

Nutrition and Children's Neurocognitive Development: A Critical Study

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Abstract

Cognition represents a complex set of higher mental functions subserved by the brain, and includes attention, memory, thinking, learning, and perception. Cognitive development in pre-schoolers is predictive of later school achievement. Schooling builds human capital - skills, abilities, and resources—which ultimately shapes health and well-being. Indeed, more education has been linked to better jobs, higher income, higher socio-economic status, better health care access and housing, better lifestyle, nutrition, and physical activity, which are all well-known health determinants. Education increases an individual's sense of personal control and self-esteem; these factors have also been shown to influence better health behaviour. Academic achievement is important for future personal health, and is therefore a significant concern for public health.

Key-words: *Nutrition; Micronutrients; Overall diet; Cognitive development.*

Introduction

Cognitive development is influenced by many factors, including nutrition. There is an increasing body of literature that suggests a connection between improved nutrition and optimal brain function. Nutrients provide building blocks that play a critical role in cell proliferation, DNA synthesis, neurotransmitter and hormone metabolism, and are important constituents of enzyme systems in the brain. Brain development is faster in the early years of life compared to the rest of the body, which may make it more vulnerable to dietary deficiencies.

The understanding of the functional and structural development of the human brain has emerged from a range of methodologies (including clinical lesion and experimental animal studies) and lately as a result of greatly improved neuroimaging methods, in particular Positron Emission Tomography and Magnetic Resonance Imaging (MRI). Brain development is a temporally extended and complex process, with different parts and functions of the brain developing at different times. By 5 weeks after conception in humans, the anterior-posterior and dorsal-ventral axes of the neural tube have already developed. The cortical plate (which is the forerunner of the cerebral cortex) and some inter-neuronal connections form from 8 to 16 weeks of gestation. From 24 weeks of gestation until the perinatal period, the neurons in the cortical plate die and are replaced by more mature cortical neurons. During this time, significant refinement in neural connections take place. From 34 weeks post-conception until 2 years of age, peak synapse development, and significant brain growth occurs. By preschool

age, synaptic density has reached the adult level. The myelination of some parts of the brain (particularly those that control higher cognitive functions, such as the frontal lobes) continues well into adolescence, whilst myelination occurs earlier in other parts of the brain that coordinate more primary functions. Although the gray matter (which contains the bodies of nerve cells) reaches asymptote by the age of 7–11 in different regions of the brain, it is thought that the growth of the white matter (which represents axonal nerve tracts) continues beyond 20 years of age. Studies have shown that the maturation of specific brain areas during childhood is associated with development of specific cognitive functions such as language, reading, and memory. The development of the frontal lobes, which are believed to control higher cognitive functions (including planning, sequencing and self-regulation), appears to occur in growth spurts during the first 2 years of life, and then again between 7 and 9 years of age and also around 15 years of age. The development of some subcortical structures including the basal ganglia, amygdala, and hippocampus (which are also centrally involved in some mediating higher cognitive functions, including memory, executive functions, and emotion) also continues until late adolescence. In addition, a meta-analysis has confirmed a connection between the size of the hippocampus and memory performance during brain development in children and young adults. Overall, the research evidence suggests that cognitive development is strongly connected with micro and macro-anatomical changes which take place throughout childhood.

Individual brain development follows a genetic program which is influenced by environmental factors including nutrition. Environmental influences may modify gene expression through epigenetic mechanisms, whereby gene function is altered through the processes of DNA methylation, histone modification and the modulating effect of non-coding RNAs, without the alteration of the gene sequence *per se*. These epigenetic factors can cause long lasting or even heritable changes in biological programs. It has been shown in animal and more recently in human studies that nutrition is one of the most salient environmental factors, and that nutrition can have a direct effect on gene expression. One of the first and best known human studies in the rapidly growing field of “Nutritional Epigenomics” relates to the Dutch Hunger Winter during the 1940's in which the offspring of mothers exposed to famine during pregnancy had an increased risk of cardiovascular, kidney, lung, and metabolic disorders and reduced cognitive functions. More specifically, evidence has been obtained of hypo- and hyper-methylated DNA segments from the blood cells of the affected individuals.

Evidence suggests that the timing of nutritional deficiencies can significantly affect brain development. For example, it is well known that folic acid deficiency between 21 and 28 days after conception (when the neural tube closes) predisposes the foetus to a congenital malformation, called a neural tube defect. Hence, this is a critical period, because during that time an irreversible change in the brain structure and function occurs if there is inadequate folic acid present. A critical period is a specific period within a sensitive timeframe (Knudsen, 2004). A sensitive period tends to reflect a broader timeframe; during such a developmental period the brain is more sensitive to specific interventions. However, skills and abilities can still be acquired outside this time period, albeit with less proficiency. An example is that deaf children who receive cochlear implants within a sensitive period for brain development (i.e., before the age of 3–5 years) show better language development than those who receive a cochlear implant after this period.

Since rapid brain growth occurs during the first 2 years of life (and by the age of 2 the brain reaches 80% of its adult weight), this period of life may be particularly sensitive to deficiencies in diet. Adolescence is also a significant and sensitive developmental period, with research indicating that structural reorganization, brain and cognitive maturation and—in particular—major developments in the prefrontal cortex take place during puberty.

Micronutrients and cognitive development

Omega-3 fatty acids

In recent years, there has been an increasing interest in the effect of essential fatty acids, particularly long chain polyunsaturated fatty acids (LCPUFA), on cognitive brain development. Of the human brain's dry weight 60% is comprised of lipids, of which 20% are docosahexaenoic acid (DHA; which is an omega-3 fatty acid) and arachidonic acid (AA; an omega-6 fatty acid). These represent the two core fatty acids found in gray matter. Furthermore, the supply of LCPUFAs from food, especially the omega-3 fatty acids, including DHA and eicosapentaenoic acid (EPA), is frequently inadequate for children as well as for adults.

Essential fatty acids play a central functional role in brain tissue. They are not only the basic components of neuronal membranes, but they modulate membrane fluidity and volume and thereby influence receptor and enzyme activities in addition to affecting ion channels. Essential fatty acids are also precursors for active mediators that play a key role in inflammation and immune reaction. They promote neuronal and dendritic spine growth and synaptic membrane synthesis, and hence influence signal processing, and neural transmission. In addition, essential fatty acids regulate gene expression in the brain. Therefore, the existing literature strongly suggests that essential fatty acids are critical for brain development and function.

It has been suggested that the fast growth of the human cerebral cortex during the last two million years was strongly related to the balanced dietary intake of LCPUFAs, specifically with an equal ratio of omega-6 and omega-3 fatty acids in the diet. Evidence proposes that the modern Homo sapiens, whose brain developed significantly relative to its ancestors, lived near rivers and oceans, where seafood and fish were abundant. The rise in intellectual and brain development in Homo Sapiens also coincided with tool making and language development. During the last 150 years, it is believed that the balance of omega-6 to omega-3 fatty acids has shifted in favor of omega-6 fatty acids in the diet, resulting in a ratio of 20–25:1 and a dietary deficiency in omega-3 fatty acids. A diet that is deficient in omega-3 fatty acids may have health and developmental implications.

Some published studies have also considered supplementation in lactating mothers in order to examine the effect of increased omega fats in breast milk on the cognitive development of children. Reviews of these studies have concluded that there are indications that supplementing lactating mothers with fish oil may positively influence cognitive development in children.

Thus, the current findings show inconsistencies in the efficacy of maternal supplementation with omega-3 fatty acid. In seeking to account for the contrasting findings, it seems that the following considerations may be relevant: the interventions were applied in different groups of women, using a wide range of DHA dosage, with different durations of supplementation, and the outcomes were measured on different cognitive instruments and at different ages. The more consistent results obtained in epidemiological studies (compared with supplementation trials using only omega-3 fatty acid) may be explained by the possibility that fish is a whole food, and it contains other nutrients important to cognitive development. Furthermore, by eating fish rather than taking fish supplements, other possibly unhealthy or potentially inflammatory foods may also be displaced—i.e., red meat and processed meats. Epidemiological studies may also be better powered but they may also potentially have less control for confounding. Since brain development continues through childhood, there have been much interest in the association between cognitive development and omega-3 fat levels through diet and/or supplementation in children.

Vitamin B12, folic acid, and choline

B12 and folate deficiency resulting in anaemia is rare around the world. However, it can occur in both developing and developed countries especially in older people, in those with absorption problems and in vegetarians. Folate fortification of bread products has been made mandatory in Australia and in many other countries, which has reduced this deficiency significantly. In recent years, there has been an increasing interest in the association between vitamin B12, folic acid, choline metabolism, and cognitive development. Folate affects neural stem cell proliferation and differentiation, decreases apoptosis, alters DNA biosynthesis, and has an important role in homocysteine and S-adenosylmethionine biosynthesis. It is believed that choline has similar roles in brain development as folate. Furthermore, folate, choline and vitamin B12 metabolism are interconnected at the homocysteine-methionine-S-adenosylmethionine pathway. S-adenosylmethionine is one of the main methyl donors in different metabolic methylation reactions, including DNA methylation. Therefore, choline and folate deficiency may result in DNA hypomethylation, thereby altering gene transcription. In addition, choline is a component of phospholipids in cell membranes and a precursor for the neurotransmitter acetylcholine. Vitamin B12 has a role in axon myelination that is important for impulse conduction from cell to cell, and it also protects neurons from degeneration. Vitamin B12 may also alter the synthesis of different cytokines, growth factors and oxidative energy metabolites such as lactic acid.

Zinc

Zinc deficiency appears to be a major problem worldwide, affecting 40% of the global population. Recent research suggests that toddlers, adolescents, older people and individuals with diabetes are possibly at a higher risk of zinc deficiency in Australia. Animal studies have established a relationship between zinc and neurodevelopment. It is believed that zinc is a vital nutrient for the brain, with important structural and functional roles. More specifically, zinc is a cofactor for more than 200 enzymes that regulate diverse metabolic activities in the body including protein, DNA and RNA synthesis. In addition, zinc plays a role in

neurogenesis, maturation, and migration of neurons and in synapse formation. Zinc is also found in high concentrations in synaptic vesicles of hippocampal neurons (which are centrally involved in learning and memory), and seems to modulate some neurotransmitters including glutamate and gamma- aminobutyric acid (GABA) receptors.

Iron

One of the most common nutritional deficiencies in both developing and developed countries is iron deficiency. In some parts of the world, such as in Sub-Saharan Africa and South-East Asia, the prevalence is more than 40%. In developed countries—including Australia—it could be as high as 20%, particularly in pregnant women and in children. Over the past decades, a considerable literature has been published on the association between iron status/anaemia and cognitive development in children, as well as in animal model. It is believed that iron is involved with different enzyme systems in the brain, including: the cytochrome c oxidase enzyme system in energy production, tyrosine hydroxylase for dopamine receptor synthesis, delta-9- desaturase for myelination, and fatty acid synthesis, and ribonucleotide reductase for brain growth regulation. In addition, iron appears to modify developmental processes in hippocampal neurons by altering dendritic growth.

In summary, there is a lack of epidemiological evidence or data from well-designed intervention trials demonstrating the impact of maternal iron supplementation on the cognitive development of healthy children. There is evidence that older anaemic children benefit from iron treatments. However, cognitive performance tests including the Bayley Scales of Infant Development and the Denver Developmental Screening Test may not be sensitive enough to detect small changes in short-term supplementation or treatment in young children. Furthermore, if iron deficiency occurs in very early life, the damage may be irreversible, and it may not be possible to reverse this damage with iron treatment.

Iodine

Iodine deficiency is a significant worldwide public health issue, especially in children and during pregnancy. In India, the majority of children and pregnant women are mildly deficient in iodine, with some groups reaching moderate to severe deficiency. Iodine deficiency in the soils in many countries has led to food fortification, most commonly the use of iodized salt. The relationship between iodine and cognitive development is extensively researched. It is well known today that severe iodine deficiency during pregnancy may cause “cretinism” in children. The clinical manifestation of cretinism depends on the severity of iodine deficiency; the features may include mental retardation, speech and hearing impairment, upper motor neuron and extrapyramidal lesions. Iodine is necessary for the production of thyroid hormones in the body; 70–80% of it is found in the thyroid gland. Iodine deficiency manifests in hypothyroidism, causing underproduction of thyroid hormones including triiodothyronin (T3) and thyroxin (T4). Thyroid hormones play an important role in neurodevelopment and numerous neurological processes including neuronal cell differentiation, maturation and migration, myelination, neurotransmission, and synaptic plasticity. In addition, in animal models hypothyroidism alters neurogenesis and the development and functions of synapses in the hippocampus.

Multivitamin and mineral supplementation

Although it is important to investigate nutrients individually, deficiencies of nutrients rarely occur in isolation, and an inadequate diet typically causes multiple micronutrient deficiencies. In addition, nutrients interact with each other and do not work separately. Thus, it is important to investigate the association between multiple mineral and vitamins supplementation or deficiencies and cognitive development.

Overall diet, food, and cognitive performance

Breastfeeding

A considerable amount of literature has been published on the possible connection between breastfeeding and cognitive development. Many of these studies demonstrate significantly positive associations between the two; however, the associations typically diminish or are no longer significant after controlling for confounders including maternal IQ, which is believed to be the strongest predictor of children's intelligence. Furthermore, it remains unclear whether the remaining, diminished associations between breastfeeding and child cognitive development are further confounded by factors that have not been controlled for. A meta-analysis of 20 studies undertaken in the late 1990's found that breastfeeding in normal birth weight infants increased IQ by 2.7 points and in low birth weight children by 5.2 points, but only six of the studies controlled for maternal IQ. Three critical reviews conducted in the early 1990's concluded that the evidence linking breastfeeding and cognitive development has not yet been comprehensively demonstrated.

The debate concerning whether breastfeeding and cognitive development have a positive association appears to continue, but with more advanced neuroimaging technologies now available, future research may offer greater insights. Nevertheless, breast milk provides the best nutritional intake for infants, regardless of its putative association with cognitive development.

Conclusion

The majority of studies, which have investigated the association between nutrition and cognitive development, have focused on individual micronutrients, including omega-3 fatty acids, vitamin B12, folic acid, zinc, iron, and iodine. The evidence is more consistent from observational studies, which suggest these micronutrients play an important role in the cognitive development of children. However, the results from intervention trials of single nutrients are inconsistent and inconclusive, prompting the need for better controlled and more adequately powered studies in the future. It is plausible that children living in poor countries may encounter more multiple micronutrient deficiencies, as opposed to children living in rich countries who are reasonably well nourished (and where a small deficiency in one nutrient may not result in measurable, long-term change in cognitive outcomes, due to compensation over time). These are important considerations, because nutrients do not act alone; rather, they have in some contexts synergistic and in other contexts antagonistic effects with each other. Individuals consume combinations of food and poor overall diet can cause multiple macro-and micronutrient deficiencies and imbalances. If an overall healthy diet

synergistically enhances cognitive development in children, then public health interventions should focus on the promotion of overall diet quality rather than isolated micronutrients or dietary components consumed by children and adolescents.

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