



## Food neuropsychology and child brain development

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DOI: 10.31665/JFB.2021.XXXX

Received: March 22, 2021; Revised received & accepted: March 28, 2021

Citation: Lange, K.W., and Lange, K.M. (2021). Food neuropsychology and child brain development. J. Food Bioact. 000: 000–000.

### Abstract

Accumulated adverse events, including insufficient nutrition, throughout pregnancy and infancy can disrupt brain development as well as early learning and cognition. Food neuropsychology research in childhood investigates the pathway from prenatal and postnatal nutrient supply to long-term brain function and mental health. Adequate food supply and nutrition from conception through infancy play an essential role in normal brain development and cognitive functioning and may also influence vulnerability to mental disease later in life. Neurodevelopmental processes, such as neuron proliferation, myelination and synaptogenesis, occur rapidly during pregnancy and infancy and are critically dependent on a sufficient supply of a variety of nutrients, including protein, omega-3 polyunsaturated fatty acids, iodine, iron and zinc. The investigation of the molecular basis of food effects on cognition and mood will help ascertain early-life nutritional requirements in order that brain functions and mental fitness may be enhanced. There is currently no convincing evidence of beneficial effects of nutrients or food bioactives in child mental disorders. Numerous issues in the examination of the effects of specific nutrients, including the identification of nutrients critical at different phases of brain development and the optimal dosage and duration of supplementation, require further research.

**Keywords:** Food neuropsychology; Brain development; Child cognition; Mental health; Prevention.

### 1. Introduction

Neural processes underlying early learning are influenced by genetic, epigenetic and environmental factors and have significant effects on subsequent development and health (Weaver, 2014). Adverse experiences early in the life course are linked to adult health (Black et al., 2017) and can have long-term disrupting effects on brain development and cognitive functioning (Shonkoff and Garner, 2012; Luby, 2015). Among various adversities, inadequate nutrition in prenatal and early postnatal stages carries the risk in affected individuals of failure to attain their developmental potential with respect to education, professional prospects, social relations and mental health (Lake and Chan, 2015; Walker et al., 2007). The important role of certain nutrients in the ontogenetic development of the central nervous system is well established (Georgieff and Rao, 2001; Kretchmer et al., 1996). Adequate nourishment and micronutrient supply is particularly important during pregnancy and

infancy, when the brain develops most rapidly. Brain growth and function are dependent on a wide range of nutrients, but certain of these play key roles during early development. For example, folate is needed for neural tube development (Hibbard and Smithells, 1965) and iodine plays a vital role in neuronal plasticity (John et al., 2017). Other nutrients with significant effects on brain development include protein, essential fatty acids, choline, iron and zinc (Georgieff, 2007).

Most of the evidence regarding the biological mechanisms through which nutrient deficiencies may interfere with neurodevelopment at molecular and cellular levels stem from animal experiments. Neurodevelopmental processes that can be affected by these deficiencies in early life include proliferation of neurons, growth of axons and dendrites, myelination of neuronal membranes, formation of synapses and neuronal apoptosis (Prado and Dewey, 2014). While findings of animal studies have demonstrated the important role of food components in brain development,

**Table 1. Macronutrients and micronutrients in prenatal and infant brain development**

Nutrient	Main role in developmental brain physiology	Main effects of deficiency
Protein	Cell proliferation and differentiation, dendritic arborization, synaptogenesis	Mild neurodevelopmental abnormalities (e.g. impaired visual recognition memory)
Omega-3 fatty acids	Myelination, synaptogenesis	Cognitive deficits (e.g. attention, information processing); child mental disorders?
Folate	Neural tube development	Spina bifida, encephalocele
Iodine	Cerebral cortex cytoarchitecture	Cognitive impairment
Iron	Energy metabolism, myelination and neurotransmitter production	Abnormal neurological reflexes and impaired auditory recognition memory at birth; poorer neurodevelopment at school age
Zinc	Neurogenesis, neuronal migration, myelination and synaptogenesis	Cognitive deficits (e.g. attention, learning, memory)

the development of permanent cognitive deficits or mental disorders as a consequence of inadequate nutrition in early ontogenesis depends on the interaction of these components with various other factors. Food neuropsychology is concerned with the way in which food and its components influence the nervous system, brain-behavior interactions, cognition, emotion and motor functions. The present short review summarizes the main scientific findings on food and child brain development and provides suggestions for future research.

## 2. Food neuropsychology and child cognition

The main macro- and micronutrients that have been identified as necessary in prenatal and infant brain and cognitive development include protein, omega-3 polyunsaturated fatty acids (PUFAs), iodine, iron and zinc (see Table 1).

### 2.1. Protein

The findings of animal models have demonstrated that protein restriction in early life results in reduced brain size, a less complex dendritic architecture, reduced synaptic numbers and a decrease in neurotransmitter and growth factor levels (Jones and Dyson, 1981; Wiggins et al., 1984; Winick, 1985). The special importance of protein, among other macronutrients, in achieving full neurodevelopment during the prenatal period and early childhood has also been shown in human studies (Pollitt et al., 1995). Fetal protein and/or energy malnutrition in humans causes intrauterine growth retardation (Low and Galbraith, 1974), which may be associated with impaired prenatal growth of the head (Strauss and Dietz, 1998) and mild neurodevelopmental abnormalities, including impairment of visual recognition memory (Gotlieb et al., 1988; Spinillo et al., 1993).

### 2.2. Omega-3 fatty acids

Omega-3 PUFAs are constituents of cell membranes and are essential for normal brain function. Animal studies have demonstrated that omega-3 PUFAs, particularly docosahexaenoic acid (DHA), are involved in neurogenesis, neuronal migration, synaptogenesis as well as fatty acid composition and fluidity of neuronal membranes (Innis, 2008). Since omega-3 PUFAs are essential for brain growth and development during pregnancy and infancy (Kris-

Etherton et al., 2009), sufficient dietary supply is indispensable for normal cognitive and motor development in childhood (Clandinin et al., 1980a, 1980b; Colombo et al., 2004; Helland et al., 2003; Luxwolda et al., 2014). Dietary deficiency of omega-3 fatty acids appears to impair learning and memory in rodents (Bourre et al., 1989; Moriguchi et al., 2000). In non-human primates, early PUFA levels have been found to have modulatory effects on prefrontal cortex functions, such as attention, impulsivity and inhibition (Neuringer et al., 1986). The findings of studies in preterm humans have suggested beneficial effects of DHA for retinal and cognitive development (O'Connor et al., 2001; SanGiovanni et al., 2000). The results of other human studies of potential benefits of omega-3 PUFA supplementation during gestation, lactation and infancy on attention and cognition have been mixed (Delgado-Noguera et al., 2010; Simmer, 2001). However, long-term follow-up appears to be essential in food supplementation studies, since benefits of PUFAs administered in the first year of life may become apparent only at age 3–6 years (Colombo et al., 2013). The accumulation of omega-3 PUFAs in neuronal membranes may contribute to increased information processing, improved attention and enhanced cognition in children (Vollet et al., 2017). Maternal supplementation with omega-3 PUFAs during pregnancy and lactation has been reported to augment children's intelligence quotient at 4 years of age (Helland et al., 2003). Dietary enrichment with PUFAs has also been shown to positively impact children's general cognitive competence as well as learning, memory and language (Øyen et al., 2018). Furthermore, omega-3 PUFA supplementation was associated with a decrease in deficits in reading and spelling in children with developmental coordination disorder (Richardson and Montgomery, 2005). In children deemed "normal" in their general ability but "not fulfilling their potential at school", improved school performance was seen in those receiving omega-3 PUFAs (Portwood, 2006). This finding needs to be confirmed by high-quality randomized trials.

### 2.3. Iodine

The role of iodine in brain development is related to thyroid hormone synthesis. An insufficient intake of iodine in prenatal stages and infancy can permanently and irreversibly disturb the cytoarchitecture of the cerebral cortex (John et al., 2017; Williams, 2008). Animal studies have shown that prenatal iodine deficiency is linked to deficient neurogenesis and neuronal migration, while postnatal deficiency affects dendritogenesis, synaptogenesis and myelination (Dong et al., 2005; Navarro et al., 2015). Behavioral

abnormalities observed in animals include impairments in learning and memory and sensory gating as well as increased anxiety-like behaviors (Navarro et al., 2015). Severe prenatal iodine deficiency in humans can cause cretinism with irreversible changes in brain development, including deficits in hearing, speech and motor functioning (Skeaff, 2011), as well as a reduced intelligence quotient (Bath et al., 2013).

#### 2.4. Iron

A key role of iron in human brain development, including energy metabolism, myelination and neurotransmitter synthesis, has been demonstrated in numerous studies (Beard and Connor, 2003). Rodent experiments have found that iron is necessary for the structural, neurochemical and functional development of the fetal brain (Carlson et al., 2009; Greminger et al., 2014; Lozoff et al., 2006). Behavioral consequences of iron deficiency in rodents include deficits in trace recognition memory (McEchron et al., 2005), procedural memory (Beard and Connor, 2003) and spatial navigation (Felt and Lozoff, 1996). Human infant iron deficiency has been shown to be associated with abnormal neurological reflexes (Armony-Sivan et al., 2004) and impaired auditory recognition memory at birth (Siddappa et al., 2004). Infants with low cord serum levels show poorer neurodevelopment at five years of age (Tamura et al., 2002).

#### 2.5. Zinc

Zinc is a cofactor in enzymes involved in the biochemistry of proteins and nucleic acids (Sandstead, 1985), and fetal zinc deficiency leads to a reduced brain content in DNA, RNA and protein (Duncan and Hurley, 1978). Animal studies have shown that zinc is needed for neurogenesis, neuronal migration, myelination and synaptogenesis (Adamo and Oteiza, 2010). Behavioral effects of zinc deficiency in early life in humans include disturbed attention, learning, memory and mood (Golub et al., 1995), and a positive impact of zinc supplementation in early infancy has been reported (Black et al., 2004; Colombo et al., 2014). Fetuses of zinc-deficient mothers have been observed to show reduced movement and heart rate variability, which suggests impaired stability of the autonomic nervous system (Merialdi et al., 2004).

### 3. Food neuropsychology and child mental disorders

Food and diet are increasingly recognized as critical not only for early brain development and cognition but also as potentially modifiable factors influencing mental health outcomes in children (Lange, 2018a). While the factors contributing to mental health are manifold and complex, maternal nutrition and early-life diet appear to be associated with behavioral and emotional dysregulation and neuropsychiatric conditions in childhood (O'Neil et al., 2014). Severe macronutrient deficiencies during early development have been linked to the pathogenesis of depressive and psychotic disorders (Brown et al., 1995; Susser and Lin, 1992). Furthermore, the findings of several prospective cohort studies have shown that prenatal and early postnatal nutrition are associated with internalizing and externalizing problems in children aged 5–7 years (Jacka et al., 2013; Pina-Camacho et al., 2015; Steenweg-de Graaff et al., 2014). In addition, various vitamins, trace elements and omega-3 fatty acids have been suggested to play a role in child mental dis-

orders (Lange, 2017, 2018b, 2020a; Lange et al., 2017). For example, dietary omega-3 PUFA deficiency has been associated with an increase in the risk of several mental disorders in children, such as attention deficit/hyperactivity disorder (ADHD), autism spectrum disorders (ASD) and mood and psychotic disorders (Lange, 2020b, 2020c). However, epidemiological studies reporting correlations between nutrient levels and the presence or severity of psychiatric symptoms do not allow any conclusions on causality. Since numerous intervention studies examining the potential therapeutic effects of nutrients in mental disorders have employed study designs lacking an appropriate control group, the results reported may be due to placebo effects. Long-term randomized controlled trials are largely absent. There is therefore no convincing evidence of beneficial effects of nutrients or food bioactives in child mental disorders.

#### 3.1. Elimination diets

In addition to nutrient deficiencies, antigenic properties of food components have been hypothesized to be involved in child mental disorders. For example, a causal involvement of the proteins gluten and casein in the pathogenesis of ASD has been suggested (Lange et al., 2015), and gluten-free/casein-free diets are believed to be capable of ameliorating the behavioral symptoms in children. However, the scientific rigor of many available intervention studies is low, and rigorous scientific evaluations found no evidence of effectiveness of the gluten-free/casein-free diet in the treatment of ASD (Reissmann et al., 2020).

On the basis of the hypothesis that artificial food additives may be involved in the occurrence of ADHD symptoms, elimination studies have examined the effects of the exclusion of artificial food additives or of a few-foods diet in children with ADHD. A meta-analytical review reported a small effect size of food additive elimination (Nigg et al., 2012). Furthermore, the small effect sizes found for artificial food color elimination in placebo-controlled trials provide no convincing evidence of its therapeutic efficacy, while the medium-to-large effects of the few-foods diet suggest that this approach may offer a treatment option (Pelsler et al., 2017). In addition, the use of oligoantigenic diets and subsequent reintroduction of nutrients can reveal food-related intolerances or allergies. This approach is currently under investigation (Dölp et al., 2020).

### 4. Future directions

While various nutritional deficiencies, such as chronic undernutrition and insufficient iodine and iron supply, have clearly been shown to impair brain development, evidence of the effects of micronutrient powder supplementation and salt iodization is scarce, and further investigations are therefore called for.

#### 4.1. Time, extent and duration of nutrient deficiency

The effects of nutrient deficiencies on early brain development depend on time, extent and duration (Kretchmer et al., 1996). The time of nutrient deficiencies appears to be of particular importance (Cusick and Georgieff, 2012). Critical or sensitive ontogenetic periods are times of particular receptiveness or vulnerability to certain environmental and other factors, such as maternal health, social stimulation and deprivation, stress, toxins or nutrients. These factors are of critical importance for normal brain development,

with a deficiency resulting in irreversible long-term consequences for brain structure or function (Bornstein, 1989; Colombo, 1982). For example, the hippocampus develops earlier than the prefrontal cortex and therefore the time period of insufficient supply of a nutrient affecting the arborization of neuronal dendrites will determine which of these brain regions sustains more profound damage. A neuronal circuit requiring a balanced input from both hippocampus and prefrontal cortex, such as the ventral tegmental area, may show significant behavior-related pathology, e.g. related to psychotic disorders, as a consequence of unbalanced input (Tseng et al., 2009; White and McDonald, 2002).

The significance of the stage in infant development during which iron supply is deficient has been investigated. While iron/folic acid supplementation during pregnancy produced better results in the offspring in tests of intellectual, executive and motor function in comparison with placebo controls (Christian et al., 2010), supplementation in children aged 12–35 months showed no effect (Murray-Kolb et al., 2012). Furthermore, excessive administration of iron may lead to worse neurodevelopmental outcomes. In a 10-year follow-up study of iron supplementation in 6-month-old infants, those with high hemoglobin receiving iron performed significantly worse 10 years later in a neurodevelopmental task battery, while infants with low hemoglobin receiving iron showed a significantly better performance (Lozoff et al., 2012). These findings demonstrate that a nutrient may be beneficial at one dose or time and toxic at another.

Research on specific nutrients has yet to ascertain both the effects of individual compounds during critical phases of brain development and the optimal dosage and duration of supplementation.

#### 4.2. Combination of nutrients and dietary patterns

The majority of available studies have investigated the brain-related and behavioral effects of individual nutritional components, food bioactives or supplements. However, individual nutrients can interact with one another and may have synergistic (or antagonistic) effects on specific functions. Food research has therefore focused increasingly on dietary pattern analysis (Hu, 2002). Multi-ingredient supplementation may be needed to achieve beneficial effects in mental disorders in particular, since they are clinically complex and etiologically heterogeneous.

In a study assessing cognitive functioning, children aged 6–12 years receiving a beverage containing omega-3 fatty acids and various micronutrients (iron, zinc, folate and vitamins A, B6, B12 and C) showed higher scores in tests assessing learning, memory and verbal intelligence after 6 and 12 months (Osendarp et al., 2007). In order to separate out the role of individual nutrients in the improved test results, it would be necessary to perform several concurrent studies examining single components. However, certain dietary components may act in an additive or synergistic fashion, and the assessment of dose-response relationships for all potentially relevant nutrients poses numerous logistic challenges.

A possible role of dietary patterns has been investigated in children and adolescents diagnosed with ADHD. A large population-based cohort study reported that ADHD diagnosis was associated with a higher score for a ‘Western’ dietary pattern, but not with a ‘healthy’ dietary pattern (Howard et al., 2011). An inverse association has been found between ADHD and a nutrient pattern rich in zinc, protein and other minerals (Zhou et al., 2016). Furthermore, low adherence to a Mediterranean diet was associated with an increase in the prevalence of ADHD diagnosis (Ríos-Hernández et al., 2017). Hyperactivity was positively correlated with the con-

sumption of processed meat and salty snacks and negatively associated with the consumption of vegetables, coarse cereals, aquatic foods, beef and mutton (Liu et al., 2014). However, the findings are based on observational study designs which allow no conclusions regarding causal relationships between ADHD and diet.

There is a paucity of randomized controlled trials examining the effectiveness of dietary change in mental health. Emerging evidence in adults suggests that adherence to a Mediterranean-style diet has beneficial effects on mental health in individuals with depression (Parletta et al., 2019; Sánchez-Villegas et al., 2019), and significant improvements in mood and decreased anxiety levels have been observed in adults with major depression (Jacka et al., 2017; Jacka et al., 2018). However, randomized controlled trials assessing the Mediterranean or other diets in early life are not available.

#### 4.3. Role of the microbiome

Research on the interaction between intestinal microbiota and the brain has come into focus in research, since the microbiome appears to provide a link between the gut and brain function (Dinan et al., 2015; Fernandez-Real et al., 2015; Sarkar et al., 2018). In particular, gut microbiota have been suggested to play a role in responses to stress (Dinan and Cryan, 2012) and the risk of childhood mental disorders, such as ADHD and ASD (Lange et al., 2020). However, the recent hype in microbiome research, including claims that interventions targeting intestinal microbiota might offer potential avenues for the enhancement of cognition or the treatment of mental disorders, needs to be put into perspective. The available studies have shown correlational but no causal relationships and have been unable to detect distinct microbiota patterns related to different mental disorders (Lange et al., 2020). Large-scale, prospective trials need to investigate the clinical relevance of findings in animals and the validity of the intestinal microbiome as a target in the prevention or treatment of mental disorders.

#### 4.4. Adverse effects of food supplements

In regard to the administration of nutritional supplements, possible adverse effects of seemingly natural and healthy nutrients should be taken into consideration. For example, long-term omega-3 PUFA administration may be associated with an elevated cancer risk, possibly due to PUFAs, their oxidation products or added  $\alpha$ -tocopherol (Lange et al., 2019). Therefore, caution is needed when food supplements are administered over extended periods of time and during vulnerable phases of life, especially in infancy and childhood. Adverse effects may become apparent many years after supplementation and their cause may therefore fail to be recognized.

#### 4.5. Further aspects

In addition to the above mentioned aspects of time, extent and duration of nutrient deficiency, a child’s psychosocial environment should be considered in the design of future research. In a recent cross-sectional cohort study of early school-aged children, caregiving behaviors, such as quality of parent-child relationship and parental stress, have been shown to modify the association of children’s gut microbiome with socioeconomic risk and behavioral dysregulation (Flannery et al., 2020). Nutritional supplementation may produce positive effects on development only if combined

**Table 2. Research issues of food neuropsychology and child brain development**

Further identification of foods critically important for normal brain development
Effects of time, extent and duration of nutrient deficiencies on early brain development
Long-term effects of early nutritional deficiency on behavior, cognition and mental health across the entire lifespan
Role of single nutrients versus dietary patterns and whole diets
Obesity and mental health problems in later life
Correlational or causal association of gut microbiota with cognition or mental disorders
Identification of distinct microbiota patterns related to different child mental disorders
Interaction of food-related factors with psychosocial and environmental factors
Food neuropsychology and public health policies

with a certain amount of stimulation from the environment. For example, developmental benefits following zinc supplementation were seen in Jamaican infants aged 9–30 months only if they participated in a psychosocial stimulation intervention (Gardner et al., 2005). Thus, improvement of nutrition alone may be insufficient to improve brain development.

Child brain development may be affected not only by nutritional deficiency but also by an overabundance of food resulting in overweight and obesity. Maternal obesity during pregnancy appears to be associated with an elevated risk for a wide range of physical health, cognitive and mental health problems in offspring across the entire lifespan (Contu and Hawkes, 2017). High prenatal maternal body mass index has been found to be associated with differences in cognitive performance of offspring at age 5 years (Basatemur et al., 2013) and in affective and social functioning at ages 5–6 years (Jo et al., 2015; Robinson et al., 2013; Rodriguez, 2010). Elevated prenatal body mass index has also been associated with ADHD and ASD in early and middle childhood (Getz et al., 2016; Sanchez et al., 2018). Furthermore, changes in fetal brain connectivity, as assessed using functional MRI, have recently been shown to be associated with elevated maternal body mass index during pregnancy, with a tendency for elevated within-hemisphere connectivity and a decrease in cross-hemisphere connectivity (Norr et al., 2020). This may have implications for the long-term cognitive development and mental health of the offspring. Little is known about the associations between brain development and overweight or obesity in children. In a group of over 3,190 children with a mean age of 10.0 years, those with a higher body mass index were found to exhibit lower thickness of 18 regions of the cerebral cortex, with the greatest correlation observed in the prefrontal cortex (Laurent et al., 2020). In addition, body mass index was inversely correlated with scores in tests of executive functions, such as working memory (Laurent et al., 2020). These findings suggest that child obesity is associated with the development of the prefrontal cortex. In addition, the complex relationships between obesity and mental health are thought to potentiate the severity and interdependence of each other (Small and Ablasca, 2016).

Research on the role of nutrients in mental disorders is hampered by their problematic classification and heterogeneous nature. An objective and reliable classification based on biological hypotheses is needed (Haber and Rauch, 2010; Insel and Cuthbert, 2009). Most mental disorders are ill-defined constructs and lack biological or neuropsychological markers underpinning their validity. At present, the preventive or therapeutic efficacy of nutrients in child mental disorders can be evaluated using only subjective and questionable symptom ratings rather than objective pathophysiological measures or neuropsychological biomarkers.

Major research issues of food neuropsychology and child brain development are presented in Table 2.

## 5. Conclusion

Normal brain development is critically dependent on sufficient food supply and nutrition. A balanced diet from conception through infancy is essential in providing an adequate nutrient supply to allow an undisturbed development of brain and cognitive function. Furthermore, food and diet seem to be modifiable intervention targets for the prevention of common mental disorders.

Current epidemiological findings on food and mental health cannot establish causality or provide information on the underlying mechanisms. Further scientific evidence demonstrating an unequivocal link between nutrition and mental health is therefore needed. Foods and dietary components critically important for brain health and possibly mental disease as well as the timing, dosage and duration of nutritional interventions providing preventive and therapeutic efficacy require further investigation.

The effects of dietary factors normally become apparent in the long term and their importance for public health is therefore frequently underestimated. Nutritional deficiencies during pregnancy and infancy may have effects on behavior, cognition and mental health throughout childhood, adolescence and adulthood. Thus, prevention of nutritional deficits in early life may have long-term benefits for individuals and societies. The findings of food neuropsychology and nutritional research on child mental development should inform public health nutrition practice and policy-making related to promoting healthy brain development.

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