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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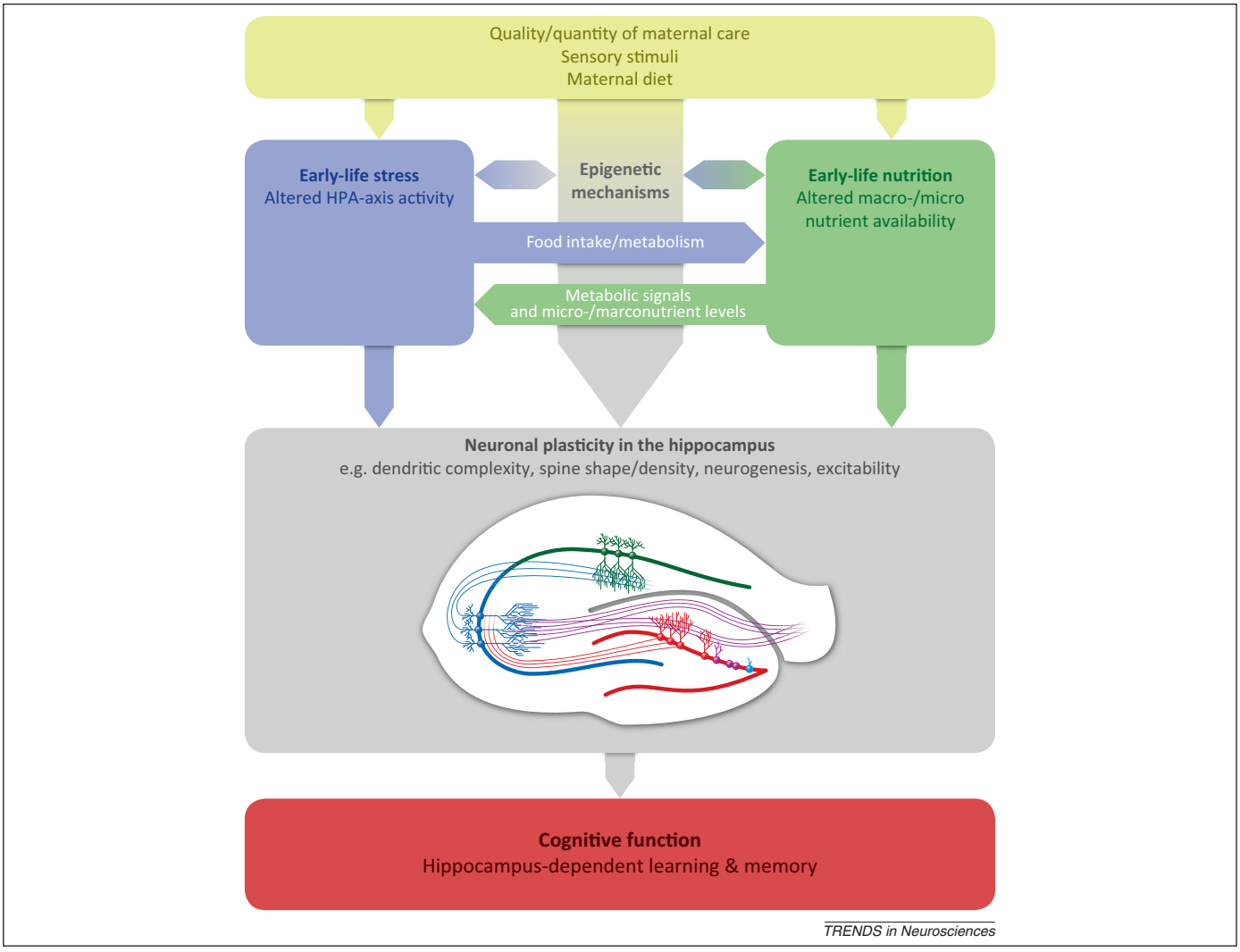

Figure 1. Schematic representation of the pathways via which alterations in the quality and/or quantity of maternal care, sensory stimuli, and maternal diet during early life influence both hypothalamic–pituitary–adrenal (HPA)-axis activity and micro-/macronutrient availability. Although early-life stress 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