Lead Article

Facts and hypotheses about the programming of neuroplastic deficits by prenatal malnutrition

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Studies in rats have shown that a decrease in either protein content or total dietary calories results in molecular, structural, and functional changes in the cerebral cortex and hippocampus, among other brain regions, which lead to behavioral disturbances, including learning and memory deficits. The neurobiological bases underlying those effects depend at least in part on fetal programming of the developing brain, which in turn relies on epigenetic regulation of specific genes via stable and heritable modifications of chromatin. Prenatal malnutrition also leads to epigenetic programming of obesity, and obesity on its own can lead to poor cognitive performance in humans and experimental animals, complicating understanding of the factors involved in the fetal programming of neuroplasticity deficits. This review focuses on the role of epigenetic mechanisms involved in prenatal malnutrition–induced brain disturbances, which are apparent at a later postnatal age, through either a direct effect of fetal programming on brain plasticity or an indirect effect on the brain mediated by the postnatal development of obesity.

INTRODUCTION

A renewed interest in the effects of nutrition on fetal growth and adult health has emerged in the past 2 decades as a result of some epidemiological and experimental studies showing a relationship between maternal malnutrition and adult chronic diseases, such as hypertension and type 2 diabetes. These diseases, together with obesity, dyslipidemia, and ischemic cardiac disease, are part of a more general syndrome, the metabolic syndrome. Fetal malnutrition may lead to a diversity of structural and functional alterations in the brain, including deficits in neuroplasticity. In general, all of these disorders seem to be a consequence of fetal programming, whereby a stimulus or insult at a critical period of early life can result in long-term changes in physiology or metabolism, as proposed by Barker's hypothesis,[1–3] which in turn is part of the so-called developmental origins of health and disease (DOHaD) (for review, see Gluckman et al[4]). Since those early reports, the fetal programming theory has extended to encompass many other tissues and organs in mammals, including the brain.[5–7] Thus, fetal programming, as a subset of DOHaD, should be viewed as a part of a broader biological mechanism termed developmental plasticity, by which organisms, in response to cues such as nutrition, adapt their phenotypes to their environment.

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Key words: epigenetic regulation, fetal programming, neuroplasticity, prenatal malnutrition.

doi: 10.1093/nutrit/nuy047

Neuroplasticity refers to the capacity of the nervous system to adapt (functionally and structurally) in response to experience and injury. It relies on the efficacy of existing synapses or on changes in neural connectivity by the formation and/or deletion of synapses, as well as on extra-synaptic mechanisms such as regulation of neuronal excitability, regulation of synapse formation, and stabilization of total synaptic strength and dendritic arborization.[8] Repeated patterns of synaptic transmission in the brain lead to diverse forms of synaptic plasticity at excitatory and inhibitory synapses (eg, long-term potentiation [LTP] and long-term depression), whereby the efficacy of synaptic transmission becomes up- or downregulated, respectively. Many forms of synaptic potentiation depend primarily on excitation of synaptic ionotropic glutamate receptors (ie, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], kainate, and N-methyl-D-aspartate [NMDA] receptors) and downstream protein kinase–dependent signaling that affects trafficking and the synthesis of a variety of proteins involved in sustaining and perpetuating the neuronal response.[9] They may also depend on the activation of some receptor-dependent modulatory pathways that regulate synaptic plasticity by interacting at various levels with various signal transduction pathways (ie, γ-aminobutyric acid–ergic [GABAergic], dopaminergic, noradrenergic, serotonergic, cholinergic, purinergic, and neurotrophin receptors).[10–13] Thus, neuroplasticity emerges as a major intrinsic property of neural tissue that constitutes the neurobiological basis of learning and memory.

It has been found that neuroplasticity may be influenced by fetal programming because various types of prenatal insults (malnutrition, stress, hormones, drugs) could deeply affect learning and memory processes in the offspring. Such responses include early and short-term changes in physiology and behavior; however, responses to modifications of the gestational environment may also be expressed at later offspring life stages. Fetal programming relies on epigenetic regulation of specific genes via stable and heritable chromatin modifications independently of the underlying DNA sequence, giving rise to the appearance of different phenotypic traits in the cells generated during development (for reviews, see Burdge and Lillycrop[14] and Laubach et al[15]). Changes in chromatin structure arise mainly from 4 distinct mechanisms: DNA methylation, histone modifications, ATP-dependent chromatin remodeling, and noncoding RNAs. Each of these mechanisms could affect neuroplasticity at later stages of development.

DNA methylation, by which a methyl group is attached to a cytosine nucleotide in CpG islands, is a reaction catalyzed by a family of DNA methyltransferases (DNMTs). Methylation depends on methyl group donors and cofactors involved in methionine and folate 1-carbon metabolism, which are usually found in ingested food.[15–17] Much of the methionine formed is converted into S-adenosylmethionine (SAM), a universal methyl group donor in numerous reactions. In addition, SAM is demethylated and subsequently hydrolyzed to homocysteine, which may be methylated back to methionine by methionine synthase depending on the availability of methyl donors such as 5-methyltetrahydrofolate (derived from folic acid) or betaine (derived from choline). Thus, DNA methylation depends on folate and choline availability, as well as on vitamin B6 and B2 (required to catalyze the conversion of tetrahydrofolate to 5-methyl- tetrahydrofolate) and vitamin B12 (a precursor to methionine synthase).[16,17] In the organism, low concentrations of homocysteine favor remethylation, whereas high homocysteine concentrations promote transsulfuration, which may remove homocysteine from the methionine cycle and catabolize the methionine excess, at least in the liver, kidney, intestine, pancreas, and brain. As a corollary, it seems clear that dietary amino acids, folate, and vitamin B should be balanced to prevent adverse changes in fetal metabolic pathways, such as hyper- or hypomethylation of DNA. In this regard, increased DNA methylation is generally associated with gene silencing, whereas decreased methylation is related to gene activation.[18] DNMT1 and DNMT3a, which are involved in maintenance and in de novo methylation, respectively,[19] are expressed in postmitotic neurons in the brain; double-knockout mice lacking both DNMTs showed defective LTP in the hippocampal CA1 region, together with deficits in learning and memory.[20]

Histone modification includes histone acetylation, methylation, and other types of modification that may either activate or deactivate transcription by changing the way DNA wraps around the nucleosome. Histone acetylation, which is regulated by histone acetyltransferases (HATs) and a variety of histone deacetylases (HDACs), is considered as an open chromatin mark associated with gene activation, whereas histone methylation can act either as an open (gene activation) or condensed (transcription repression) mark, depending on the residue where methylation occurs.[21] For instance, H3K4 methylation is considered a gene activation signal, whereas H3K9 and H3K27 methylation are correlated with transcription repression.[22] Consistently, transgenic mice with reduced intrinsic HAT activity of the CREB binding protein in the hippocampal CA1 and dentate gyrus showed impaired long-term memory (which indicates that HAT activity of CREB is required for long-term memory consolidation), whereas acetylated histone levels and long-term memory were

rescued by administration of an HDAC inhibitor.[23] More recently it has been found that folate deficiency leads to reduced proliferation and enhanced apoptosis in hippocampal cells via increased expression of HDAC4, -6, and -7, whereas cell treatment with an HDAC inhibitor led to a noticeable improvement of the folate deficiency–associated alterations of differentiation.[24] Additionally, it has been found that mice deficient in H3K4 methyltransferase exhibited memory impairment in contextual fear conditioning learning,[25] whereas reduced methylation of H3K9 produced the opposite effect.[26]

ATP-dependent chromatin remodelers use ATP hydrolysis to unwrap or disrupt the association between DNA and histones, to relocate or to evict nucleosomes along DNA, or to exchange 1 histone variant for another. A family of ATP-dependent chromatin remodeling complexes, called BAF, has been found to greatly contribute to the establishment of the diversity, stability, and plasticity of the nervous system. In particular, mice with selective genetic manipulations of the neuron-specific BAF53b subunit have severe deficits of long-term memory and were unable to consolidate hippocampal LTP.[27]

Finally, small and long noncoding RNAs, which are required to maintain chromatin structure by bridging the interaction between proteins and DNA, can interact with chromatin modifiers or act as molecular scaffolding to regulate epigenetic mechanisms within the cell. For instance, small noncoding RNAs (miRNAs) have been found to be relevant in memory consolidation by regulating CREB[28] in a serotonin-dependent synaptic plasticity mechanism.[29] Interestingly, methyl donor deficiency during pregnancy can induce persistent brain defects in pups by reducing Stat3 signaling targeted by miRNA-124.[30] Late maternal folate supplementation rescued rats from brain defects associated with methyl donor deficiency by restoring Let-7 and miR-34 pathways, 2 miRNAs known to be regulated by methylation.[31] Thus, methyl donors could affect the epigenetic landscape in the developing brain through various mechanisms, including methylation of DNA and associated histones, as well as of noncoding miRNAs, thereby highlighting the important epigenetic role of methyl donors in neuronal development. In contrast, the role of long noncoding RNAs on neuroplasticity has received less attention.[32] A recent report indicates that the long noncoding RNA BC048612 coregulates, together with miRNA 203, the expression of the neuronal growth regulator 1 cell adhesion protein in neurons.[33]

The foregoing data are consistent with the notion that the prenatal epigenetic profile exerts a prominent and profound influence on the formation and/or consolidation of the nervous system during development.[21] However, it seems also clear that in postmitotic, fully differentiated neurons epigenetic modifications might be highly dynamic and could thereby support neuronal functions and plasticity.[34] Moreover, epigenetic mechanisms that alter gene expression may impact adult sensory cortical plasticity, memory, and sensory discrimination ability by modifying the threshold of induction for robust and persistent memories, thereby enabling information encoding in sensory cortices (for review, see Phan and Bieszczad[35]).

How can maternal dietary calories and proteins program the emergence of complex diseases during postnatal life? Several recent reviews have focused on fetal programming of disease,[16,36] including metabolic syndrome,[37,38] diabetes,[38,39] insulin resistance,[40] hypertension and cardiac disease,[41] obesity,[38,42,43] reproductive function,[44] and placental development.[45] The effects of prenatal malnutrition on brain programming deserve more attention (but see reviews by Manuel-Apolinar et al,[46] Grissom et al,[47] and Moody et al[48]). Although there is vast literature regarding epigenetic modifications induced in a variety of organs by undernutrition early in life, the role of epigenetics in the effects of fetal malnutrition on the developing brain has begun to be understood only recently. As an example, in 2001 Tucker claimed that "there is no evidence for an involvement of methylation in plastic CNS [central nervous system] processes, such as synaptic or dendritic remodeling,"[49] whereas in 2008 Borrelli et al[50] published a review that aimed to identify the epigenetic mechanism associated with neuronal plasticity. Ascribing the neuroplastic deficits found in previously malnourished adults to an altered fetal programming of the brain—as frequently stated in the literature—is a hypothetical issue because prenatal malnutrition can also program, for example, obesity, which may lead to neuroplastic deficits too. Conceptually, elucidating this aspect is not a purely academic question because, if neurodevelopmental alterations are a consequence of obesity developed during postnatal life but programmed in utero, they should then be prevented by precluding development of overweight. On the contrary, if they are a direct consequence of epigenetic intrauterine programming of the brain via phenotypic diversity of neural/glial mediators, transporters, receptors, and other proteins, which are mainly sensitive to epigenetic nutritional influences only during the narrow period of prenatal life and lactation,[21] they could be present at adulthood irrespective of the dietary regime adopted later in postnatal age.

The current review focuses on the role of epigenetic mechanisms in prenatal malnutrition–induced brain disturbances, which are apparent at later postnatal age, either via a direct effect of fetal programming on brain

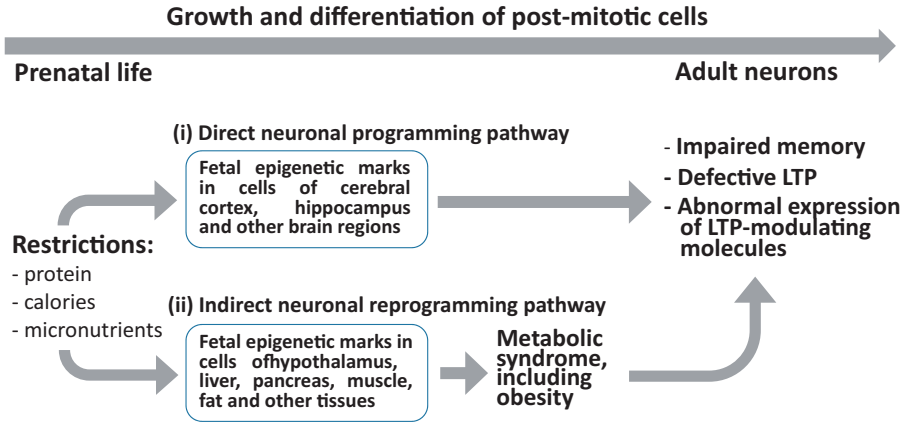

Figure 1 **Scheme depicting how dietary restrictions during prenatal life (proteins, calories, micronutrients) can lead to the emergence of disturbances in neuroplasticity at adulthood (impaired memory, defective long-term potentiation, abnormal expression of neurotransmitters/mediators and their receptors) via 2 alternative coexisting pathways:** 1) direct neuronal programming (epigenetic marks in fetal progenitor cells and developing neurons that will form the cerebral cortex, hippocampus and other brain regions involved in neuroplasticity); and/or 2) indirect neuronal reprogramming of postnatal/adult neurons mediated by obesity (as part of the metabolic syndrome), which develops in postnatal life as a consequence of epigenetic marks on fetal cells that will form organs involved in growth, metabolism, and hunger and satiety mechanisms (hypothalamus, liver, pancreas, muscle, fat and other tissues). *Abbreviation:* LTP, long-term potentiation.

plasticity or via an indirect effect on the brain mediated by the postnatal development of obesity as an alternative (or rather complementary) programming mechanism (see Figure 1). Two objectives are pursued. First, this review seeks to provide a summary of the effects of prenatal malnutrition on brain development and function, with emphasis on the consequences in neuroplasticity, and to present the existing evidence for epigenetic mediation. Second, this review seeks to summarize the programming effects of prenatal malnutrition on obesity and metabolic syndrome in later life, highlighting both their repercussions on brain plasticity and the epigenetic mechanisms involved.

PRENATAL MALNUTRITION: EFFECTS ON BRAIN DEVELOPMENT AND FUNCTION AND THE ROLE OF EPIGENETICS

Human population studies

In 2008, the prevalence of babies with intrauterine growth restriction in developing countries was reported to be as high as 10.8%.[51] Nutritional deficits during pregnancy may ultimately result in impairment of higher brain functions at later stages of life. Moreover, nourishment restrictions during pregnancy lead to fetal growth restriction and may cause permanent brain dysfunction, particularly cognitive and behavioral deficits in humans.[52,53] Studies in children who are small for gestational age (SGA), a crude anthropometric parameter used for the clinical diagnosis of intrauterine undernutrition, have revealed that these children are at a high risk for exhibiting subnormal intellectual quotients and experiencing learning deficits.[54,55] It has been reported that the intelligence quotient (IQ) score at school age is linked to birth weight among low birth weight babies[56] and that there are associations between birth weight and cognitive function at subsequent ages,[57] indicating that birth weight at the bottom end of the normal range (which mainly results from moderate maternal undernutrition) is related to impaired higher mental function in later life. A recent systematic review examining neurodevelopmental outcomes in SGA children[58] reported that these infants were particularly impaired in cognitive (global cognitive ability, memory, processing ability, learning, problem solving, perceptual performance, spatial orientation) and behavioral (attention, personal social ability, adaptive behavior) developmental domains. These findings were subsequently confirmed in a meta-analysis showing that school-age SGA children show lower cognitive scores (verbal and performance IQ, as revealed by Wechsler intelligence scales) and higher incidence of behavioral disorders (checked on standardized tests) than controls born appropriate for gestational age[59] (Table 1).[58–61]

There are also very clear data in the literature showing fetal programming of methyl donor deficiency, another condition of prenatal malnutrition. Folates and vitamin B12 are needed for methionine synthesis, the precursor of SAM. Therefore, they play a key role in nutrition and epigenomics by providing monocarbons required for methylation of DNA and gene regulators. In humans, low maternal erythrocytes folate concentration in early pregnancy was specifically associated with behavioral problems such as hyperactivity and peer problems in 9-year-old children, and this association was

Table 1 **Effects of prenatal malnutrition on cognition and behavior: outcomes from children born small for gestational age**

Nutritional condition at birth	Type of study	Type of test	Age range at evaluation	Effect	References
SGA	Meta-analysis	Cognitive IQ[a]	5–19 y	Lower verbal IQ scores Lower performance IQ scores	Chen et al 2016[59]
SGA	Meta-analysis	Behavioral scores[b]	5–19 y	Considerably different behavior scores	Chen et al (2016)[59]
SGA	Systematic review	Cognitive scores[c]		Cognitive impairment (global cognitive ability, memory, processing ability, learning, problem solving, perceptual performance, spatial orientation)	Murray et al (2015)[58]
SGA	Systematic review	Behavioral scores[d]	3 mo to 10 y	Impaired behavioral development (attention, personal social ability, adaptive behavior)	Murray et al (2015)[58]
SGA	Review	Cognitive IQ[e]	Not reported	Considerably lower IQ	de Bie et al (2010)[60]
SGA	Systematic review	IQ, cognitive scores, educational achievement[f]	Not reported	Minor association between SGA and cognitive outcome	Noeker (2005)[61]

Abbreviations: IQ, intelligence quotient; SVG, small for gestational age.

[a]Tests used included the following: Wechsler Intelligence Scale for Children; Revised Wechsler Intelligence Scale for Children; Third Wechsler Intelligence Scale for Children; Wechsler Preschool and Primary Scale of Intelligence; Revised Wechsler Preschool and Primary Scale of Intelligence.

[b]Tests used included the following: Child Behavior Check List; Conner Abbreviated Parent Rating Scale; Strengths and Difficulties Questionnaire.

[c]Tests used included the following: Bayley Scales of Infant Development; Wechsler Intelligence Scale for Children; Kaufman Assessment Battery for Children; Visual Auditory Digit Span; Rey Auditory Verbal Learning Test; Rey Osterrieth Complex Figure Test; Wechsler Preschool and Primary Scale of Intelligence; Radial Arm Maze; Raven's Progressive Matrices; Revisie Amsterdamse Kinder Intelligentietest; British Abilities Scale; Clinical Adaptive/Clinical Linguistic Auditory Milestone Age.

[d]Tests used included the following: Mental Development Index; Child Behaviour Checklist; Ages and Stages Questionnaire; Mother and Baby Scales; Minnesota Infant Development Inventory; Infant Behaviour Questionnaire—Revised; Behaviour Rating Scale in Bayley Scales of Infant Development; Strengths and Difficulties Questionnaire.

[e]Cognitive tests for IQ evaluation were not reported.

[f]Tests used included the following: Child Behavior Checklist; Hamburg-Wechsler; Raven's Progressive Matrices; Wide Range Achievement Test; Kaufman-Assessment Battery for Children.

apparently mediated by fetal head growth.[62] In addition, maternal folate deficiency was found to be associated with poorer performance on neurodevelopmental tasks in infancy[63] and childhood.[64] In contrast, higher maternal folate intake in early pregnancy was related with higher general intelligence in 3-year-old children.[65] More recently, it has been found that moderately elevated preconception fasting total plasma homocysteine, a marker closely linked to folate deficiency, is inversely associated with psychomotor and cognitive development scores in infants and children.[66] In addition, folate insufficiency in early pregnancy, as revealed by insufficient plasma folate concentrations (<8 nmol/L) in pregnant mothers, was found to produce a long-lasting, global effect on brain development, which was associated with poorer cognitive performance.[67] Finally, human population studies performed by Yajnik and collaborators in India showed that low maternal folate and vitamin B12 concentrations measured during pregnancy were correlated to adverse effects on brain development of offspring at 2 years of age (motor, mental, and social development),[68] whereas in childred aged 9–10 years low folate but not low vitamin B-12 concentrations during pregnancy were associated with poor cognitive function scores.[64] On the contrary, folate and vitamin B-12 supplementation for six months in children aged 6–30 months improved gross motor and problem-solving skills,[69] which indicates that treatment at later postnatal ages with methyl donors could result in beneficial effects on neurodevelopment. The Western diet provides about 0.2 mg of natural folate/day, whereas 0.4 mg folate/day is recommended. The beneficial effects of folic acid supplementation >0.5 mg daily are still controversial.[70] In this regard, recent evidence suggests that the use of folic acid supplementation dosages exceeding ≥1000 mg/day during pregnancy should be monitored and prevented as much as possible, unless medically prescribed.[71]

Studies on experimental animals

The vast bulk of data available on the effects of fetal malnutrition on brain development and function arises

from studies in rodents. Most frequent models of prenatal malnutrition include either a deficiency of a particular component in the maternal diet (eg, reduction of the protein content or deficiency in a micronutrient such as folic acid) or a deficiency in total dietary calories (eg, a reduction in the amount of diet given daily to pregnant rats). Table 2[72,73,75,96–103] shows a summary of the effects of prenatal malnutrition on behavioral, electrophysiological, and molecular neuroplasticity correlates taken from animal models subjected to malnutrition (protein, caloric, or micronutrient restrictions) during pregnancy and fed by well-nourished mothers after birth.

Maternal protein restriction and brain function in the offspring. In the last decades, several animal studies have shown that severe protein restriction during gestation (reduction to 6% of the casein content in the maternal diet, calorically compensated by carbohydrate excess) correlates with a low weight gain of pups as well as with a broad range of behavioral disorders. These studies have revealed that rats born from dams subjected to severe malnutrition during pregnancy, showed numerous and sometimes irreversible deficits in exploration, social behavior, sleep-wake cycle, emotionality, avoidance conditioning, learning, and memory once they had reached adulthood.[72,73,75,96–101] In addition, the brains of severely prenatally undernourished rats exhibit long-lasting modifications in structure, chemistry, and function, especially in brain regions providing the anatomical and functional substrate of cognitive processes.[102,103] For instance, undernutrition in utero results in decreased excitability,[76,77] reduced number of neurons[78] and brain-derived neurotrophic factor (BDNF) concentration in the hippocampal formation of pups,[74] and impaired learning and memory ability in the Morris water maze.[74] These rats also showed decreased levels of basal dopamine in the prefrontal cortex.[79] Additionally, prenatally malnourished adult rats are less sensitive to the amnesic effect of the medial septal infusion of chlordiazepoxide,[104] which is indicative of a functional loss of GABAergic response. In contrast, those animals show increased sensitization to cocaine-induced stereotypy[105] and sensitivity to the NMDA antagonist MK-801,[106] suggesting that prenatal malnutrition affects the physiological properties of dopaminergic and glutamatergic neurotransmitter systems. It has been reported that severe protein malnutrition during gestation reduced the expression of the microtubule-associated protein 1B (formerly called MAP 5) in the rat brain, whereas the microtubule-associated protein 1A (formerly called MAP 1) is increased until adulthood.[80] Because both proteins play key roles in anchoring ionotropic neurotransmitter receptors to microtubules,[107] their expression changes in the brain of prenatally undernourished offspring could likely be related to the reported learning and memory deficits in these animals via a GABAergic and/or glutamatergic dysfunction. Studies on other forms of intrauterine undernutrition resulting from lesser insufficiencies in dietary protein (reduction to 8% of the casein content in the maternal diet, calorically compensated by excess carbohydrate) revealed that these prenatally malnourished rat pups, unlike severe 6% casein prenatally malnourished pups, do not show a body weight deficit at birth; therefore these animals were called "hidden" malnourished pups.[108] However, the pups arising from those pregnant dams whose diet was mildly restricted continue to exhibit alterations in their central neurochemical profiles when compared with eutrophic controls,[108] as evidenced by increased concentrations and release of cortical noradrenaline during early postnatal life, followed by decreased cortical release of noradrenaline at adulthood.[109,110] Some morphometric studies have also revealed that this model of prenatal protein malnutrition results in a reduced cross-sectional area of the corpus callosum of mice,[111] as well as in increased neuronal density and suppression of the normal maturational dorsolateral gradient in the rat cerebral cortex.[110] In addition, electrophysiological studies have shown that hidden prenatally malnourished rat pups exhibit, as a whole, a reduced spontaneous discharge rate by cortical neurons,[112] a diminished cortical excitability to callosal inputs,[109] an increased fatigability of transcallosal responses,[109] and a diminished ability of callosal-cortical synapses to perform temporal summation and to develop LTP in all frontal, visual, and entorhinal cortices.[81,83,84] Besides, the neocortex of these prenatal malnourished rats showed an increased expression of $\alpha 2$ C adrenoceptors[81,85,86] (whose activation is related to decreased memory formation[113]) and a decreased expression of both $\beta 1$ and $\beta 2$ adrenoceptor subtypes[82,84] (whose activation is associated with increased cerebral cortex LTP[114] and memory facilitation.[115] On the other hand, behavioral studies have shown that those animals exhibit lower performance in delayed spatial alternation tasks,[116] as well as reduced visuospatial memory,[81] indicating that prenatal malnutrition during fetal life can induce deficits in the consolidation of long-term memories. It is noteworthy that most of these deleterious effects of hidden prenatal malnutrition were detected in adulthood, even though the animals were subjected to nutritional rehabilitation since birth.

Maternal caloric restriction and brain function in the offspring. Severe purely prenatal caloric restriction (25% of normal caloric intake) has been shown to induce

Table 2 **Effects of prenatal malnutrition on neuroplasticity: evidence from animal models submitted to malnutrition (protein, caloric, or micronutrient restrictions) during gestation and nursed by well-nourished dams after birth**

Treatment during gestation	Diet composition	Species	Offspring age	Effect	References
Protein restriction	6% casein, isocaloric	Rat	PND 160	Impaired acquisition of a DRL task	Tonkiss et al (1994)[72]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 20–27, 70–71, 220–221	Preserved spatial navigation in Morris water maze	Tonkiss et al (1990)[73]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 29–36	Impaired spatial navigation in Morris water maze	Wang and Xu (2007)[74]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 90	Deficits in attentional set shifting and decrease of metabolic activity in prelimbic, infralimbic, anterior cingulate, and orbitofrontal cortices	McGaughy et al (2014)[97]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 15, 30, and 90	Defective LTP in hippocampus	Bronzino et al (1991)[76] Bronzino et al (1991)[77]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 90	Reduced number of neurons in hippocampus	Lister et al (2006)[78]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 36	Decreased expression of BDNF in hippocampus	Wang and Xu (2007)[74]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 90	Adverse consequences on the quality and quantity of adult sleep in rats.	Datta et al (2000)[75]
Protein restriction	6% casein, isocaloric purified diet	Rat	PND 90–120	Decreased levels of dopamine in the prefrontal cortex	Mokler et al (2007)[79]
Protein restriction	5% casein, isocaloric purified diet	Rat	PND 14 and 63	Reduced expression of the microtubule-associated protein 1B in brain but increased expression of 1A	Gressens et al (1997)[80]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 56–70	Decreased visuo-spatial performance on 8-arm radial Olton maze	Soto-Moyano et al (2005)[81] Sáez-Briones et al (2015)[82]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 55–60	Impaired LTP in prefrontal and visual cortices	Soto-Moyano et al (2005)[81]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 55–60	Impaired LTP in entorhinal cortex	Hernández et al (2008)[83]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 55–60	Impaired LTP in prefrontal cortex	Flores et al (2011)[84] Sáez-Briones et al (2015)[82]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 60	Impaired LTP in occipital cortex	Barra et al (2012)[85]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 8 and 60	Increased expression of α_{2C} adrenoceptors in frontal and occipital cortices	Soto-Moyano et al (2005)[81]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 8	Increased expression of α_{2C} adrenoceptors in frontal and occipital cortices	Sierralta et al (2006)[86]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 60	Increased expression of α_{2C} adrenoceptors in occipital cortex	Barra et al (2012)[85]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 60	Decreased expression of β_1-adrenoceptors in frontal cortex	Flores et al (2011)[84]
Protein restriction	8% casein, isocaloric purified diet	Rat	PND 60	Decreased expression of β_2-adrenoceptors in frontal cortex	Sáez-Briones et al (2015)[82]
Protein restriction to 8% casein	8% casein, isocaloric purified diet	Rat	PND 55–60	Decreased expression of BDNF in entorhinal cortex	Hernández et al (2008)[83]
Caloric restriction	40% restriction of caloric intake	Rat	PND 45–50	Suppression of the interhemispheric asymmetry of visual evoked responses	Soto-Moyano et al (1993)[87] Soto-Moyano et al (1994)[88] Soto-Moyano et al (1998)[89]
Caloric restriction	40% restriction of caloric intake	Rat	PND 45–52	Decrease of myelinated and unmyelinated fiber diameters in corpus callosum	Olivares et al (2012)[90]
Caloric restriction	40% restriction of caloric intake	Rat	PND 2 and 40	Increased expression of CRH mRNA and protein in hypothalamus	Núñez et al (2008)[91]

(continued)

Table 2 **Continued**

Treatment during gestation	Diet composition	Species	Offspring age	Effect	References
Caloric restriction	40% restriction of caloric intake	Rat	PND 40	Decreased sensitivity of paraventricular neurons to glucocorticoids	Pérez et al (2010)[92]
Caloric restriction	50% restriction of caloric intake	Rat	PND 0 (at birth)	Decreased expression of collapsin response mediator proteins in brain	Aravidou et al (2013)[93]
Methyl donors deficiency	Diet lacking vitamin B2, B12, folate, and choline	Rat	PND 80	Impaired spatial memory, brain accumulation of homocysteine	Blaise et al (2007)[94]
Vitamin B12 deficiency	Diet lacking vitamin B12	Rat	PND 90	Impaired cognitive performance in Morris water maze, decreased BDNF in cortex and hippocampus	Sable et al (2013)[95]

Abbreviations: BDNF, brain-derived neurotrophic factor; CRH, corticotropin-releasing hormone; DRL, differential reinforcement of low rates of responding; LTP, long-term potentiation; PND, postnatal day.

hyperactivity of the hypothalamo-pituitary-adrenocortical axis, as revealed by increased blood levels of adrenocorticotropic hormone (ACTH) and corticosterone.[117] Similarly, reduction of the caloric intake of rats to 40% during pregnancy results in elevated blood levels of corticotropin-releasing hormone (CRH) and corticosterone in the offspring, together with enhanced expression of CRH mRNA and CRH protein in the hypothalamus,[91] and in decreased sensitivity of paraventricular neurons to glucocorticoid receptor ligands.[92] Those animals also showed a reduction of the corpus callosum total area, partial areas, and perimeter, as compared with normal animals, with the splenium of corpus callosum (posterior fifth) clearly decreasing the myelinated and unmyelinated fiber diameters.[90] These structural changes correlate with functional alterations of brain interhemispheric communication, as revealed by decreases in amplitude and projecting field of transcallosal-evoked responses and suppression of the interhemispheric asymmetry of visual-evoked responses found in adult rats submitted to caloric restriction during fetal life.[87–89] Finally, it has been found that rat pups born from mothers submitted to 50% caloric restriction during pregnancy exhibit downregulated expression of collapsin response mediator proteins in the brain.[93] These are proteins exclusively expressed in the nervous system, which are involved in the regulation of crucial process for growth and development of the brain, such as neuritogenesis in dendrites and spines,[118] and in functions beyond cytoskeletal regulation, including axonal transport, vesicle trafficking, and neurotransmitter release.[119]

Maternal restriction in micronutrients and brain function in the offspring. Folate deficiency deregulates epigenomic mechanisms related to fetal programming through decreased cellular availability of SAM and produces intrauterine growth retardation and birth defects. Folate and vitamin B12 deficiencies produce long-lasting cognitive disabilities through impaired hippocampal cell proliferation, differentiation, and plasticity, as well as atrophy of the hippocampal CA1 region,[94,95] mimicking the effect of knockout mice lacking DNMTs.[20] The combined deficiency of vitamin B12 and folate during rat pregnancy has also been found to decrease the expression of synapsins in the cerebellum of the offspring, an effect that depends on impaired estrogen receptor α/Src tyrosine kinase pathway and subsequent reduced phosphorylation of synapsins.[120]

Fetal programming of neuroplasticity and the role of epigenetics

Brain plasticity depends on molecular and cellular mechanisms that are regulated by genes, which may be

subject to epigenetic regulation by dietary components, highlighting the importance of adequate maternal protein nutrition during pregnancy for subsequent brain plasticity and for achieving proper brain development during adulthood. On these grounds, it is believed that neuroplastic deficits found in the adult life of prenatal malnourished individuals are a consequence of an altered fetal programming of brain development and function,[121,122] but to what extent are they a direct effect of intrauterine epigenetic programming of neural components and/or an indirect consequence of other prenatally programmed postnatal factors, such as obesity, remain to be clarified.

An early hypothesis to explain fetal brain programming followed the observation that the fetus is protected against high glucocorticoid levels provided by the mother through the placental barrier enzyme 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2). This enzyme converts physiological glucocorticoids into inactive 11-keto derivatives. Both protein[123] and food restrictions[124] in pregnant rats lead to decreased placental 11βHSD2 activity, resulting in overexposure of the fetus to maternal glucocorticoids. Such a deficiency is observed in newborns with reduced body weight at birth.[125,126]

In turn, overexposure to maternal glucocorticoids caused by prenatal undernutrition can reduce glucocorticoid receptor expression in the offspring's hippocampus,[124] hypothalamus[126,127] and pituitary gland,[128] resulting in a decreased negative feedback control by glucocorticoids and, therefore, in increased hypothalamus-pituitary-adrenal (HPA) activity,[129] which leads to chronically increased endogenous glucocorticoids levels that extend to postnatal age.[130]

Fetal glucocorticoid overexposure has detrimental effects on human brain function, as revealed by impaired cognitive development[131] and decreases in verbal and visuospatial abilities and narrative memory.[132] However, it remains unclear whether those alterations are a consequence of enhanced exposure of the brain to maternal glucocorticoids during fetal life or to increased endogenous glucocorticoids during postnatal life. More recently, prenatal malnutrition has been associated with epigenetic alterations that affect glucocorticoid functionality. For example, the placenta of intrauterine growth-restricted infants exhibit higher methylation levels at the 11βHSD2 gene promoter.[133] Those infants show a poorer quality of movement, a marker of adverse neurobehavioral outcomes.[133] Those observations suggest that an adverse intrauterine environment leading to growth restriction may enhance the exposure of the fetal brain to cortisol (thereby producing downstream adverse effects) by reducing 11βHSD2 expression via increased methylation of its gene promoter region.[133]

Concerning the epigenetic control of the glucocorticoid receptor, experimental studies have shown that rat maternal undernutrition (30% reduction of ad libitum standard diet) throughout gestation increased methylation of the glucocorticoid receptor gene promoter and reduced glucocorticoid receptor expression in the liver of the adult progeny.[134] However, epigenetically mediated programming of brain glucocorticoid receptor downregulation has not yet been described. In addition to epigenetic modifications in the expression of proteins concerned with corticoids functionality, some studies indicate that gestational protein deficiency in the rat results in reduced expression of the Wnt2 protein, together with a highly variable methylation pattern of the Wnt2 gene promoter region.[135] Wnt2 is a signaling glycoprotein critically involved in placental vascularization,[136] and its expression is downregulated in women with severe eclampsia.[137] Epigenetically-controlled Wnt2 expression is induced by fetal undernutrition and is associated with impaired growth and development of the human fetus.[138] However, the importance of those alterations for mature brain function remains unexplored. *Wnt* genes play an important role in cell signaling mechanisms, controlling fundamental developmental processes of the central nervous system by inducing expression of BDNF and other members of the BDNF signaling pathway in glial cells.[139,140]

Wnt signaling is a critical component of activity-mediated synapse formation in the adult brain.[141–143] Recent studies have shown that Wnt signaling is also essential for the neuroendocrine control of the hypothalamus,[144] a crucial brain center in energy balance regulation. Recently, using microarray gene expression analysis, it was shown that the offspring of pregnant rats submitted to 50% restriction of 6% protein diet showed postnatal downregulated expression of genes encoding for the transcriptional activator Creb1 and its co-activator Crebbp in the hippocampus (which are largely involved in hippocampal plasticity via regulation of BDNF transcription), together with hypermethylation of gene *Slc2a1*, which is associated with cognitive impairment.[145] Thus, BDNF expression could be altered in the brain of prenatally malnourished animals via epigenetic regulation of both Wnt and CREB signaling. Additionally, evidence of epigenetic regulation of *Dnmt1* and *Dnmt3a* genes has been found in the adult mammalian brain,[20,146] where it can exert a variety of roles in memory formation via regulation of BDNF expression.[146] This clearly indicates that epigenetic regulation is not restricted to early development but also can be of physiological relevance in the adult brain via a reprogramming process. Thus, all the aforementioned studies represent initial steps toward the characterization of the epigenetic modifications that ultimately may

explain how fetal malnutrition may play a substantial role in programming neuroplasticity deficits at later ages in the offspring.

Taken together, the data summarized above indicate that hidden prenatal malnutrition induces substantial changes in brain structure, neurochemistry, and function. Some of these disorders are possibly the result of epigenetic modifications, which is consistent with the concept of fetal programming by early nutritional cues.[147] Although this is an expanding area of research, it is presently unknown whether changes in brain plasticity after prenatal malnutrition are a direct consequence of epigenetic intrauterine programming of neural/glial mediators, receptors, and other proteins or whether they are indirectly mediated, at least partially, by other programmed postnatal events such as obesity and the associated metabolic syndrome.

PRENATAL MALNUTRITION: PROGRAMMING OF OBESITY AND METABOLIC SYNDROME IN LATER LIFE AND REPERCUSSIONS ON BRAIN PLASTICITY

Developmental origins of the metabolic syndrome rest on the fact that the fetus may adapt and survive to a hostile environment (prenatal undernutrition, stressor, or other factor) during determined time frames of epigenetic plasticity, anticipating future metabolic responses by reprogramming its genome-wide gene expression profile. This reprogramming favors early survival and prepares the fetus for an adverse postnatal environment, as stated by the Barker's thrifty phenotype hypothesis, but potentially causes a predisposition to disease in later stages of life, once postnatal environmental conditions and resources are favorable to survival.[1–3] The original Barker's hypothesis assumes an intrauterine period of developmental plasticity where fetal programming does occur, that is, a time framework of epigenetic plasticity that finishes during the early postnatal period, leaving the organism at risk to develop overweight and obesity during postnatal life, among other metabolic imbalances, when the offspring is exposed to food abundance, contrary to the environment anticipated by maternal undernutrition. This hypothesis is supported by studies from the Dutch famine (a famine from December 1944 to April 1945, where the official daily ration was only 400–800 calories), which revealed an atherogenic lipid profile, altered glucose tolerance, increased risk for coronary heart disease in adulthood, and a declination of cognitive function in individuals exposed to famine as fetuses.[148,149] Studies demonstrating the increased incidence of adult metabolic syndrome among low-birth-weight children have further been repeated, and the findings have been confirmed worldwide.[150,151]

Most features of the metabolic syndrome have been replicated in animal studies. A 50% maternal nutrient restriction (ie, hidden prenatal malnutrition) during rat pregnancy results in slightly smaller offspring that develop the metabolic syndrome in adulthood, showing obesity (especially greater fat mass index), hypertension, and glucose intolerance, along with elevated leptin, insulin, and triglyceride plasma levels.[152,153] Additionally, a study by Bieswal et al[154] found that adult rats (60 d of age) born from mothers given a 50% nutrient restricted diet, nursed by eutrophic dams, and fed on normal chow ad libitum after weaning show all fat compartments (subcutaneous, perirenal, periepididymal, and mesenteric) augmented by more than 50% compared with eutrophic controls; they also presented higher circulating levels of triglycerides and leptin. Moreover, undernourished mice and rats born from mothers submitted to either 8% protein diet[155] or 10% casein diet[156] developed obesity during postnatal life, thus indicating that dietary restriction of protein content leads to increased weight gain in the postnatal life of the offspring.[157]

Nutrient restriction during fetal life leads to the metabolic syndrome during postnatal life through three possible mechanisms: modifications to the cellular response to stress; alterations in adult organ morphology or cell number; or alterations of tissue or systemic responses.[121,158–160]

Modifications to the cellular response to stress

Possible causes of adaptive responses to stress may include epigenetic changes of chromatin induced by downregulation of the DNA methyltransferase-1 in the offspring of rats submitted to diet restriction,[161] mitochondrial dysfunction induced by an enhancement of mitochondrial biogenesis generated by an increased insulin sensitivity due to upregulation of sirtuin 1,[162] oxidative stress and lipid peroxidation of β cells of adult offspring arising from mothers exposed to diet restriction during pregnancy,[163] or differential expression of transcription factors generated by a decrease in the hepatic levels of the key glycolytic enzyme glucokinase in intrauterine growth-restricted rats.[150]

Alterations in adult organ morphology or cell number

These changes may arise from the adaptation to low-protein availability during pregnancy, which may lead to hypertension due to a reduced number of functional nephrons,[164] together with obese retroperitoneal fat deposition and insulin resistance.[165]

Alterations of tissue or systemic responses

Maternal undernutrition may result in both a decreased expression of placental 11βHSD2, causing low birth weight, and impaired glucose-insulin homeostasis.[123] Thus, prenatal malnutrition may program obesity and metabolic disturbances in the later life of humans and animals by several mechanisms, most them under epigenetic control. Indeed, the existence of epigenetic regulation of the mitochondrial genome,[166] oxidative stress,[167] expression of transcription factors,[168] and the cell number in adipose tissue[169] as contributing factors in postnatal obesity is generally accepted.

Epidemiological studies have found an association between obesity and poor cognitive performance.[170] General overweight (body mass index >25 kg/m^2) and obesity (body mass index >30 kg/m^2) have been strongly associated with poor cognition scores in the Mini-Mental State Examination, especially in the presence of abdominal obesity.[171] Whereas obese, hypertensive men performed poorly in cognitive tasks (learning, memory, executive functioning, and abstract reasoning), the best performance was achieved by lean, normotensive men.[172] More recently, a study that included >2000 children associated increased body weight with decreased visuospatial organization and lower mental ability.[173] The fact that obesity associates with cognitive deficits, especially in executive functions, throughout the lifespan[174] highlights the need for more obesity research at basic and clinical levels. Quantification of central obesity is a better predictor of cognitive deficits than body mass index, and both parameters may be enhanced by the presence of other risk factors such as hypertension and diabetes.[162] Although cardiovascular risk factors may be linked to obesity and cognition, the literature shows that the relationship between overweight/obesity and cognition remains despite accurate control for cardiovascular risk factors.[175,176] The mechanisms by which obesity results in cognitive impairment are uncertain. Risk factors include hyperglycemia, hyperinsulinemia, and vascular damage to the central nervous system,[177] as well as dyslipidemia.[178] Triglycerides may impair the transport of leptin across the blood-brain barrier,[179] which may in part account for the peripheral leptin resistance observed in obesity. Despite the latter, none of the epidemiological studies mentioned above addresses a possible link between intrauterine malnutrition and obesity, which would be critical for correlating fetal malnutrition to obesity and later brain function disabilities.

Since the early study of Greenwood and Winocur[180] that showed that a diet high in saturated fatty acids can impair learning and memory performance in rats exposed to some mazes, several more recent preclinical studies have found that adiposity on its own is specifically associated with reduced performance on learning and memory task.[181,182] It has also been reported that manipulation of brain triglyceride levels has an immediate and direct adverse effect on cognition, as revealed by impaired acquisition in the T maze, the Morris water maze, and food reward lever press, most likely due to defective hippocampal LTP.[182] Because most of these neuroplastic responses involve NMDA receptor function, Farr et al[182] suggested that either endogenous triglycerides (which are elevated in obese animals) or exogenously administered triglycerides may alter NMDA functionality, thereby impairing LTP and learning performance. More recently, it was reported that glial glutamate carrier proteins were upregulated in mice fed a high-fat diet, whereas glutamate-degrading enzymes and the NR2B NMDA subunit (which plays an essential role in learning, memory, and neuronal pattern formation) were downregulated,[183] thus providing mechanistic support for the deleterious effect of obesity on cognitive functions. A high-fat diet suppressed expression of the insulin-sensitive neuronal glucose transport proteins GLUT3/GLUT4 and suppressed the ERK/CREB pathway, leading to decreased LTP in the CA1 region of hippocampus.[184] Other studies have shown that diet-induced obesity causes ghrelin resistance in hypothalamic neurones.[185] Because ghrelin is involved in a variety of functions, including regulation of food intake, body weight gain, insulin release, β-cell survival, adiposity, and control of energy homoeostasis, dysregulation of the ghrelin system has been directly implicated in the development of obesity and the repercussions of the metabolic syndrome in brain function.[186] Studies performed on either ob/ob or melanocortin 4 receptor–null obese mice have also shown defective neuroplasticity concerning cognitive processes. Adult obese diabetic mice (ob/ob) exhibit impaired LTP in the hippocampal CA1 area and reduced expression levels of synaptophysin.[187] In addition, genetically predisposed obese mice (melanocortin 4 receptor-knockout) failed the long-term object memory recognition.[188]

Thus far, the experimental evidence indicates that obesity induces poor cognitive performance in humans and experimental animals via different neuroendocrine mechanisms. Among these, those affecting neuroplasticity, at least in the hippocampus, have been recently reviewed by Kanoski and Davison[189] and Francis and Stevenson[190] and include impaired glucoregulation, reduced levels of hippocampal brain-derived neurotrophic factor, brain neuroinflammation produced by increased levels of proinflammatory cytokines, loss of blood-brain barrier integrity, and altered adult neurogenesis in the hypothalamus and hippocampus.[191]

However, as pointed out by Stranahan and Mattson,[192] because diet-induced obesity models exhibit alterations across many metabolic and endocrine factors that could contribute to cognitive deficits, it is hard to establish whether changes in 1 particular factor could account for 1 specific memory phenotype. Notwithstanding this drawback, it seems apparent now that obesity by itself may reprogram epigenetically mediated alterations of brain plasticity mechanisms because it induces changes in DNA methylation of memory-associated genes, including Sirtuin1, in the hippocampus of adult mice.[193] Nevertheless, regardless of the fact that obesity may alter mRNA expression of various hippocampal enzymes known to alter subsets of epigenetic regulators that control histone acetylation (eg. Sirt1, histone deacetylases Hdac5, and Hdac9),[194] the downstream mechanism that couples adiposity to memory-associated genes remains unknown. In this regard, it has been proposed that some proinflammatory cytokines and adipokines may play a role in this coupling: first, interleukin 1b secreted from peripheral fat depots mediates the obesity-linked memory impairment in db/db mice,[195] an obesity model wherein leptin receptor activity is deficient because the mice are homozygous for a point mutation in the gene for the leptin receptor; second, deficits in spatial memory found in mice fed a high-fat diet after weaning occurred concomitantly with a desensitization of the protein kinase B (Akt) pathway coupled to hippocampal leptin receptors.[196] All of this evidence is consistent with the notion that various obesity signals may mediate high-fat-diet–induced alterations in the epigenetic landscape within the brain.

CONCLUSION

The studies presented in this review are intended to highlight the fact that prenatal malnutrition may lead to neuroplastic deficits at later ages. If neuroplastic deficits are caused by obesity, they should be prevented by precluding overweight development during postnatal life; on the contrary, if they result from an epigenetic intrauterine programming of neural components, they could be present at adulthood irrespective of the nutritional regime adopted later in a postnatal age. Despite the fact that the latter still remains to be subjected to experimental testing, the currently available data presented herein support the following: 1) prenatal nutritional scarcity has an adverse impact on brain architecture and circuits and affects lifelong behavior, metabolism, and mental health; 2) nutritional restriction during fetal life exerts its effects through epigenetic mechanisms leading to long-term changes in gene expression; 3) prenatal malnutrition, even moderated, programs obesity and metabolic disturbances in later life by epigenetic modifications in protein expression interfacing the environmental calorie supply and the energy requirements; and 4) obesity on its own can cause poor cognitive performance via neuroendocrine mechanisms, including epigenetically mediated reprogramming of adult neurons. Nevertheless, further investigation is required to generate new data that may describe the mechanisms involved in each of these relevant aspects, reflecting the functional link between malnutrition and pathological programing of neuroplasticity.

Acknowledgments

Author contributions. R.B. was responsible for supervision and editing of the entire review. C.M. was responsible for analysis of the epigenetic influences of the nutrition models. P.S.-B. was responsible for analysis of the effect of nutrition in neural plasticity. M.R.-P. was responsible for the section on the effect of folic acid/folate and nutrients in neural plasticity. H.B. was responsible for the analysis of the effect of nutrition in neural plasticity. B.M. was responsible for the section on the effect of folic acid/folate and nutrients in neural plasticity. A.H. was responsible for the analysis of the epigenetic influences of the nutrition models.

Funding. This work was supported by postdoctoral grant 3130573 from Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) given to R.B., grant 1161524 from FONDECYT given to BM, and DICYT grants 021501RP and 021643HK from Dirección de Investigación Científica y Tecnológica of Universidad de Santiago de Chile.

Declaration of interest. The authors have no relevant interests to declare.

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