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Review Article

Impact of Key Nutrients on Brain and Executive Function Development in Infants and Toddlers: A Narrative Review

Nithya Franklyn[1], Dhanasekhar Kesavelu[2, *], Prameela Joji[3], Rahul Verma[4], Arun Wadhwa[5], Chandan Ray[6]

[1]Department of Pediatrics, Vihaa Multispeciality Hospital, Chennai, India

[2]Department of Pediatrics, Apollo Children's Hospital, Chennai, India

[3]Pediatrics ICU and Medical Support, KIMS Health, Trivandrum, India

[4]Department of Neonatology and Pediatrics, Sir HN Reliance Foundation Hospital, Mumbai, India

[5]Department of Pediatrics, Dr. Arun Wadhwa Clinic, New Delhi, India

[6]Department of Pediatrics, Bhagirathi Neotia Women and Child Care Centre, Kolkata, India

Email address:

drdskgastro@gmail.com (D. Kesavelu)

[*]Corresponding author

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Abstract: Executive function skills are an essential aspect of cognition and are influenced in early life by multiple factors. One of the significant factors that influence brain development is nutrition, which plays a specific role in the brain's developmental processes and functioning from fetal to adult age. Infants in their early life rely on breastmilk for nutrition. Knowledge of the composition of breast milk and the biochemical composition of the brain has led to the identification of critical nutrients needed for the brain's growth, development, and functioning. Key nutrients for brain development are those that, when deficient during the precise, sensitive periods of early brain development, could have long-term adverse effects on brain functioning. This narrative review highlights the importance of some key nutrients in early brain development and executive functions, including cognitive performances in infants and toddlers. Lipids are crucial for brain development. Long-chain polyunsaturated fatty acids (LC-PUFA) and sphingomyelin are the key ingredients to influence cognitive performance potentially. Early development of executive function precursors in infants and toddlers is an essential foundation for executive functions outcomes in early childhood or adulthood. Evidence suggests that specific nutrients such as phospholipids, including sphingomyelin and LC-PUFAs (docosahexaenoic acid), are essential for developing higher-level cognitive functions.

Keywords: Executive Function, Cognitive Skills, Brain Development, Long-chain Polyunsaturated Fatty Acids, LC-PUFA, Sphingomyelin, Docosahexaenoic Acid, DHA

1. Introduction

Optimal nutrition is vital for brain development. [1] Nutrition plays an indispensable role in several processes, including cell proliferation, deoxyribonucleic acid (DNA) synthesis, neurotransmitters synthesis, hormone metabolism, and other crucial constituents of enzyme systems in the brain. [2] Infancy is a critical period for brain development, setting the stage for cognitive, motor, and socio-emotional skills development from childhood to adulthood. [1] As the brain grows rapidly in the first 2 years of life, it is during this period that it is also vulnerable to nutritional insults. [2]

This narrative review describes brain development during infancy, highlighting the landmark processes in

neurodevelopment. The development of cognitive and executive functions in infants and the importance of postnatal nutrition, focusing on specific nutrients that affect brain development and executive function, are discussed here. It further evaluates the evidence of the impact of supplementing specific nutrients such as sphingomyelins and long-chain polyunsaturated fatty acids (LC-PUFA) on cognitive and executive functions.

2. Methodology

PubMed, Google Scholar, Cochrane library, some non-indexed Indian journals were searched for interventional studies, descriptive studies, cross-sectional studies, and review articles concerning the role of micronutrients in brain development and executive functions, including cognitive functions performances. The key search words included "brain development AND infants and toddlers", "micronutrients AND cognitive function", "nutrients AND brain growth and development", "executive function development in infants and toddlers AND nutrients", "protein-energy malnutrition AND cognitive development", "LC-PUFAs AND cognition", "iron AND psychomotor performance" "sphingomyelin AND cognition," "Vitamin B12 AND cognition," "folate AND cognition."

3. Human Brain Development

The human brain has around 80 to 100 billion neurons and close to 100 billion glial cells (since the glia to neuron ratio is less than 1:1). [3, 4] The neurons form more than a quadrillion synapses. [5] The average length of neurons in the human brain is nearly 100 km, and the brain vasculature extends over 600 km of capillaries. Therefore, each neuron is within 20 µm of a capillary. [6] Although the human adult brain is about 2% of the body weight, its oxygen consumption is about 20% and utilizes up to 25% of calories available to the body. [7]

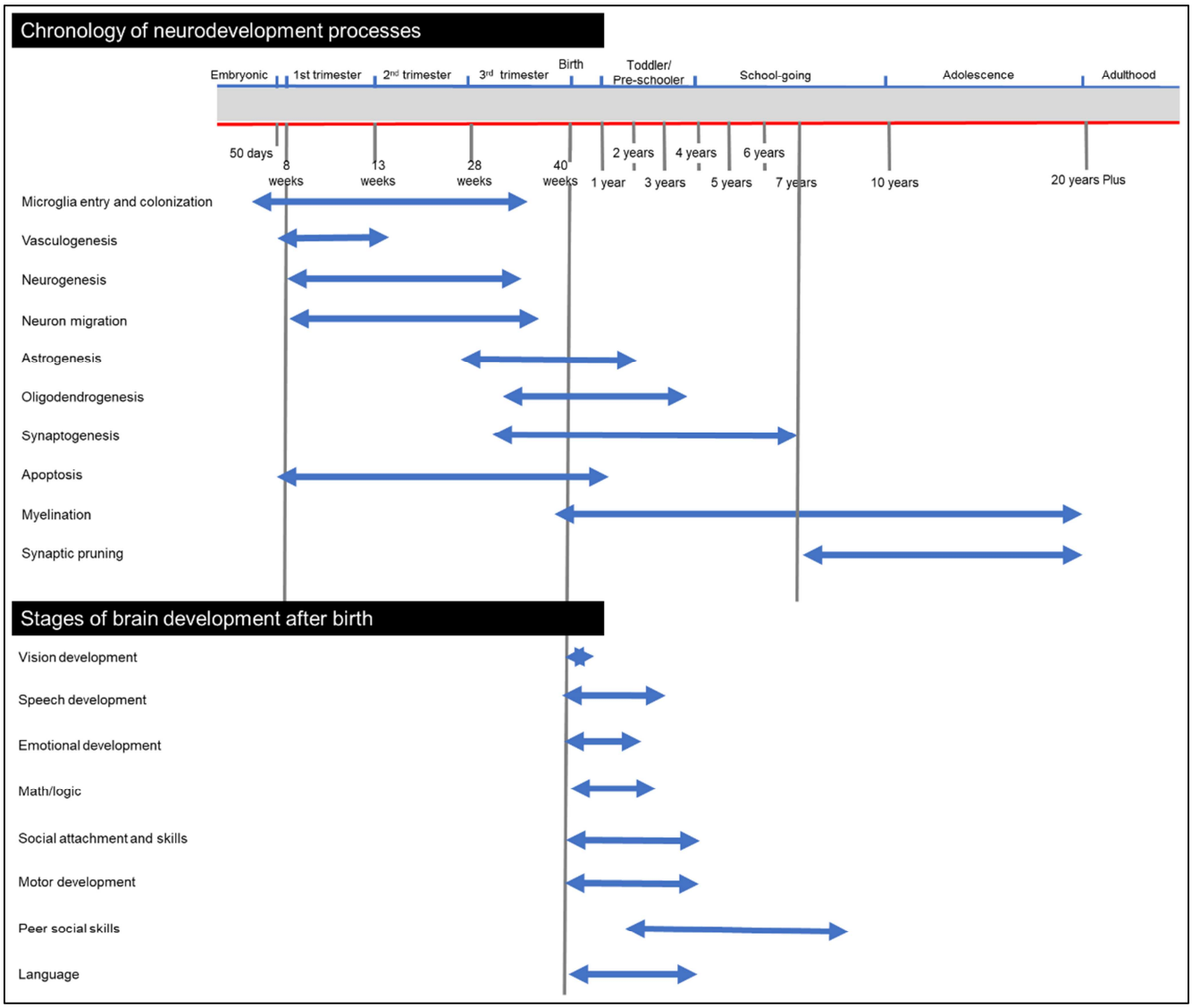

Figure 1. *The sequence of events in brain maturation [7–9].*

Critical Processes Involved in Neurodevelopment

The fundamental physiological processes involved in brain development include neurogenesis, migration, synaptogenesis, apoptosis, myelination, and arborization of axons (Figure 1). [7, 8] The sequence of brain maturation begins with neurulation or the development of neurons, followed by several cycles of neurogenesis or the production of new neurons. Subsequently, synaptogenesis enables the establishment of new connections between neurons. Simultaneously, apoptosis facilitates the elimination of under-utilized neurons. Axons that connect neurons are insulated by fatty myelin through myelination, which helps to insulate and hasten action potentials traveling between the neurons. Further dendritic ramifications (arborization) enable the dendrites to branch throughout life. [7–9]

The neurulation begins around preconception, and the neurogenesis begins at around 6 weeks and continues until 26 weeks of gestation. Synaptogenesis begins around 20 weeks of gestation and continues postnatally to peak at 2–3 years. Synaptic pruning through apoptosis starts at 6 weeks of gestation and continues till 4 years of postnatal age. Myelination begins around 12 weeks of gestation and continues until the sixth decade of life. While dendritic and axonal arborization also follows a similar pattern as myelination. [7, 8]

Brain development is continuous with differing time-stamps and comprises anatomical, cognitive, and psychosocial developments. Brain growth occurs through a sequence of various physiologically overlapping processes, which begin at a very early stage *in utero* and continue to the sixth decade of life. [7] It has been well established that the growth and development of the brain are very rapid in the first few years of life.

The brain volume of neonates is about 25%–30% of its adult volume; it doubles in the first year of life, increases to 80% of adult size by 2 years, and reaches 90–92% by 9 years. [10, 11] The brain volume achieved by the first year of life determines the intelligence in the coming years. [10] Although the basic structural and functional development occurs rapidly in the first 2 years of life, the brain matures slower during childhood. [11]

The developmental trajectories of the brain accelerate during the early years of life but are different for different structural/anatomical sites and functional levels. For instance, there is robust grey-matter growth and slower cortical white-matter growth in the first year of life. [11] Further, the development of the cerebral cortex and myelination of the white matter are hallmark processes that occur during infancy and childhood. [12]

4. Development of Cognitive and Executive Functions in Infants and Toddlers

The development of monoamine neurotransmitter systems such as dopaminergic, noradrenergic, serotonergic, and histaminergic begins at the pre-natal stage and rapidly progresses until 3 years. The hippocampus, involved in mediating recognition and spatial memory, grows rapidly for at least the first 18 months. The intense growth of the prefrontal cortex occurs during the first 6 months. The rapid development of the hippocampus is evident up to 18 months. [13] The neurotransmitters mediate several psychological functions. [13] The hippocampus mediates several cognitive functions such as spatial, short-term, or working memories, while the prefrontal cortex is involved in executive functions. [14, 15]

Executive functions develop rapidly during infancy and childhood. [16] Executive functions collectively refer to complementary skills of inhibitory control, working memory, and cognitive flexibility, which assists in reasoning, problem-solving, and planning. [17, 18] The age between 3 to 5 years is critical for developing executive functions. A rapid increase in inhibitory control could be witnessed between 5 and 8 years. [19] While working memory is distinctly observed between 3 and 4 years. [20] Researchers believe that performance of executive functions in early life is likely to predict outcomes, such as academic achievements in terms of goal-setting, planning, and organizing; general intelligence; social skills; health; or wealth, in later childhood or life. [16, 18]

The seat of executive functions in the prefrontal cortex and up to 3–6 years (i.e., preschool to kindergarten), the executive functions depend on the development of the prefrontal cortex and the interconnected neural regions—cortical and subcortical structures. [19] Besides brain development, several positive, negative, direct, or indirect early life experiences also impact the development of executive functions. Some of the factors that can cause a significant impact are [20, 21]:

1. Child-related factors (gestational age, weight at birth).
2. Activities of the child (physical activity, sleep, media use).
3. Early education.
4. Environment (socioeconomic status, interactions with parents and teachers).
5. Nutrition (healthy vs. unhealthy diet).

5. Key Nutrients Involved in Brain Development

Critical nutrients for brain development are those that, when deficient during the precise, sensitive periods of early brain development, could have long-term adverse effects on brain functioning. [13] Based on preclinical and experimental studies, certain vital nutrients have been identified to modulate the development of the brain during fetal and early postnatal life (Table 1). [22–25] During childhood, the brain consumes 60% of the basal energy in the form of glucose. [7] Nutrients can influence neuroanatomy, neurophysiology, and

neurochemistry. Nutrients such as protein, iron, zinc, selenium, iodine, folate, vitamin A, choline, and LC-PUFA are essential for neuronal cell growth and development. Nutrient deficiency affects the processes of neural cell development, including cell differentiation, synaptogenesis, and dendritic arborization. In addition, nutrients also influence neurochemistry (neurotransmitter synthesis, receptor synthesis, and neurotransmitter reuptake mechanisms) and neurophysiology (changes in metabolism and signal propagation). [22]

The neurodevelopmental processes are rapid between 24 and 42 weeks of gestation, making the brain highly susceptible to nutrient insufficiency. Protein-energy malnutrition and postnatal growth failure chiefly affect neurodevelopment, with preclinical studies suggesting the outcome as smaller brains with global deficits. [13, 22] Iron deficiency during the neonatal period is associated with modifications in myelination, amino acid/ biogenic amine neurotransmitter synthesis, and energy metabolism in the hippocampal. Autonomic nervous system regulation and the development of hippocampal and cerebellar structures are vulnerable to zinc deficiency. [22] Thus, it is crucial to provide optimal nutrition during the early years of life.

Table 1. *Key nutrients in brain growth and development [22–25].*

Nutrient	Neurological processes or functions affected by key nutrients
Protein-energy	Cell proliferation, cell differentiation, synaptogenesis
α-lactalbumin	Neurotransmitter synthesis
Long-chain polyunsaturated fatty acids	Myelin formation, synaptogenesis
Phospholipids	Myelination
Iron	Monoamine synthesis, neuronal and glial energy metabolism, myelin formation
Copper	Neurotransmitter synthesis, antioxidant activity, neuronal and glial energy metabolism
Zinc	DNA synthesis, the release of neurotransmitters
Vitamins B_1, B_2, B_6, B_{12}, and folate	Neurotransmitter synthesis and functioning, myelination, brain energy metabolism
Choline	*DNA methylation, myelin synthesis, neurotransmitter synthesis
Lutein	Brain electrical activity

*DNA: Deoxyribonucleic acid.

A longitudinal birth cohort study (n=1559) assessed children for malnutrition at 3 years and found that those malnourished had had a 15.3-point deficit in intelligence quotient at age 11 years independent of psychosocial adversity. [26] Chronically protein-energy malnutrition adversely impacted higher cognitive processes as children (n=40) performed poorly on attention, working memory, learning and memory, and visuospatial ability tests. However, children performed well on the test of motor speed and coordination. [27] Few studies included in a systematic review of placebo-controlled randomized controlled trials on n-3 LC-PUFA showed a positive effect on cognition when omega-3 index equivalence was higher than >6%. Studies providing intervention with a daily supplementation dose of ≥450 mg DHA + EPA showed improved cognition. [28] When supplemented with soy-derived phosphatidylserine, children with ADHD (n=36) showed significant improvement in short-term auditory memory and visual sustained attention performance (inattention and impulsivity). [29] Psychomotor evaluation in children with iron deficiency and iron-deficiency anemia showed slow development in four functional areas of development on the Denver II Developmental Screening Test (social/personal, fine motor function, language, and gross motor functions). [30] In the Pune Maternal Nutrition Study (n=108), children born to mothers with low plasma vitamin B12 (<77 pM at 28 weeks of gestation) lagged on tests reflective of sustained attention and short-term memory compared to children born to mothers with high plasma vitamin B12 (>224 pM). [31] In a subcohort of an interventional study, cobalamin and folate status was significantly linked to cognitive performance. The mental development index score increased by 1.3 for every 2-fold increment in plasma cobalamin concentration. Independent of cobalamin status, folate levels in plasma were positively associated with mental development index scores. [32] Evidence from clinical studies supports the relevance of certain vital nutrients in supporting executive functions and higher-order cognitive functions among infants and children (Table 2). [25–39]

Table 2. *Role of critical nutrients in executive functions of the brain [26–32].*

Nutrient	Role in executive functions	Age group and study type
Protein	Working memory, comprehension, attention capacity, learning, and memory	3-11 years (Longitudinal study) 5–7 years and 8–10 years (Observational cohort study)
LC-PUFAs (DHA, EPA, ARA)	Working memory, attention, reasoning, information processing, verbal learning, and memory	4–25 years (Systematic review)
Phospholipids	Visual sustained attention	4–14 years (Randomized control trial)
Iron	Cognition, socio-emotional and motor skills	6 to 12 months; 13 to 36 months; and 37 to 72 months (Observational study)
Vitamin B12 and folate	Cognition and motor skills	12–18 months (cohort from a randomized interventional trial)

LC-PUFA: Long-chain polyunsaturated fatty acid; DHA: Docosahexaenoic acid; ARA: Arachidonic acid; EPA: Eicosapentaenoic acid.

6. Significance of Lipids in Brain Development and Functioning

To understand the significance of lipids in brain development and function, understanding the lipid composition of the brain is important. Lipids are one of the predominant components of the human brain, making up over 50% of the brain matter. [40] The brain also contains about 25% PUFA in the form of docosahexaenoic acid (DHA; 12–14% of total fatty acids) and arachidonic acid (AA; 8–10% of total fatty acids). [41] Phospholipids form an integral part of cell membranes and are also found in high levels in dendrites, myelin sheath, and synapses. Phospholipids help in the signaling function of brain cells. [42] Glycerophospholipids, sphingolipids, and cholesterol are the major components of neural cell membranes and are the essential lipids necessary for brain development and the maintenance of cellular processes. [43]

Analysis of breast milk indicates that sphingomyelin is one of the major phospholipids, accounting for approximately 37% of the phospholipid fraction of breast milk fat. [44]. Long-chain PUFAs account for 15% of 15% of the total lipids in breast milk. [45]. Preterm breast milk had higher concentrations of sphingomyelin and other lipids/polar lipids than term breast milk. [46]

6.1. Role of LC-PUFA in Infants and Toddlers

Rapid accretion of DHA in the brain by 30-folds is evident from early trimester (week 30) to 2 years, postnatal. This period signifies a rapid increase in brain volume. The accretion of DHA postnatally, during lactation, is approximately 70–80 mg/day. [47] Docosahexaenoic acid is an indispensable brain nutrient and plays a critical role in several neurological processes and functions related to cognitive performance. [48] Docosahexaenoic acid supports normal IQ development and helps preserve visuospatial learning and memory. In children, low levels of LC-PUFA, including DHA in the blood, have been associated with specific developmental and behavioral disorders, including attention deficit hyperactivity disorder, dyslexia, and dyspraxia. [49]

Evidence supports the role of LC-PUFAs in improving long-term cognitive outcomes. Colombo *et al.* assessed cognition beyond 18 months and longitudinal cognitive change from 18 months to 6 years between children who were fed variable amounts of DHA (0.32%, 0.64%, and 0.96% of total fatty acids) and ARA (0.64%) and children who were not fed LC-PUFAs as infants. A positive effect on cognitive assessments (rule learning and inhibition tasks, Peabody Picture Vocabulary Test, and Weschler Primary Preschool Scales of Intelligence) was observed over 3–6 years. [34]

Similarly, Willatts *et al.* studied the effects of dietary LC-PUFAs in infancy on measures of cognitive function at 6 years of age. For 4 months, infants were randomly assigned to receive formula containing either DHA and ARA or no LC-PUFAs. Breastfed infants were included as the control group. Although there was no difference in the IQ scores between infants fed with LC-PUFAs or without LC-PUFAs, infants fed with LC-PUFAs were able to process information at a faster rate than those who did not receive LC-PUFAs at the age of 6. [39]

6.2. Role of Sphingomyelins in Infants

Sphingomyelin is a critical and abundantly found sphingolipid in the central nervous system. It is abundant in the myelin sheath surrounding the neuronal axons. [25, 44] Data highlights that sphingomyelin levels increase from 2% at birth to 15% at 3 years of age, which correlates with the critical process of myelination. Lipid rafts of the human cortex contain nearly 38% sphingomyelin. [50] The presence of a significant quantity of sphingomyelin in breast milk and the central nervous system adds evidence to its role in cognitive development. [44]

An exploratory observational study investigated the link between early dietary sphingomyelin and later cognitive development. The study reported higher milk sphingomyelin levels correlated to better verbal development ($r=0.65$, $p<0.001$) and higher myelin content. *In-vitro* models further reiterated the role of sphingomyelin in augmenting the maturation and differentiation of oligodendrocytes. Thus, the authors concluded that dietary sphingomyelin significantly influences cognitive development in healthy children and, this is achieved potentially by increased axonal myelination. [44]

Timby and colleagues conducted a randomized controlled trial to compare the cognitive scores among infants receiving experimental formula containing low protein, low energy, and fortified with sphingomyelin; standard formula or breastmilk up to 6 months of age. Their cognitive scores were assessed at 12 months of age. As assessed with Bayley Scales of Infant and Toddler Development, Third Edition, the cognitive score was higher in those who received sphingomyelin-fortified milk compared to those infants who had received standard formula. Based on the outcome of this study, the author opined that sphingomyelin-fortified milk could be an option for reducing the gap in cognitive development between breastfed and formula-fed infants. [51]

6.3. Role of Sphingomyelins in Toddlers

In toddlers, the significance of nutrition and specific nutrients such as sphingomyelin, an essential component of myelin, is remarkable because myelination is associated with learning, information processing, or cognitive performance and sphingomyelin is important for myelination. [46]

Between 1 and 5 years, myelination occurs early in the somatosensory, motor, visual, and auditory cortices but late in frontal and temporal cortices. The cognitive ability and intelligence across childhood are affected by variations in the morphology and difference in the rate of development of the cortices. [52] In a relatively large cohort of infants, toddlers, and young children aged between 10 months and 4 years,

Deoni et al. reported quantitative differences in patterns of brain development. Infant formula with higher levels of DHA, ARA, choline, and sphingolipids was associated with increased levels of myelin development, while myelin development was slowest among infants on formula with lower levels of sphingolipids and lipids. Further, a marked decline in cognitive activity was evident in children who had received formula with the lowest sphingolipids/other lipids. The cognitive activity in infants with rapid myelination was comparable to infants fed with breastmilk. [53]

As early nutrition significantly impacts the brain and cognitive development, it is impossible to rule out a strong relationship between brain structure and cognitive performance. Deoni et al. compared the longitudinal trajectories of brain and neurocognitive development in exclusively breastfed children with formula-fed (three different formulas with varying quantities of DHA, ARA, choline, and sphingolipids, folic acid, vitamin B12, and iron) infants. This study was part of an ongoing longitudinal study, the Brown University Assessment of Myelination and Behavior Across Maturation (BAMBAM). This study enrolled children between birth and 5 years of age. Myelin development was increased in infants fed with formula with higher DHA, ARA, choline, and sphingolipids. Myelin development was slowest in infants fed with the lowest DHA, ARA, choline, and sphingolipids. A marked decline in cognitive function observed across early childhood in those with the slowest myelination corresponded to the degree of myelination. A formula with a similar trend in myelination to breastfeeding also showed a similar trend in cognitive tendencies. Therefore, among the key ingredients in the formula (ARA, DHA, folic acid, iron, choline, sphingomyelin, B12, and phosphatidylcholine) that is involved in myelination, sphingomyelin and phosphatidylcholine have a profound effect on the whole brain, while the rest of the nutrients are actively involved in the development in focal brain areas. [53]

A recent policy statement published by the American Academy of Pediatrics calls on healthcare providers to help children meet specific nutritional demands for building a healthy brain during the critical window between conception and age 2. [54]

7. Summary

Infancy is characterized by rapid brain growth and development. Executive function skills are an essential aspect of cognitive processing and are characterized by attention-regulation skills involved in conscious, goal-directed problem-solving action. Nutrition influences the development of the brain and has a role in the development of executive functions. While several nutrients are necessary for brain growth and functioning, certain vital nutrients like LC-PUFAs (DHA, ARA), phospholipids including sphingomyelin, play a vital role in brain development and function during the early years of life. The role of sphingomyelins in functional and structural aspects of neuronal myelination may render it essential for cognitive development and executive function precursors in infants and toddlers.

Conflict of Interest

None

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