Early Programming of Brain Development

Cristina Campoy, Prof, MD, PhD

The concept of "programming" defines the role of environmental factors such as diet, socioeconomic status, environmental pollutants and toxins, personal lifestyle, and familial habits during early stages of life that influence optimal neurological,[1] psychological, and physiological development.[2-4] These programming mechanisms encompass the type of susceptibility to metabolic,[2,5,6] cardiovascular,[7,8] cancer,[9] bone,[10] and mental diseases.[11] Epigenetic programming is increasingly recognized as an important mechanism underlying health and disease. Exposure to diet, drugs, and early life adversity during sensitive windows of life can lead to lasting changes in gene expression that contribute to the display of physiological and behavioral phenotypes.[12,13] Diet is a potent modulator of epigenetic marks, especially during prenatal and early postnatal life. For example, it has been shown that diets high in choline, methionine, folate, and vitamins B_6 and B_{12} increase DNA and histone methylation, alter gene expression, and can result in permanent changes in development.[14]

The human fetal brain grows to arrive at birth weighing 400 g. During the first 4 years of life, the brain continues to grow up to 1200 g (≈200 g less than an adult's brain). During the next 10-15 years, brain growth continues, involving different brain compartments in a slightly different way. For example, the thickness of the different regions of the cerebral cortex changes between the ages of 5 and 18 years at different paces, with the regions important for reasoning, planning, and social communication maturing last.[15] Because the brain is one of the most sensitive organs to suffer malprogramming due to its long period of development and specialization, there are a number of critical windows. The consequences of early malprogramming of the brain affect its structure and the rest of body functions, because not only is the brain one of the most sensitive organs during development, it also is involved in the control of endocrine and inflammatory signaling from different brain-body axes, regulating all metabolic processes involved in growth and development.

Mothers may contribute to infant brain development and behavioral dispositions directly through milk constituents that build and fuel the brain (eg, long-chain polyunsaturated fatty acids [LCPUFAs]), or indirectly by providing the caloric

energy for infant activities and experiences that, in turn, shape brain development.[16] Recently, Herba et al[17] demonstrated that exclusive breastfeeding was associated with more optimal brain development than bottle feeding. Breastfed babies showed important structural differences in the brain and nonspecific differences in neural development compared to those who received infant formula. (This study, however, did not describe the type of infant formula used or indicate whether the formula contained supplemental LCPUFAs.)

Brain Malprogramming by Early Malnutrition

It is well known that nutrients are vital to brain development, not only to the morphological development, but also to brain neurochemistry and neurophysiology. During late fetal and early neonatal life periods, regions such as the hippocampus, the visual and auditory cortices, and the striatum undergo rapid development characterized by the morphogenesis and synaptogenesis that make them functional.[18] Early malnutrition causes a decrease of cell proliferation, thereby affecting cell number,[19] volume, and width of the cerebral cortex.[20] Neurochemical alterations include changes in neurotransmitter synthesis, receptor synthesis, and neurotransmitter reuptake mechanisms.[21] Neurophysiologic changes reflect changes in metabolism and signal propagation.

Evidence from both epidemiological studies and animal models indicates that maternal diet and metabolic status play a critical role in programming the neural circuitry that regulates behavior. This happens directly by impacting the intrauterine environment and indirectly by modulating maternal behavior, resulting in long-term consequences for offspring behavior. Early malnutrition could predispose directly to externalizing behavior problems by impairing brain mechanisms such as those in the prefrontal cortex that are thought to regulate emotions and inhibit impulsive aggressive behavior.[22] Malnutrition also could predispose to externalizing behavior problems more indirectly by impairing cognitive functioning, which in turn predisposes to externalizing behavior problems.[23] Poor cognitive ability has been found consistently to predispose to externalizing behavior problems.[24] Malnourished children have less activity, more anxiety, and less imagination in solving a problem than well-nourished children.[25] Furthermore, malnourished children exhibit decreased exploration of the environment, as well as decreased verbal activity.[26] They are more deficient in arithmetic, standardized reading and vocabulary, as well as in literacy and general knowledge than well-nourished children.[27,28] Low-birth-weight children born to malnourished women show deficits in mental and psychomotor development indexes.[24,29]

Deregulation of the hypothalamic-pituitary-adrenal (HPA) axis and impaired stress response are common to different behavioral phenotypes such as depression and anxiety and visceral obesity.[30] Excessive release of steroids during vulnerable periods of life can be one of the mechanisms by which gut microbiota modulate HPA neuroplasticity,[31] and hence may enhance or reduce the risk of developing related disorders such as anxiety and depression later in adulthood. Offspring born to malnourished mothers also exhibit structural disorganization and malprogramming of the appetite-regulating system in the hypothalamus, central leptin resistance, and are predisposed to adiposity, displaying alterations in adipose tissue noradrenergic innervations and thermogenesis.[32]

Micronutrients play a determinant role in the development of brain substrates for language. In a recent study, thiamine deficiency during the 1st year of life was found to affect children's abilities selectively, yielding specific impairments in the language domains of syntax and lexical retrieval, without conceptual or general cognitive deficits.[33] Other nutrients such as iron have shown modest effects on psychomotor development in supplemented infants and toddlers <3 years of age,[34] although iron supplements do not seem to alter mental development or behavior.[35] Other studies have shown that perinatal iron deficiency produced an altered neurochemical profile of the developing hippocampus in children.[36] A recent study of the Avon Longitudinal Study of Parents and Children cohort within the NUTRIMENTHE EU Project showed that iodine deficiency was common (pregnant and breastfeeding women need 250 µg per day[37]), affecting two-thirds of women in the UK. Their children went on to have slightly lower IQs at the age of 8 years and worse reading ability at age 9. Three-point IQ differences were found between children who were born to mothers with low iodine in early pregnancy and children who were born to mothers above the cut-off. All these studies showed that an individual nutrient deficiency resulted in the impairment of multiple systems, and the development of the brain was influenced by various nutrients simultaneously.

Systematic reviews and meta-analysis have shown that the use of multivitamin-containing folic acid supplementation during pregnancy is associated with no benefit to the mental performance in children.[38] However, the Generation R study within the NUTRIMENTHE EU Project demonstrated that use of folic acid supplements protected from both internalizing and externalizing problems.[39] Low maternal folate status during early pregnancy was associated with a smaller head circumference, smaller transcerebellar diameter, and higher risk of emotional problems in the offspring.[40] In India, a recent study showed that low maternal vitamin B_{12} and high folate status could contribute to the epidemic of adiposity and type 2 diabetes.[41]

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Meta-analysis and meta-regression analysis have shown that the beneficial properties of LCPUFAs remain probable but not convincing for a robust effect on visual acuity, cognition, and mental performance.[1,42] The Nutrition and Health Lifestyle (NUHEAL) study[43] has demonstrated that arachidonic acid status at birth is a better predictor of visual development at 5.5 years of age than LCPUFA status. Folic acid status during pregnancy also is related to processing speed, working memory, and attention in children at 8 years of age. Recently, new confounder factors such as common polymorphisms of the genes fatty acid desaturase 2 (FADS2, encoding Δ-6 desaturase) and FADS1 (encoding Δ-5 desaturase) are being considered as important in the evaluation of long-term effects of early nutrition. These polymorphisms are found in about one quarter of the European population and are associated with markedly reduced plasma LCPUFA concentrations.[44] First results suggest marked effects of genetic variation in the FADS gene cluster on relevant clinical end points, including cognitive development.[45] Koletzko et al,[46] within the NUTRIMENTHE EU Project, showed a consistent significant association of rare single-nucleotide polymorphism (SNP) alleles with lower amounts of docosahexaenoic acid (DHA) in red blood cell phospholipids of pregnant women, which may be of major relevance for child outcomes. It is tempting to speculate that genetic heterogeneity in fatty acid metabolism may be one of the reasons for the apparent inconsistent results of different studies that investigated effects of DHA perinatal supply on developmental outcomes.[1]

The following table summarizes recently published systematic reviews and meta-analyses of early nutrition interventions on mental and motor development in infants and toddlers.

Table. Early Nutrition and Mental and Motor Development: Recently Published Systematic Reviews and Meta-Analyses

Intervention	Reference	Population	Conclusion
Breastfeeding	US AHRQ[47]	Term infants	NS
	US AHRQ[48]	Preterm infants	No definitive conclusion
	Herba et al, 2013[17]	Term infants	Positive structural effects
LCPUFA	Simmer et al, 2008[49]	Preterm infants	NS
	Smithers et al, 2008[50]	Preterm infants	Findings varied according to whether BSID-I or BSID-II was used
	Simmer et al, 2008[51]	Term infants	NS
	Campoy et al, 2012[1]	Term infants	NS
	Gould et al, 2013[42]	Term infants	NS
Iron	Logan et al, 2001[52]	Infants & toddlers	Modest effect
	Sachdev et al, 2005[34]	<3 years	No convincing evidence
	Szajewska et al, 2010[35]	Infants & toddlers	Modest effect
Multiple micronutrients	Eilander et al, 2010[53]	0-18 years	Fluid intelligence NS
	Skórka et al, 2012[38]		Crystallized intelligence NS
			Other cognitive domains NS

AHRQ=Agency for Healthcare Research and Quality, NS=not significant, BSID=Bayley Scales of Infant Development

Brain Malprogramming by Mother's Obesity

Obesity and associated comorbidities (eg, metabolic syndrome and diabetes) constitute a major health concern among diet-related diseases worldwide, with a prevalence of about 30% expected in the EU population aged 40-65 years by 2015, which is similar to the situation in the United States. Consequences of obesity for mental health and cognitive development are not established to the same degree as those for chronic diseases.

The proportion of reproductive-aged women who are obese in the EU and US populations is increasing sharply. Approximately 60% of women desiring pregnancy in the US are overweight, with the incidence rising exponentially over the last 15 years.[54] The percentage of pregnant women in EU countries such as UK, Italy, and Spain who are overweight or obese can be as high as 30%, rising

to nearly 50% in older women. This indicates that the obesity epidemic could become accelerated through different generations independently of other genetic or environmental factors.[55] Maternal obesity, a diet rich in calories, or excess gestational weight gain may lead to lifelong risk of obesity and related disorders in the child.[56] Overweight and obese women experience poorer reproductive outcomes than normal-weight women, including increased rates of infertility and pregnancy loss, as well as fetal and neonatal problems such as developmental delay and neurological deficits, respectively.[57-60] Obese women commonly deliver macrosomic infants, but it has been reported an overall incidence of small-for-gestational-age (SGA) births at 18%—significantly higher than 10% in the general population.[61] In addition, children born to obese mothers are more likely to acquire childhood obesity. There is also an increase in perinatal death rates, and babies who are large at birth have nine times higher risk of becoming obese as adults.

In relation to early programming of brain development, obese women have a significantly increased risk of neural tube defects, cardiovascular anomaly, septal anomaly, cleft palate and cleft lip and palate, anorectal atresia, hydrocephaly, and limb reduction anomaly.[59] Maternal obesity predisposes their infants to a greater risk of neurodevelopment delay[62] and atypical neurodevelopment[63,64] than those born to healthy, lean women. Offspring exposed to maternal obesity and high-fat diet consumption during development are more susceptible to developing mental health and behavior disorders such as anxiety, depression, attention deficit hyperactivity disorder, and autism spectrum disorders.[65] A recent review examining 12 studies concluded that the offspring of obese women may be at increased risk of behavior and cognitive deficits in childhood, as well as eating disorders in adolescence and psychotic disorders in adulthood.[66] In response to such findings, the Institute of Medicine has highlighted neurodevelopment as an important potential long-term consequence of gestational weight gain that needs further investigation.[67] Offspring of overfed or obese mothers also exhibit malprogramming of the appetite-regulating system in the hypothalamus, show central leptin resistance, and are predisposed to adiposity.[30,32]

In the PREOBE study (PREOBE Excellence Project - P06-CTS-02341) in Spain,[68] 51% of the obese mothers showed iron deficiency at delivery, compared to 25% of healthy, lean pregnant women. There was an association between iron deficiency and an increase of birth weight. The mechanisms underlying this effect are unknown, but there are several hypotheses: a) a greater demand for iron from a larger newborn,[69] b) an increase of placental vascularity determining an increase of nutrient transport,[70] and c) an increased incidence of newborns large for gestational age in anemic mothers.[71] The placental transferrin receptor (pTfR)

expression was not significantly related to maternal preconceptional body mass index (BMI), and was higher in iron-deficient women, independently of mothers' preconceptional BMI.[72] In placental tissue, the genes encoding important proteins such as peroxisome proliferator-activated receptor gamma (PPARG) and toll-like receptor 4 (TLR-4), involved in fatty acids transport and energy regulation, were overexpressed and DNA (cytosine-5)-methyltransferase 1 (DNMT-1), as a biomarker of DNA methylation, was higher in overweight/obese and diabetic mothers, indicating the adaptation to the metabolic environment and the presence of epigenetic effects. The follow-up of the PREOBE children showed that babies born to obese mothers at 6 months of age scored higher in cognition, communication and language skills (Bayley III) than those born to healthy mothers, but this effect disappeared by 18 months. An adequate weight gain during pregnancy was related to better psychomotor score at 6 months of age in the offspring.

The understanding of the mechanisms associating early nutrition and later healthy brain developmental outcomes may have an enormous preventive potential, given the major public health implications, including opportunities for an improvement of cognition and an effective primary prevention of childhood and adult behavior and mental diseases.

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