into the origins of delinquent behaviour. *Br. Med. J.* 1, 570–573
4 Baram, T.Z. *et al.* (2012) Fragmentation and unpredictability of early-life experience in mental disorders. *Am. J. Psychiatry* 169, 907–915
5 de Souza, A.S. *et al.* (2011) Effects of maternal malnutrition and postnatal nutritional rehabilitation on brain fatty acids, learning, and memory. *Nutr. Rev.* 69, 132–144
6 Yehuda, R. *et al.* (2005) Transgenerational effects of posttraumatic stress disorder in babies of mothers exposed to the World Trade Center attacks during pregnancy. *J. Clin. Endocrinol. Metab.* 90, 4115–4118
7 Maselko, J. *et al.* (2011) Mother's affection at 8 months predicts emotional distress in adulthood. *J. Epidemiol. Community Health* 65, 621–625
8 Mueller, S.C. *et al.* (2010) Early-life stress is associated with impairment in cognitive control in adolescence: an fMRI study. *Neuropsychologia* 48, 3037–3044
9 Teicher, M.H. *et al.* (2012) Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proc. Natl. Acad. Sci. U.S.A.* 109, 563–572
10 Laus, M.F. *et al.* (2011) Early postnatal protein-calorie malnutrition and cognition: A review of human and animal studies. *Int. J. Environ. Res. Public Health* 8, 590–612
11 de Rooij, S.R. *et al.* (2010) Prenatal undernutrition and cognitive function in late adulthood. *Proc. Natl. Acad. Sci. U.S.A.* 107, 16881–16886
12 Benton, D. (2010) The influence of dietary status on the cognitive performance of children. *Mol. Nutr. Food Res.* 54, 457–470
13 Roseboom, T.J. *et al.* (2011) Hungry in the womb: what are the consequences? Lessons from the Dutch famine. *Maturitas* 70, 141–145
14 de Groot, R.H. *et al.* (2011) Prenatal famine exposure and cognition at age 59 years. *Int. J. Epidemiol.* 40, 327–337
15 Isaacs, E.B. *et al.* (2010) Impact of breast milk on intelligence quotient, brain size, and white matter development. *Pediatr. Res.* 67, 357–362
16 Pijlman, F.T.A. *et al.* (2003) Physical and emotional stress have differential effects on preference for saccharine and open field behaviour in rats. *Behav. Brain Res.* 139, 131–138
17 Wiener, S.G. *et al.* (1976) Influence of maternal malnutrition on pituitary-adrenal responsiveness to offspring. *Physiol. Behav.* 17, 897–901
18 Spencer, S.J. (2013) Perinatal programming of neuroendocrine mechanisms connecting feeding behavior and stress. *Front. Neurosci.* 7, 109
19 Squire, L.R. (1992) Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. *Psychol. Rev.* 99, 195–231
20 Joels, M. and Baram, T.Z. (2009) The neuro-symphony of stress. *Nat. Rev. Neurosci.* 10, 459–466
21 Arnold, S.E. and Trojanowski, J.Q. (1996) Human fetal hippocampal development: I. Cytoarchitecture, myeloarchitecture, and neuronal morphologic features. *J. Comp. Neurol.* 367, 274–292
22 Altman, J. and Bayer, S.A. (1990) Migration and distribution of two populations of hippocampal granule cell precursors during the perinatal and postnatal periods. *J. Comp. Neurol.* 301, 365–381
23 Kempermann, G. *et al.* (2004) Functional significance of adult neurogenesis. *Curr. Opin. Neurobiol.* 14, 186–191
24 Lucassen, P.J. *et al.* (2010) Regulation of adult neurogenesis by stress, sleep disruption, exercise and inflammation: Implications for depression and antidepressant action. *Eur. Neuropsychopharmacol.* 20, 1–17
25 Shors, T.J. *et al.* (2001) Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410, 372–376
26 Ivy, A.S. *et al.* (2010) Hippocampal dysfunction and cognitive impairments provoked by chronic early-life stress involve excessive activation of CRH receptors. *J. Neurosci.* 30, 13005–13015
27 Chen, Y. *et al.* (2010) Correlated memory defects and hippocampal dendritic spine loss after acute stress involve corticotropin-releasing hormone signaling. *Proc. Natl. Acad. Sci. U.S.A.* 107, 13123–13128
28 Zuena, A.R. *et al.* (2008) Prenatal restraint stress generates two distinct behavioral and neurochemical profiles in male and female rats. *PLoS ONE* 3, e2170
29 Lemaire, V. *et al.* (2000) Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. *Proc. Natl. Acad. Sci. U.S.A.* 97, 11032–11037
30 Oomen, C.A. *et al.* (2010) Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *J. Neurosci.* 30, 6635–6645
31 Yang, J. *et al.* (2006) Prenatal stress modifies hippocampal synaptic plasticity and spatial learning in young rat offspring. *Hippocampus* 16, 431–436
32 Yaka, R. *et al.* (2007) Effect of varied gestational stress on acquisition of spatial memory, hippocampal LTP and synaptic proteins in juvenile male rats. *Behav. Brain Res.* 179, 126–132
33 Weinstock, M. (2011) Sex-dependent changes induced by prenatal stress in cortical and hippocampal morphology and behaviour in rats: an update. *Stress* 14, 604–613
34 Odagiri, K. *et al.* (2008) Psychological prenatal stress reduced the number of BrdU immunopositive cells in the dorsal hippocampus without affecting the open field behavior of male and female rats at one month of age. *Neurosci. Lett.* 446, 25–29
35 Van den Hove, D.L.A. *et al.* (2006) Prenatal stress and neonatal rat brain development. *Neuroscience* 137, 145–155
36 Kawamura, T. *et al.* (2006) Prenatal stress suppresses cell proliferation in the early developing brain. *Neuroreport* 17, 1515–1518
37 Huot, R.L. *et al.* (2002) Neonatal maternal separation reduces hippocampal mossy fiber density in adult Long Evans rats. *Brain Res.* 950, 52–63
38 Aisa, B. *et al.* (2007) Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. *Psychoneuroendocrinology* 32, 256–266
39 Rice, C.J. *et al.* (2008) A novel mouse model for acute and long-lasting consequences of early life stress. *Endocrinology* 149, 4892–4900
40 Brunson, K.L. *et al.* (2005) Mechanisms of late-onset cognitive decline after early-life stress. *J. Neurosci.* 25, 9328–9338
41 Champagne, D.L. *et al.* (2008) Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and differential responsiveness to glucocorticoids and stress. *J. Neurosci.* 28, 6037–6045
42 Oomen, C.A. *et al.* (2011) Early maternal deprivation affects dentate gyrus structure and emotional learning in adult female rats. *Psychopharmacology* 214, 249–260
43 Leventopoulos, M. *et al.* (2007) Long-term effects of early life deprivation on brain glia in Fischer rats. *Brain Res.* 1142, 119–126
44 Bredy, T.W. *et al.* (2003) Maternal care influences neuronal survival in the hippocampus of the rat. *Eur. J. Neurosci.* 18, 2903–2909
45 Mirescu, C. *et al.* (2004) Early life experience alters response of adult neurogenesis to stress. *Nat. Neurosci.* 7, 841–846
46 Oomen, C.A. *et al.* (2009) Opposite effects of early maternal deprivation on neurogenesis in male versus female rats. *PLoS ONE* 4, e3675
47 Heine, V.M. *et al.* (2004) Suppressed proliferation and apoptotic changes in the rat dentate gyrus after acute and chronic stress are reversible. *Eur. J. Neurosci.* 19, 131–144
48 Oomen, C.A. *et al.* (2007) Brief treatment with the glucocorticoid receptor antagonist mifepristone normalizes the reduction in neurogenesis after chronic stress. *Eur. J. Neurosci.* 26, 3395–3401
49 Korosi, A. *et al.* (2012) Early-life stress mediated modulation of adult neurogenesis and behavior. *Behav. Brain Res.* 227, 400–409
50 Nederhof, E. and Schmidt, M.V. (2012) Mismatch or cumulative stress: toward an integrated hypothesis of programming effects. *Physiol. Behav.* 106, 691–700

51 McEchron, M.D. *et al.* (2005) Perinatal nutritional iron deficiency permanently impairs hippocampus-dependent trace fear conditioning in rats. *Nutr. Neurosci.* 8, 195–206
52 Beard, J.L. *et al.* (2006) Moderate iron deficiency in infancy: biology and behavior in young rats. *Behav. Brain Res.* 170, 224–232
53 Bhate, V. *et al.* (2008) Vitamin B12 status of pregnant Indian women and cognitive function in their 9-year-old children. *Food Nutr. Bull.* 29, 249–254
54 Tonkiss, J. *et al.* (1994) An analysis of spatial navigation in prenatally protein malnourished rats. *Physiol. Behav.* 55, 217–224
55 Coupé, B. *et al.* (2009) Perinatal undernutrition modifies cell proliferation and brain-derived neurotrophic factor levels during critical time-windows for hypothalamic and hippocampal development in the male rat. *J. Neuroendocrinol.* 21, 40–48
56 Matos, R.J.B. *et al.* (2011) Nutrient restriction during early life reduces cell proliferation in the hippocampus at adulthood but does impairs the neuronal differentiation process of the new generated cells. *Neuroscience* 196, 16–24
57 Diáz-Cintra, S. *et al.* (1991) Effects of prenatal protein deprivation on postnatal development of granule cells in the fascia dentata. *J. Comp. Neurol.* 310, 356–364
58 Mokler, D.J. *et al.* (1999) The effects of median raphé electrical stimulation on serotonin release in the dorsal hippocampal formation of prenatally protein malnourished rats. *Brain Res.* 838, 95–103
59 Bronzino, J.D. *et al.* (1996) Diet-induced alterations in the ontogeny of long-term potentiation. *Hippocampus* 6, 109–117
60 Guéant, J. *et al.* (2013) Molecular and cellular effects of vitamin B12 in brain, myocardium and liver through its role as co-factor of methionine synthase. *Biochimie* 95, 1033–1040
61 Jones, D.G. and Dyson, S.E. (1981) The influence of protein restriction, rehabilitation and changing nutritional status on synaptic development: a quantitative study in rat brain. *Brain Res.* 208, 97–111
62 Benítez-Bribiesca, L. *et al.* (1999) Dendritic spine pathology in infants with severe protein-calorie malnutrition. *Pediatrics* 104, e21
63 Fenoglio, K.A. *et al.* (2006) Hippocampal neuroplasticity induced by early-life stress: functional and molecular aspects. *Front. Neuroendocrinol.* 27, 180–192
64 Korosi, A. and Baram, T.Z. (2010) Plasticity of the stress response early in life: mechanisms and significance. *Dev. Psychobiol.* 52, 661–670
65 Liu, D. *et al.* (2000) Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nat. Neurosci.* 3, 799–806
66 van Hasselt, F.N. *et al.* (2012) Adult hippocampal glucocorticoid receptor expression and dentate synaptic plasticity correlate with maternal care received by individuals early in life. *Hippocampus* 22, 255–266
67 Chatterjee, D. *et al.* (2007) Maternal isolation alters the expression of neural proteins during development: "Stroking" stimulation reverses these effects. *Brain Res.* 1158, 11–27
68 Feldman, R. *et al.* (2010) Touch attenuates infants' physiological reactivity to stress. *Dev. Sci.* 13, 271–278
69 Chen, J. *et al.* (2012) Maternal deprivation in rats is associated with corticotropin releasing hormone (Crh) promoter hypomethylation and enhances Crh transcriptional responses to stress in adulthood. *J. Neuroendocrinol.* 24, 1055–1064
70 Weaver, I.C.G. *et al.* (2004) Epigenetic programming by maternal behavior. *Nat. Neurosci.* 7, 847–854
71 Murgatroyd, C. *et al.* (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat. Neurosci.* 12, 1559–1566
72 Roth, T.L. *et al.* (2009) Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol. Psychiatry* 65, 760–769
73 Liu, D. *et al.* (1997) Maternal care, hippocampal glucocorticoid receptors, and hypothalamic-pituitary-adrenal responses to stress. *Science* 277, 1659–1662
74 Ivy, A.S. *et al.* (2008) Dysfunctional nurturing behavior in rat dams with limited access to nesting material: a clinically relevant model for early-life stress. *Neuroscience* 154, 1132–1142
75 Fenoglio, K.A. *et al.* (2005) Enduring, handling-evoked enhancement of hippocampal memory function and glucocorticoid receptor expression involves activation of the corticotropin-releasing factor type 1 receptor. *Endocrinology* 146, 4090–4096
76 Lajud, N. *et al.* (2011) Periodic maternal separation decreases hippocampal neurogenesis without affecting basal corticosterone during the stress hyporesponsive period, but alters HPA axis and coping behavior in adulthood. *Psychoneuroendocrinology* 37, 410–420
77 Kamphuis, P.J.G.H. *et al.* (2003) Long-lasting effects of neonatal dexamethasone treatment on spatial learning and hippocampal synaptic plasticity: involvement of the NMDA receptor complex. *FASEB J.* 17, 911–913
78 Claessens, S.E.F. *et al.* (2012) Acute effects of neonatal dexamethasone treatment on proliferation and astrocyte immunoreactivity in hippocampus and corpus callosum: towards a rescue strategy. *Brain Res.* 1482, 1–12
79 Brunson, K.L. *et al.* (2005) Hippocampal neurogenesis is not enhanced by lifelong reduction of glucocorticoid levels. *Hippocampus* 15, 491–501
80 van Oers, H.J. *et al.* (1999) Persistent effects of maternal deprivation on HPA regulation can be reversed by feeding and stroking but not by dexamethasone. *J. Neuroendocrinol.* 11, 581–588
81 Korosi, A. *et al.* (2010) Early-life experience reduces excitation to stress-responsive hypothalamic neurons and reprograms the expression of corticotropin-releasing hormone. *J. Neurosci.* 30, 703–713
82 Avishai-Eliner, S. *et al.* (2001) Altered regulation of gene and protein expression of hypothalamic-pituitary-adrenal axis components in an immature rat model of chronic stress. *J. Neuroendocrinol.* 13, 799–807
83 Wang, X. *et al.* (2011) Forebrain CRF1 modulates early-life stress-programmed cognitive deficits. *J. Neurosci.* 31, 13625–13634
84 Tyrka, A.R. *et al.* (2009) Interaction of childhood maltreatment with the corticotropin-releasing hormone receptor gene: effects on hypothalamic-pituitary-adrenal axis reactivity. *Biol. Psychiatry* 66, 681–685
85 Duclos, M. *et al.* (2005) Corticosterone-dependent metabolic and neuroendocrine abnormalities in obese Zucker rats in relation to feeding. *Am. J. Physiol. Endocrinol. Metab.* 288, 254–266
86 Tannenbaum, B.M. *et al.* (1997) High-fat feeding alters both basal and stress-induced hypothalamic-pituitary-adrenal activity in the rat. *Am. J. Physiol.* 273, 1168–1177
87 Sebaai, N. *et al.* (2004) Perinatal food deprivation induces marked alterations of the hypothalamo-pituitary-adrenal axis in 8-month-old male rats both under basal conditions and after a dehydration period. *Neuroendocrinology* 79, 163–173
88 Benedict, C. *et al.* (2009) Early morning rise in hypothalamic-pituitary-adrenal activity: a role for maintaining the brain's energy balance. *Psychoneuroendocrinology* 34, 455–462
89 Wren, A.M. *et al.* (2002) The hypothalamic mechanisms of the hypophysiotropic action of ghrelin. *Neuroendocrinology* 76, 316–324
90 Schmidt, M.V. *et al.* (2006) Metabolic signals modulate hypothalamic-pituitary-adrenal axis activation during maternal separation of the neonatal mouse. *J. Neuroendocrinol.* 18, 865–874
91 Walker, C. (2010) Maternal touch and feed as critical regulators of behavioral and stress responses in the offspring. *Dev. Psychobiol.* 52, 638–650
92 Walker, C. *et al.* (2008) Perinatal maternal fat intake affects metabolism and hippocampal function in the offspring: a potential role for leptin. *Ann. N. Y. Acad. Sci.* 1144, 189–202
93 D'Asti, E. *et al.* (2010) Maternal dietary fat determines metabolic profile and the magnitude of endocannabinoid inhibition of the stress response in neonatal rat offspring. *Endocrinology* 151, 1685–1694
94 Trottier, G. *et al.* (1998) Increased fat intake during lactation modifies hypothalamic-pituitary-adrenal responsiveness in developing rat pups: a possible role for leptin. *Endocrinology* 139, 3704–3711
95 Sasaki, A. *et al.* (2013) Perinatal high fat diet alters glucocorticoid signaling and anxiety behavior in adulthood. *Neuroscience* 240, 1–12
96 Bertram, C. *et al.* (2001) The maternal diet during pregnancy programs altered expression of the glucocorticoid receptor and type 2 11β-hydroxysteroid dehydrogenase: potential molecular mechanisms underlying the programming of hypertension *in utero*. *Endocrinology* 142, 2841–2853
97 Dutriez-Casteloot, I. *et al.* (2008) Tissue-specific programming expression of glucocorticoid receptors and 11β-HSDs by maternal perinatal undernutrition in the HPA axis of adult male rats. *Horm. Metab. Res.* 40, 257–261

98 Brown, A.S. *et al.* (2000) Further evidence of relation between prenatal famine and major affective disorder. *Am. J. Psychiatry* 157, 190–195
99 Heim, C. *et al.* (2010) Neurobiological and psychiatric consequences of child abuse and neglect. *Dev. Psychobiol.* 52, 671–690
100 Núñez, H. *et al.* (2008) Fetal undernutrition induces overexpression of CRH mRNA and CRH protein in hypothalamus and increases CRH and corticosterone in plasma during postnatal life in the rat. *Neurosci. Lett.* 448, 115–119
101 Laugero, K.D. *et al.* (2002) Corticosterone infused intracerebroventricularly inhibits energy storage and stimulates the hypothalamo-pituitary-axis in adrenalectomized rats drinking sucrose. *Endocrinology* 143, 4552–4562
102 Li, J. *et al.* (2010) Prenatal stress exposure related to maternal bereavement and risk of childhood overweight. *PLoS ONE* 5, e11896
103 D'Argenio, A. *et al.* (2009) Early trauma and adult obesity: is psychological dysfunction the mediating mechanism? *Physiol. Behav.* 98, 543–546
104 Purcell, R.H. *et al.* (2011) Maternal stress and high-fat diet effect on maternal behavior, milk composition, and pup ingestive behavior. *Physiol. Behav.* 104, 474–479
105 Tamashiro, K.L.K. *et al.* (2009) Prenatal stress or high-fat diet increases susceptibility to diet-induced obesity in rat offspring. *Diabetes* 58, 1116–1125
106 Ryu, V. *et al.* (2009) Post-weaning isolation promotes food intake and body weight gain in rats that experienced neonatal maternal separation. *Brain Res.* 1295, 127–134
107 Weninger, S.C. *et al.* (1999) CRH-deficient mice have a normal anorectic response to chronic stress. *Regul. Pept.* 84, 69–74
108 Daniels, W.M.U. *et al.* (2009) Maternal separation alters nerve growth factor and corticosterone levels but not the DNA methylation status of the exon 1(7) glucocorticoid receptor promoter region. *Metab. Brain Dis.* 24, 615–627
109 McGowan, P.O. *et al.* (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat. Neurosci.* 12, 342–348
110 McGowan, P.O. *et al.* (2011) Broad epigenetic signature of maternal care in the brain of adult rats. *PLoS ONE* 6, e14739
111 Levine, A. *et al.* (2011) Early life stress triggers sustained changes in histone deacetylase expression and histone H4 modifications that alter responsiveness to adolescent antidepressant treatment. *Neurobiol. Dis.* 45, 488–498
112 Naumova, O.Y. *et al.* (2011) Differential patterns of whole-genome DNA methylation in institutionalized children and children raised by their biological parents. *Dev. Psychopathol.* 24, 143–155
113 Sinclair, K.D. *et al.* (2007) DNA methylation, insulin resistance, and blood pressure in offspring determined by maternal periconceptional B vitamin and methionine status. *Proc. Natl. Acad. Sci. U.S.A.* 104, 19351–19356
114 Canani, R.B. *et al.* (2011) Epigenetic mechanisms elicited by nutrition in early life. *Nutr. Res. Rev.* 24, 198–205
115 Jiang, X. *et al.* (2012) Maternal choline intake alters the epigenetic state of fetal cortisol-regulating genes in humans. *FASEB J.* 26, 3563–3574
116 Lillycrop, K.A. and Burdge, G.C. (2011) The effect of nutrition during early life on the epigenetic regulation of transcription and implications for human diseases. *J. Nutrigenet. Nutrigenomics* 4, 248–260
117 Davis, C.D. and Uthus, E.O. (2004) DNA methylation, cancer susceptibility, and nutrient interactions. *Exp. Biol. Med.* 229, 988–995
118 Niculescu, M.D. *et al.* (2011) Maternal α-linolenic acid availability during gestation and lactation alters the postnatal hippocampal development in the mouse offspring. *Int. J. Dev. Neurosci.* 29, 795–802
119 Davison, J.M. *et al.* (2009) Gestational choline supply regulates methylation of histone H3, expression of histone methyltransferases G9a (Kmt1c) and Suv39h1 (Kmt1a), and DNA methylation of their genes in rat fetal liver and brain. *J. Biol. Chem.* 284, 1982–1989
120 Mellott, T.J. *et al.* (2004) Prenatal choline supplementation advances hippocampal development and enhances MAPK and CREB activation. *FASEB J.* 18, 545–547
121 Craciunescu, C.N. *et al.* (2010) Dietary choline reverses some, but not all, effects of folate deficiency on neurogenesis and apoptosis in fetal mouse brain. *J. Nutr.* 140, 1162–1166
122 Mehedint, M.G. (2010) Maternal dietary choline deficiency alters angiogenesis in fetal mouse hippocampus. *Proc. Natl. Acad. Sci. U.S.A.* 107, 12834–12839
123 Ilcol, Y.O. *et al.* (2005) Choline status in newborns, infants, children, breast-feeding women, breast-fed infants and human breast milk. *J. Nutr. Biochem.* 16, 489–499
124 Craciunescu, C.N. *et al.* (2003) Choline availability during embryonic development alters progenitor cell mitosis in developing mouse hippocampus. *J. Nutr.* 133, 3614–3618
125 Meck, W.H. and Williams, C.L. (1999) Choline supplementation during prenatal development reduces proactive interference in spatial memory. *Brain Res. Dev. Brain Res.* 118, 51–59
126 Petrie, L. *et al.* (2002) Serum concentrations of homocysteine are elevated during early pregnancy in rodent models of fetal programming. *Br. J. Nutr.* 88, 471–477
127 Lillycrop, K.A. *et al.* (2007) Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. *Br. J. Nutr.* 97, 1064–1073
128 Lahiri, D.K. and Maloney, B. (2010) The "LEARn" (Latent Early-life Associated Regulation) model integrates environmental risk factors and the developmental basis of Alzheimer's disease, and proposes remedial steps. *Exp. Gerontol.* 45, 291–296
129 Brawley, L. *et al.* (2004) Glycine rectifies vascular dysfunction induced by dietary protein imbalance during pregnancy. *J. Physiol.* 554, 497–504
130 Burdge, G.C. *et al.* (2009) Nutrition in early life, and risk of cancer and metabolic disease: alternative endings in an epigenetic tale? *Br. J. Nutr.* 101, 619–630
131 Burdge, G.C. *et al.* (2009) Folic acid supplementation during the juvenile-pubertal period in rats modifies the phenotype and epigenotype induced by prenatal nutrition. *J. Nutr.* 139, 1054–1060
132 Weaver, I.C.G. (2005) Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. *J. Neurosci.* 25, 11045–11054
133 Dabydeen, L. *et al.* (2008) High-energy and -protein diet increases brain and corticospinal tract growth in term and preterm infants after perinatal brain injury. *Pediatrics* 121, 148–156
134 Boullu-Ciocca, S. *et al.* (2005) Postnatal diet-induced obesity in rats upregulates systemic and adipose tissue glucocorticoid metabolism during development and in adulthood; its relationship with the metabolic syndrome. *Diabetes* 54, 197–203