The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days"

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Every child has a right to optimal cognitive, social, and emotional behavioral development. The cognitive, social, and emotional parts of the brain continue to develop across the lifespan. However, the brain's growth and development trajectory is heterogeneous across time. A great deal of the brain's ultimate structure and capacity is shaped early in life before the age of 3 years.[1] The identification and definition of this particularly sensitive time period has sharpened the approach that public policies are taking related to promoting healthy brain development. The ramifications are large, because failure to optimize brain development early in life appears to have long-term consequences with respect to education, job potential, and adult mental health.[2] These long-term consequences are the "ultimate cost to society" of early life adversity.

Among the factors that influence early brain development, 3 stand out has having particularly profound effects: reduction of toxic stress and inflammation, presence of strong social support and secure attachment, and provision of optimal nutrition.[3] This paper focuses on the provision of optimal nutrition by describing the important features of brain development in late fetal and early postnatal life, discussing basic principles by which nutrients regulate brain development during that time period, and presenting the human and preclinical evidence that underscores the importance of sufficiency of several key nutrients early in life in ensuring optimal brain development.

Brain Development in Late Fetal and Early Postnatal Life

Policymakers have recently placed a great deal of emphasis on the "first 1000 days" and "0-3" (years) as golden opportunities to influence child outcome. The first 1000 days correspond roughly with the time from conception through 2 years of age.

However, a closer examination of the trajectory of anatomic and functional brain development combined with clinical and epidemiologic studies of neurodevelopmental outcome suggests a slightly broader window extending to 3 years.[1-3] Nevertheless, the same basic principles of brain development discussed below apply.

The brain is not a homogeneous organ. Rather, it is composed of multiple anatomic regions and processes (eg, myelination), each with unique developmental trajectories.[1] Many of these regions have developmental trajectories that begin and accelerate in fetal life or shortly after birth. For example, myelination abruptly increases at 32 weeks' gestation and is most active in the first 2 postnatal years.[1] The monoamine neurotransmitter systems involved in mediating reward, affect, and mood begin their development prenatally,[4] continuing at a brisk pace until at least age 3 years. The hippocampus, which is crucial for mediating recognition and spatial memory, begins its rapid growth phase at approximately 32 weeks gestation, continuing for at least the first 18 postnatal months.[1,5] Even the prefrontal cortex, which orchestrates more complex processing behaviors, such as attention and multitasking, has the onset of its growth spurt in the first 6 postnatal months.[1,5] Keeping brain areas on developmental trajectory is critical not only for promoting behaviors served by the individual regions but, more important, to ensure time-coordinated development of brain areas that are designed to work together as circuits that mediate complex behaviors.[6]

Early life events, including nutritional deficiencies and toxic stress, can have differential effects on developing brain regions and processes based on the timing, dose, and duration of those events.[7] The importance of timing in particular should be underscored.[8] As noted, the timing of peak rates of development of the hippocampus and prefrontal cortex differ. The timing of an adverse environmental event that, for example, affects neuronal dendritic arborization determines whether the hippocampus or the prefrontal cortex sustains greater damage and compromise of functional integrity. The earlier the insult, the more likely the hippocampus will be affected more than the prefrontal cortex. In a brain circuit that requires balanced hippocampal and prefrontal input (eg, the ventral tegmental area loop), such imbalance can result in significant behavioral pathology, such as schizophrenia.[6,9]

Neuroscientists and psychologists use terms such as "critical period" and "sensitive period" to describe time epochs of opportunity and vulnerability. Critical periods are typically conceptualized as early life epochs when alterations to brain structure or function by an environmental factor (eg, nutrition) result in irreversible long-term

IUGR	Intrauterine growth restriction
LC-PUFA	Long-chain polyunsaturated fatty acids

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consequences.[10] Sensitive periods imply an epoch when the brain (or brain region) is more vulnerable to environmental factors, including nutrient deficiencies, but when the effect is not necessarily deterministic.[10,11] The term "sensitive period" can also be used in a positive manner to describe times when the brain may be particularly receptive to positive nutritional or social stimulation. Both concepts rely on the observation that the young, rapidly developing brain is more vulnerable than the older brain, but also retains a greater degree of plasticity (eg, recoverability). Over time, the distinction between critical and sensitive periods has become blurred as more research emerges. Although the distinction may become less meaningful, either concept emphasizes the need for pediatricians to focus on making sure the child is receiving adequate nutrition to promote normal brain development in a timely fashion.[12-14]

Basic Principles of Early Nutrition Effects on Brain Development

The vulnerability of a developing brain process, region, or circuit to an early life nutrient deficit is based on 2 factors: the timing of the nutrient deficit and the region's requirement for that nutrient at that time. For example, the risk of iron deficiency varies with pediatric age. Peak incidences are seen in the fetal/newborn period, 6-24 months of age, and during the teenage years in menstruating females. Each of these epochs has different iron-dependent metabolic processes occurring in the brain. Thus, the behavioral phenotype of iron deficiency varies by the child's age.[15] This type of timing and dose/duration information can be leveraged to change clinical prescription of certain nutrients. For example, consensus panels determining maternal requirements for folic acid in pregnancy based their recommendations on knowledge of the biology of folic acid in the developing fetal brain and long-term infant outcome.[16]

All nutrients are important for brain growth and function, but certain ones have particularly significant effects during early development. The effect of a nutrient deficit on the developing brain will be largely driven by the metabolic physiology of the nutrient, that is, what processes it supports in brain development and also by whether the deficit coincides with a critical or sensitive period for that process (Table). Key nutrients for brain development are defined as those for which deficiency that is concurrent with sensitive or critical periods early in life results in long-term dysfunction.

Biological proof of single nutrient effects on brain development are difficult to demonstrate in young children because of the subtlety and variability (based on timing) of nutrient effects, the limited behavioral repertoire of the youngest, most vulnerable children, the lack of brain tissue evidence of nutrient sufficiency or deficiency, the co-occurrence of multiple nutrient deficits in many at-risk populations, and non-nutritional confounding variables such as poverty and stress. Observational studies dominate the literature, but even randomized control trials are at risk for misattribution of effects or misinterpretation of lack of effects because of violations of various nutrient–brain interaction principles as outlined.[3]

Another scientific approach to the problem is cross-disciplinary, translational research that depends on combining preclinical and human studies. This approach makes the assumption that basic biological principles of nutrient–brain interactions are conserved across species. This approach has the advantage of controlling for potential confounding variables to isolate the effect of the nutritional variable of interest. The risk, however, is in failing to accurately relate the preclinical model's nutritional metabolism and brain development to the human.

In the next section, we highlight key macronutrients and micronutrients that are critical in brain development in the first 1000 days of life by presenting both human and preclinical data that underscore their significant impact. These deficiencies, and thus likely also their harmful effect on neurobehavioral development, are most prevalent in low- and middle-income countries, although they persist in high-risk, that is, low-income, refugee, and food-insecure populations in high-income countries as well.

Table. Critical processes during neurodevelopment affected by specific nutrients

Neurologic processes	Cell type	Function	Nutrient example	At risk during late gestation and 0-3 y
Anatomy	Neuron	Division (neurogenesis) migration differentiation (neurite outgrowth; synaptogenesis)	Protein, carbohydrates, iron, copper, zinc, LC-PUFA, iodine, vitamin A, vitamin B_6, vitamin D, vitamin C	Global, hippocampus, striatum, cortex, retina
	Oligodendrocyte	Myelination	Protein, carbohydrates, iron, iodine, selenium, zinc, vitamin B_6, vitamin B_{12}	Global
Chemistry	Neuron astrocyte	Neurotransmitter concentration, receptor, reuptake	Protein, iron, iodine, copper, zinc, selenium, choline, vitamin B_6, vitamin D	Global, hippocampus, nucleus, accumbens, VTA, cortex, cerebellum
Physiology and metabolism	Neuron oligodendrocyte	Electrical efficiency	Glucose, protein, iron, iodine, zinc, choline, copper	Global

VTA, ventral tegmental area.