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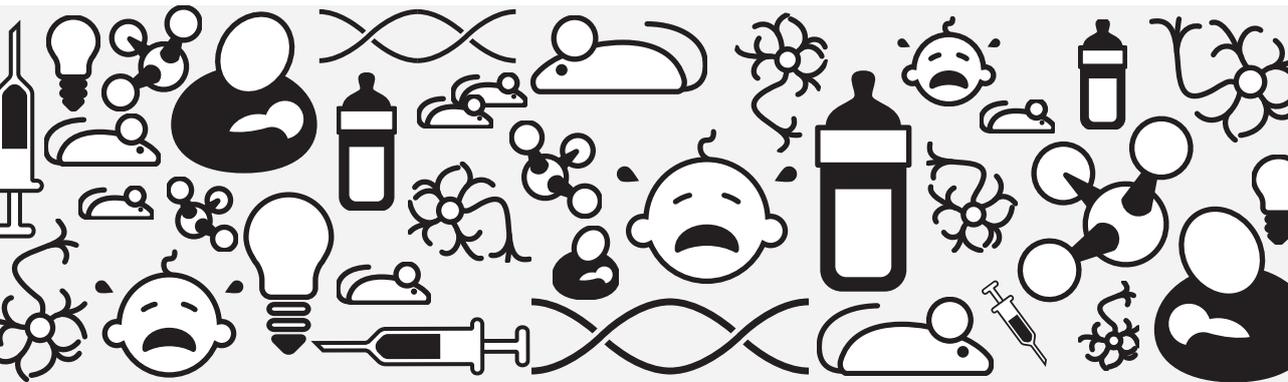
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Chapter 1

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

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ABSTRACT

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 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 all affect 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, very similar impairments to those observed following ELS are found in children exposed to perinatal 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 early-life stress and early-life malnutrition induced impairments. To develop appropriate interventions, it is important to understand the mechanisms by which early-life stress and early-life 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 very inter-related. While feeding behavior and metabolism are closely regulated by neuroendocrine mechanisms that are influenced by stressful events, malnutrition in turn affects the stress system as well (see **fig 1**).

While up to now, most research directed at understanding the processes underlying programming by EL environment views the stress

GLOSSARY

Programming:

The process whereby a stimulus or insult, given or occurring during a critical period, has irreversible long-term effects on the organism.

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 downregulated by ageing and stress.

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 if a region of DNA is open and transcriptionally active (euchromatin), or condensed and largely transcriptionally inactive (heterochromatin).

GLOSSARY (continued)

DNA-methylation:

The covalent modification of DNA by the attachment of a methyl (CH₃) group to a cytosine, usually in the context of cytosine-guanine (CpG) dinucleotide sequences. This generally results in gene silencing.

DNA methyl transferases (DNMTs):

Enzymes regulating cytosine methylation. Three DNMTs are identified in mammals: DNMT1, DNMT3a and DNMT3b. DNMT1 is considered to be a maintenance methyltransferase, while DNMT3a and DNMT3b are considered to be involved in de novo DNA methylation. DNMT3b expression peaks during embryonic development, while DNMT1 and DNMT3a are also expressed in mature neurons.

Histone modifications:

Modifications on the N-terminal tails of histone proteins (e.g. methylation, phosphorylation, acetylation and ubiquitination). These modifications largely define the state of the chromatin (euchromatin or heterochromatin).

Folate (folic acid or Vitamin B₉):

It is an essential micronutrient because most mammals cannot endogenously synthesize folate and 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 role in brain development; folate supplementation during early pregnancy protects against neural tube defects.

One-carbon metabolism (homocysteine metabolism):

The essential micronutrients 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 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), while vitamin B₆-dependent enzymes can metabolize homocysteine to form cysteine.

hormones and the nutritional elements as independent factors [16-18], 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 these mediate the programming of the brain, possibly via epigenetic mechanisms.

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

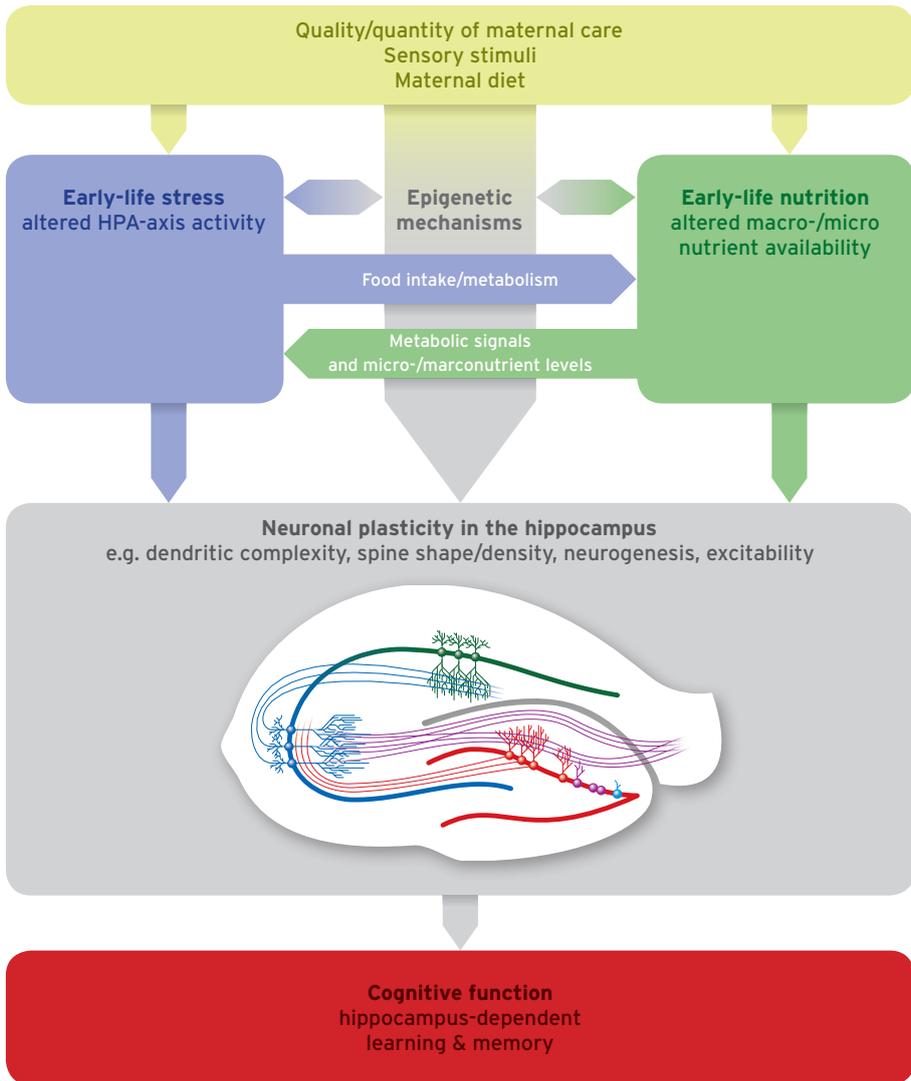


FIGURE 1.

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 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 largely 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

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 (CA) 1 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 arborisation and synapse formation/elimination continuously alter neuronal connectivity. These changes can be assessed morphologically (e.g. by characterization of dendritic arborisation 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.

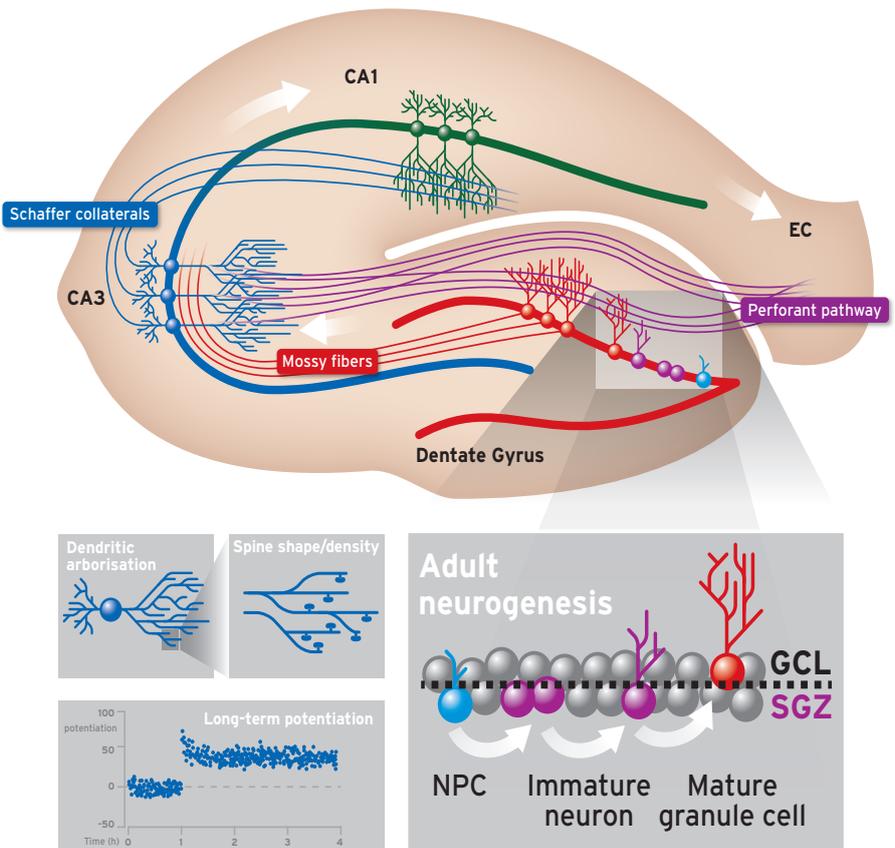


FIGURE I.
THE HIPPOCAMPAL FORMATION AND ITS FORMS OF NEURONAL AND SYNAPTIC PLASTICITY

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 largely 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] while the rodent hippocampus develops between embryonic 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 (see box 1).

Furthermore, the dentate gyrus of the hippocampus is one of the very 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 it is regulated by various factors (e.g. 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). In the following sections, we will 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 human (e.g. childhood abuse or maltreatment) [9] as well as perinatal stress in rodents (see box 2) [28-30] correlate with cognitive impairments in association 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] starting already at postnatal day 1 (P1) [35,36] and lasting up to 22 months of age [29]. Similarly, postnatal stressors in rodents like maternal deprivation [30], repeated maternal separation (MS) [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, while 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 instrumental, the specific elements in the early environment (e.g. sensory stimuli, 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 when they occur during critical stages of development these 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]. Pre-clinical 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 overall protein intake, iron, zinc, selenium, iodine, folate, vitamin A, B₆, B₁₂, choline and long-chain polyunsaturated fatty acids are 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], reduced 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 functioning [12,60] while protein malnutrition results in reduced neuronal DNA and RNA content and an altered fatty acid profile which in turn, could change neuronal function, synapse number and/or dendritic arborisation [61,62].

These data indicate that synapses in the malnourished hippocampus might be less capable to support 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 STIMULI BY 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 this sensory stimuli is established as both artificial manipulation of maternal care (via maternal separation/deprivation, chronic ELS and handling; see **box 2**) [40,63,64] as well as the natural variation in maternal care between [41,65] and within litters [66], programs brain and behaviour of the adult offspring. In line with this, importantly 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 will examine how these sensory stimuli can be affected by the other elements of the early-environment (stress and nutrition).

Next to maternal sensory stimulation, also the 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 including the lasting changes in hippocampus and cognitive functions. EL experience programs, the neuroendocrine system activated upon stress exposure (hypothalamic-pituitary-adrenal (HPA) axis). When the HPA-axis is activated, corticotrophin releasing hormone (CRH) 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 and mineralocorticoid receptors (GRs and MRs) [70], 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-CRFR1 received 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] and an elegant series of experiments

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 (see Figure 1a). Postnatal ELS can be induced by: single prolonged separation of dam and pups for 24 hours e.g. at post-natal day 3 (maternal deprivation (see Figure 1b); MD) or repeated daily separations for 2-5 hours (maternal separation (see Figure 1c); MS). Furthermore, a powerful method to induce chronic EL stress consists of reducing the amount of nesting and bedding material during the first postnatal week (see Figure 1d). This induces fragmented maternal care, thereby mimicking aspects of a human chronic ELS situation where 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 (see 1e). 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 play a role.

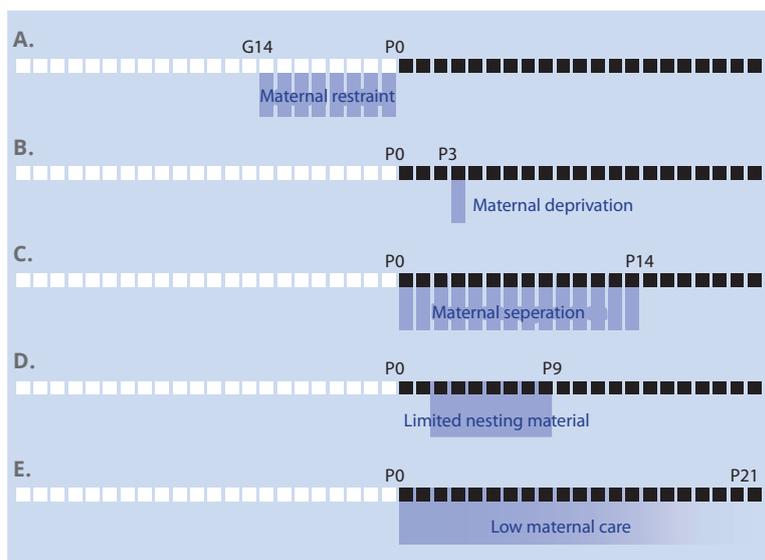


FIGURE 1. FREQUENTLY USED EXPERIMENTAL MANIPULATIONS TO INDUCE EARLY-LIFE STRESS IN RODENTS

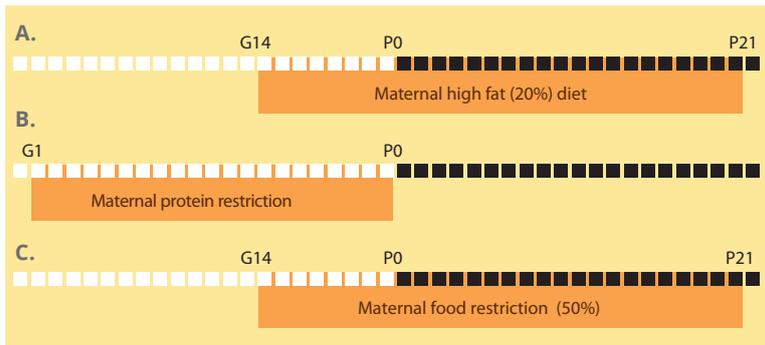


FIGURE II. FREQUENTLY USED EXPERIMENTAL MANIPULATIONS TO ALTER EARLY-LIFE NUTRITION IN RODENTS

EL malnutrition is usually induced by altering maternal diet during pregnancy and/or lactation (e.g. overnutrition with high fat diet (HF; see Figure IIa), protein intake restriction (PR; see Figure IIb) or global dietary restriction (see 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.

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 EL. In fact even though CORT is a logical candidate, there is some controversy in the literature because CORT alteration 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 rise of CORT induced by maternal deprivation does not prevent the HPA-axis alterations [80]. Thus, the complexity of corticosteroid regulation, 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 has similar effects

on hippocampal structure as chronic ELS [40]. Moreover, CRH repression is the first alteration that occurs after handling [82]. Blocking the CRF receptor type 1 (CRFR1) in control rats (P10-P17) improves cognitive functions [75] and blocking of CRFR1 after chronic ELS prevents ELS induced LTP impairment and dendritic atrophy and preserves hippocampal cognition [26]. Finally, in conditional CRFR1 knockout mice subjected to chronic ELS, cognition, LTP and spine density are restored [83]. In line with these pre-clinical data, single nucleotide polymorphisms in the *Crhr1* gene protect against depression in childhood-maltreated individual [84]. Therefore, next to behavioural intervention strategies, pharmacological targeting of GR and CRF-receptor signalling may enhance resilience to ELS-related cognitive impairment and affective disorders [40].

Interaction between maternal care, stress system and nutrient availability

Based on the studies discussed so far, it is clear that maternal tactile stimulation, stress hormones and neuropeptides and nutrient availability are instrumental in mediating lasting effects of EL experiences. While most studies consider these elements individually, for optimal intervention it is fundamental to understand how these environmental elements and molecules interact and influence each other. We will 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 (HF) diet [86] or subjected to perinatal food restriction (FR) [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 effects on HPA-axis and hippocampal GR expression, while stroking alone is not sufficient to achieve this recovery [80]. In addition to changes in HPA-axis tone, MS also reduces plasma glucose and leptin levels, and increases ghrelin levels in the offspring [90]. Blocking pharmacologically the reduction of glucose, or the increase in ghrelin, attenuates the HPA-axis response to MS [90]. This suggests that metabolic signals play an important role in triggering the HPA-axis response of the neonate to MS.

Furthermore, plasma leptin levels in the offspring are modified by the availability and the composition of the maternal milk. Maternal milk is rich in fat and is required for growth and brain development [91-93]. Feeding mothers HF diet from gestational day 14 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], increased GR expression and anxiety [95]. While this effect on HPA-axis could be directly due to the elevations in leptin levels [91], differences in maternal diet might have affected maternal behaviour as well [17], thereby contributing indirectly to the observed effects.

Similarly to fat content, protein restriction (PR) [96] and general undernutrition during gestation and/or lactation [97], affect the HPA-axis of the progeny. Next to the direct effects of PR on the quality of maternal milk, these nutritional restrictions increased CORT and decreased placental 11 β -hydroxy-steroid dehydrogenase type 2 (11 β -HSD2) gene expression possibly leading to fetal overexposure to maternal CORT, which could be partly responsible for some of the effects of maternal food restriction, exemplifying again the tight relationship between stress, nutrition and metabolic signals.

Interestingly, the effects of perinatal malnutrition on adult stress responsiveness and cognitive function resembles 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 behaviour and altered HPA-axis activity (Fig. 1). In line with this hypothesis, maternal undernutrition results in altered maternal behaviour [17] and in high plasma CORT levels in the adult offspring along with reduced GR expression [100] suggesting 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 (early-life) 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 risk to develop obesity later in life and affect feeding regulation evident both from clinical [102,103] as well as pre-clinical studies [104-106]. These effects of stress on appetite regulation and metabolism are in great part mediated by glucocorticoids and stress related peptides as CRH and Urocortins [107] affecting the neural circuits and hormones involved in the regulation of feeding behavior. A detailed analysis of how these systems interact has been extensively reviewed by Spencer [18].

In conclusion there is some evidence that, next to maternal sensory stimulation and stress hormones, the lack of key nutrients also affects the brain directly, both in the case of restricted nutrition as well as in case of perinatal stress. The next question is which molecular mechanisms mediate the programming effects of EL experience. We will here explore the role of epigenetic mechanisms.

EARLY LIFE STRESS AND EPIGENETIC MECHANISMS

Various reports have implicated epigenetic mechanisms in mediating persistent effects of EL experience [69-72] (see **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 are therefore excellent candidates to mediate 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 GR promoter [70] (but see [108]). Translational research has found lower hippocampal GR expression and increased GR promoter DNA-methylation in suicide victims with a history of childhood abuse/neglect [109].

Furthermore, ELS-induced increased AVP levels are associated with DNA-hypomethylation [71], while ELS-induced reduced BDNF expression in the prefrontal cortex is accompanied by increased DNA-methylation [72]. Maternal deprivation induced increase in CRH expression is accompanied by decreased DNA-methylation [69]. Accordingly, the handling induced reduction in CRH expression is associated with persistently elevated 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 MS in mice changed global levels of histone deacetylases [111]. Accordingly, whole-genome DNA-methylation is significantly different between institutionalized children and children raised by their biological parents [112]. Thus epigenetic mechanisms both targeted at specific genes as well as genome wide seem to be a good candidate in 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 methyl-transferases (DNMTs) or *iii*) activities of specific transcription factors [116]. What is the evidence that such mechanisms could be at play in the brain?

EARLY-LIFE INTERVENTION	GENE EXPRESSION	TISSUE	EPIGENETIC CHANGE	SPECIES	REF
LOW MATERNAL CARE	↓ GR	BRAIN (HIPPOCAMPUS)	↑ DNA METHYLATION OF EXON 17 OF GR 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 (PFC)	↑ 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 ALTERATIONS	BRAIN (FOREBRAIN)	↓ HDAC EXPRESSION ↑ H4K12AC	MICE	[111]
CHILDHOOD ABUSE/NEGLECT	↓ GR	BRAIN (HIPPOCAMPUS)	↑ DNA METHYLATION	HUMAN	[109]
INSITUATIONALIZED CHILDREN	GENOME WIDE ALTERATIONS	PERIPHERY (BLOOD)	DIFFERENTIAL PATTERNS OF DNA METHYLATION	HUMAN	[112]
POSTNATAL OVERFEEDING	↑ GR	PERIPHERY (ADIPOSE TISSUE)	?	RATS	[134]
PROTEIN RESTRICTION DURING GESTATION	↑ GR	PERIPHERY (LIVER)	↓ DNA METHYLATION OF EXON 110 OF GR PROMOTER	RATS	[127]
PERICONCEPTIONAL MATERNAL VITAMIN B/ METHIONINE RESTRICTION	GENOME WIDE ALTERATIONS	PERIPHERY (FETAL LIVER)	DIFFERENTIAL PATTERNS OF DNA METHYLATION	SHEEP	[113]
HIGH MATERNAL CHOLINE INTAKE (3 RD TRIMESTER)	↓ CRH	PERIPHERY (PLACENTA)	↑ DNA METHYLATION OF CRH PROMOTER ↑ GLOBAL DNA METHYLATION ↑ H3K9ME2	HUMAN	[115]

TABLE 1. EPIGENETIC MODIFICATIONS INDUCED BY EARLY-LIFE EXPERIENCES

Abbreviations: GR, glucocorticoid receptor; AVP, arginine vasopressin; MeCP2, methyl CpG binding protein 2; BDNF, brain derived neurotrophic factor; CRH, corticotrophin releasing hormone; NRSF, neuron restrictive silencing factor; HDAC, histone deacetylase

The dietary methyl donors: folate, vitamin B₆/B₁₂, methionine, choline and betaine all affect DNA and histone methylation [117]. Fetal choline availability is essential for brain development and maternal choline deficiency alters development and neurogenesis in the fetal mouse hippocampus [118]. Choline availability during fetal brain development induces 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 [123]. In rodents, maternal diets supplemented with choline improved offspring's memory and were associated with increases in neurogenesis in the embryonic brain [124,125].

Furthermore, perturbations in maternal diet can alter DNMT expression; pregnant rats fed a PR diet e.g. 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 1-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.

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 behaviour can be prevented and reversed by interventions in postnatal life [128]. Both folate and glycine supplementation to maternal diet reversed the effects of PR 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 PR 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 to modulate (some of) the lasting consequences of EL experience on adult brain structure and function.

CONCLUSION

In summary, adverse experiences during critical developmental periods persistently affect gene expression, which ultimately may 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 on (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 role. Non-invasive interventions, targeted at maternal nutrition, are thus relatively easy to implement and could have a significant effect on the health outcome of the offspring.

OUTSTANDING QUESTIONS

- Do the lasting alterations caused by early-life malnutrition involve the same mechanisms as the early-life stress (ES)-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 ES 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?

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