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COMMENTARY

Nutrition for the Brain

Commentary on the article by Isaacs *et al.* on page 308

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The question of whether brain function is entirely genetically determined or may be influenced by the environment or by nutrition has been debated for decades. Several studies have associated breastfeeding with improved intelligence in later life (1–5). Of course many confounding factors such as socioeconomic status, perinatal, and early childhood morbidities will influence both readiness for breastfeeding as well as direct cognitive development. Effects of studies rigorously controlling for maternal intelligence did not indeed find the same major beneficial effects of breastfeeding on later intelligence (6,7). Mechanisms by which breastfeeding is supposed to exert its effects on cognitive development is mainly fatty acid (FA) composition of human milk, containing polyunsaturated FA such as omega-3 polyunsaturated fatty acids, docosahexaenoic acid (DHA), and trophic factors such as insulin-like growth factor-1 (8), both important for organ development and in particular for the brain. The Avon Longitudinal Study of Parents and Children showed that IQ increased by 3.2 points for every 100 ng/mL increase of plasma insulin-like growth factor-1 levels and this in particular for the Verbal IQ (VIQ) compared with the Performance IQ (PIQ) (9). Polyunsaturated FA, such as DHA [22:6(n-3)] are important precursors of membrane lipids and are, as such, important components of brain growth and myelination. DHA is the most abundant (n-3) fatty acid in the mammalian brain. DHA in the brain can be obtained either as DHA itself or from one of its precursors, α-linolenic acid or eicosapentaenoic acid. However, the rates of conversion of α-linolenic acid to DHA is low in humans (less than 1% of dietary amount). Before birth, DHA is transported through the placenta *via* pathways involving fatty acid binding proteins and α-fetoprotein, before release into the fetal circulation, the rate of transfer increasing during the third trimester. High dietary intake of DHA during pregnancy results in higher maternal-to-fetal transfer (10). After birth, the infant is provided with DHA in mother's milk. However, the level of DHA can vary (from less than 0.1 to 1% of milk fatty acids) depending on the amount of DHA in the mother's diet.

For the premature infant, nutrition regularly provided by the placental transfer during the third trimester dramatically changes after birth at a time point when the organism is still dependent on nutrients transferred from the placenta. Both parental nutrition as well as breast milk of mothers after premature birth provide insufficient nutritional support to the developing brain of the premature infant and may lead to postnatal growth restriction with the known consequences of altered hormonal status including alteration of leptin expression (11). Many recent studies have therefore assessed the effects of breastfeeding and nutritional interventions on neuro-developmental outcome of premature infants (12–16), showing advantage with early breastfeeding, FA supplementation, and higher protein intake. Preterm and low birth weight infants are often growth-restricted at hospital discharge. Feeding infants posthospital discharge with calorie- and protein-enriched formula milk might therefore facilitate "catch-up" growth, but this has not been confirmed in a recent Cochrane Database review (17). The current study by Isaacs *et al.* is one of the few studies that looks at specific brain structural effects of nutritional supplementation. Human brain growth mainly takes place during the third trimester with whole brain volume more than doubling and cortical gray matter volume increasing four-fold (18) and an increase in subcortical gray matter or basal ganglia of 70% (19,20). This is also the time period in which cortical folding and gyrification take place with an increase of brain surface and degree of sulcation index (21). Conditions such as severe prematurity and cerebral white matter injury have been shown to affect brain growth and specific structural brain development with subsequent functional consequences both at birth, in infancy, early childhood, and adolescence (22–27). Regional brain growth has been shown to be different with occipital regions growing much faster than prefrontal regions and differentially affected by conditions such as prematurity affecting growth in the central regions or brain lesions affecting both central and frontal brain regions (19,21,28). All these measures have been defined *in vivo* using advanced Magnetic Resonance Image analysis tools similar to the approach taken in the study by Isaacs *et al.* The authors in this study present data on a comparison of brain structural volumes and IQ measurements in two groups of ex-preterm infants born at a gestational age below 30 wk at adolescent age treated with a different perinatal nutritional protocol. They used an atlas-based segmentation technique to define total brain and cortical gray matter volume as well as volumes of the subcortical gray matter structures, caudate nucleus, thalamus, putamen, globus pallidum, hippocampus, and amygdala and IQ testing with Wechsler Intelligence Scale for Children defining both VIQ and PIQ. The high nutrient group expreterm adolescents showed significantly better performance on VIQ ex-preterm measures with no differences in PIQ measures. Structurally the two groups showed significant differences in both left- and right-sided caudate volume, with the standard nutrition group showing lower caudate volumes which further correlated with IQ scores with lower volume indicating lower VIQ. This was a gender-specific effect with mainly male preterm infants being affected by these differences in perinatal nutrition. Subcortical gray matter

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structures have been shown to be affected by premature birth with correlations to later cognitive outcome (23,29–31) as well as in neuro-psychiatric disorders such as attention deficit hyperactivity disorder (32,33) and Depression (34). Deep nuclear gray matter volume reduction at term age has been shown in a previous study to be correlated with gestational age at birth and severity of respiratory distress syndrome, so, clearly immaturity at birth and comorbidities such as severe respiratory distress which are associated with oxidative stress lead to reduction in deep cortical gray matter volume at term. Immaturity and severity of respiratory distress syndrome on the other hand are often associated with poor nutritional status in the preterm infant, and therefore the findings of the current study by Isaacs *et al.* would suggest that some of these effects might be due to insufficient nutritional support and that some of these effects can be reversed by higher nutritional support or by additional FA such as DHA. The caudate is known to be one of the brain regions expressing high DHA content and changes can be observed after dietary depletion and repletion (35). Experimentally it is known that DHA incorporates into the membrane bilayer, and increases the degree of flexibility and direct interaction with membrane proteins. This impacts on the speed of signal transduction and neurotransmission (36). Unesterified DHA acts as ligands for brain transcription factors retinoid X receptor alpha (RXR) and peroxisome proliferator-activated receptor (PPAR), which dimerize to regulate the expression of genes involved in the control of synaptic plasticity, cytoskeleton and membrane assembly, signal transduction and ion channel formation. This gene regulation function could explain the role of DHA in many aspects of development such as neurogenesis, morphologic differentiation of catecholaminergic neurons, and activity-dependent plasticity (36,37). DHA also seems to inhibit the oxidative stress-induced induction of pro-inflammatory genes and apoptosis, and provide protection against peroxidative damage of lipids and proteins in the developing brain (37,38). Leptin regulates human eating behavior by regulating striatal brain regions (39), but is also known to regulate neuronal excitability and cognitive function in particular by influencing positively the hippocampal-dependent learning and memory (40).

Another condition by which brain development can be affected in the long term is intrauterine growth restriction (IUGR) (41). Currently the IUGR rate is the highest it has been in over 20 y and is likely to rise further due to the increasing rate of infertility treatments, multiple pregnancies, older mothers, and exposure to IUGR-inducing agents such as tobacco. All these conditions lead to poor nutritional status of the fetus and subsequent alteration of structural and functional brain development with reduction in cortical gray matter volume, reduction in striatal volume, and reduction in hippocampal volume, predominantly in boys (42–45). Children with very low birth weights have multiple rather than isolated cognitive deficits including problems with attention, memory, reading and mathematics, as well as reasoning and self regulation (46,47). These cognitive deficits are likely to have an overriding central nervous impairment with underlying brain structural changes (48). Recently epidemiologic studies assessing maternal nutrition have lead to interesting observations by which maternal consumption of seafood during pregnancy lead to higher cognitive performance in their offspring, with again the most prominent effect on VIQ (49). Fatty acid metabolism is therefore an important component of both prenatal and postnatal brain development and the current study by Isaacs *et al.* illustrates how structural and functional changes in relation to nutritional interventions can be studied. Further studies should concentrate on the combined effect of genetic background (50) and nutritional interventions on both structural and functional brain development. Understanding the effects of early antenatal, perinatal, and neonatal events on later structural and functional brain development, aberrant or regenerative, will no doubt be essential to develop interventions and treatments for preventing developmental disabilities that have their origin in early life. Research with the aim of defining which nutrient favors adequate development of brain structure and functions during gestation and early childhood, with the ultimate goal of improving cognitive development and decreasing neuro-psychiatric disorders, will be an important task in terms of public health of the future.

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