Neuroimaging of the Developing Brain and Impact of Nutrition

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Abstract
The first 1,000 days of life are increasingly viewed as laying the essential foundations for lifelong physical and mental health. Extending this age range to include childhood, that is up to 10 years of age, these early-life periods encompass the peak period of brain growth, coincide with the emergence of nearly all fundamental cognitive and behavioral skills and abilities, and overlap with the earliest onset and symptoms of a wide breadth of developmental, intellectual, and psychiatric disorders. It is increasingly recognized that altered brain development throughout this sensitive period can negatively affect cognitive and behavioral outcomes. The development of safe and noninvasive neuroimaging techniques, such as magnetic resonance imaging, has provided important new insights into patterns of early structural and functional neurodevelopment, the relationships between brain growth and emerging brain function, and the influence of environmental, genetic, and nutritional factors on shaping these brain-function relationships. In particular, nutrition is a critical and readily modifiable influence that can profoundly impact early brain maturation. Here, we overview the current understanding of early-life nutrition and its effects on the developing brain as detailed through neuroimaging.

Introduction
Early infant and childhood neurodevelopment, beginning with the first 1,000 days of life and extending up to 10 years of age, is a period of rapid and sensitive structural and functional brain growth. Following the in utero development of core brain structures and the initial establishment of axonal connections and
neural networks, activity-dependent processes, including myelination, synaptogenesis, and synaptic pruning, work in “competitive collaboration” to further shape and refine brain connectivity. These processes help to give rise to the mature and efficient neural systems that underlie specific brain functions and specialization. These processes are driven by, and responsive to, a diverse array of environmental and genetic pressures. It is increasingly recognized that alterations in brain structure and connectivity throughout this early neurodevelopment period, due to genetic miscues, harmful pre- and/or postnatal environmental exposures (e.g., placental insufficiency or lead), and/or nutritional deficiencies, can result in negative long-term cognitive and/or behavioral outcomes [1, 2]. Depending on their timing, magnitude, and regional location, developmental miscues can yield a spectrum of neurobehavioral deficits, ranging from subtle impairment through to profound deficits. Given this importance and coupled with the evolution of advanced noninvasive brain imaging methodologies, an increasing number of studies are seeking to characterize the developing brain. Results from these studies are providing new insights into the normative patterns of development; the relationship(s) linking brain growth with cognitive and behavioral maturation; alterations in diseases or disorders; and the influence of the in utero and postnatal environments, particular genes, learning, nutrition, and other factors on shaping these brain-function relationships.

Of the numerous developmental changes associated with early brain maturation, 3 hallmark processes are myelination, dendritic arborization (synaptogenesis), and synapse pruning. Myelination, as well as the elaboration of the myelinated white matter, helps to facilitate rapid and coordinated brain communication, and is crucial for normative cognitive and behavioral functioning [3]. The lipid myelin sheath forms around the axon as a tightly compacted and stable bilayer consisting of radial protein-lipid-protein-lipid lamellae [4]. The primary role of the myelin sheath is to increase the conduction velocity along the axon, thereby facilitating rapid and coordinated brain messaging. Myelination begins in mid-to-late (∼20 weeks) gestation and advances rapidly over the first 2–3 years of life in a carefully coordinated caudal-cranial and posterior-to-anterior arc. This pattern of development follows emerging cognitive abilities and skills and is tightly regulated by neural activity [5]. In step with white matter myelination, the cortical myeloarchitecture also matures through this period and plays a critical role in neural plasticity and function [6]. While all white matter and cortical regions have begun to be myelinated by 1 year of age [7], the process continues throughout childhood, adolescence, and into the 2nd and 3rd decades of life [8].

Beginning before and then occurring alongside myelination, the rate of growth of new synaptic connections (synaptogenesis) begins in early (5th week)
gestation [9] and increases throughout pregnancy. This results in an excess of synaptic connections at birth that are pruned throughout childhood and adolescence in an activity-dependent manner. Connections that are repeatedly used are maintained and strengthened, while disused connections are eliminated. Cycles of synapse generation and pruning occur throughout the life span, with peaks in activity during infancy and at the transitions from child to adolescent and adolescent to adult. While the density of connections may vary throughout childhood and adolescence, the overall pattern of axonal connections remains relatively constant after 2 years of age [9].

While myelination, synaptogenesis, and synaptic pruning all contribute to changes in brain microstructure, architecture, and organization throughout the life span, they are at their rate peak during the first 3 years of life. Not surprisingly, this window of rapid growth is also a period of increased sensitivity and vulnerability [1, 2, 10, 11]. The prolonged nature of human neurodevelopment that helps ensure flexibility and plasticity within our neural systems also places these systems at prolonged risk to insult, injury, or deviant growth. Aberrant or incomplete myelination, as well as hypo- or hyperneurogenesis, disrupts neural connectivity and is a characteristic of nearly all behavioral, intellectual, psychiatric, and neurological disorders, ranging from autism spectrum disorders [12] to schizophrenia [13].

Of the numerous and varied factors that can influence these neurodevelopmental processes, perhaps one of the most readily modifiable is nutrition. Brain development is an inherently energetic and metabolically demanding process [14]. With respect to myelination, the development and maintenance of the lipid myelin sheath requires careful and coordinated delivery of key nutrients, including lipids and fatty acids, proteins, minerals, and micronutrients. These include, but are not limited to, long-chain polyunsaturated fatty acids (LC-PUFA), choline, iron, zinc, cholesterol, and phospholipids. Deficiencies in the magnitude or delivery timing of these nutrients can significantly and negatively impact myelin content, composition, and morphology. Beyond myelination, nutrition also plays an important role in cortical development and neurogenesis [15, 16] and other aspects of brain growth and maturation. These structural irregularities can, in turn, lead to disruptions in brain connectivity and function, and, ultimately, to altered cognitive and behavioral abilities.

In this review, we examine the role of early-life nutrition (within the first 5 years of life) on brain development through the lens of past and ongoing neuroimaging studies. We overview past studies that link nutrition with cognitive and behavioral skills and how these relationships may be mediated by brain development and function. Other reviews provide a more thorough analysis of potential mechanisms and pathways by which individual nutrients, or their combina-
tions, may affect cognitive outcomes [17–20]. The goal of this review is not to replicate these other extensive summaries but rather to focus on neuroimaging insights, highlighting existing research, and identify areas of opportunity in need of further study and exploration.

**Methods**

**Pediatric Neuroimaging**

Our understanding of early brain development dates back more than 150 years to the pioneering histological work of neuroanatomists (amongst many others) Paul Flechsig, Paul Yakovlev, Richard Sidman, Hannah Kinney, and Betty Ann Brody with respect to white matter maturation and myelination; and Korbinian Brodman, Cecile and Oskar Vogt, and Walter Campbell with respect to cytoarchitecture and cortical development. The introduction of noninvasive imaging techniques, such as electroencephalography (EEG), magnetoencephalography, X-ray, computed tomography (CT), and magnetic resonance imaging (MRI), have allowed a new generation of investigations into the patterns of brain growth and the emergence of functional and structural networks. By combining neuroimaging studies with cognitive and behavioral assessments, structure-function relationships can now be directly investigated within the same children. Longitudinal investigations have brought increasing clarity of the relationships between neural and cognitive development, and the influence of genetic and environmental factors on brain development. MRI, in particular, affords the ability to study a rich and diverse range of developmental changes, including emerging brain structure, function, architecture, connectivity, and chemistry.

While important, the use of MRI in pediatric populations is not without challenge. Even with advances in rapid or motion-insensitive acquisition techniques and acoustic damping, successful artifact-free MRI requires a child to remain motionless for a prolonged period of time in an often uncomfortable and loud environment. Without sedation, this is often too much for awake infants and young children (generally less than 4 years of age) or even older children from sensitive populations (e.g., children with autism spectrum disorders or other developmental disorders).

In a research setting where sedation is not usually permissible, the usual approach is to scan children whilst asleep, either during a daytime nap [21] or at night [22]. For infants up to ~1 year of age, the feed-swaddle-and-scan technique takes advantage of the usual postfeeding nap of most infants. For older toddlers and younger children, who nap less frequently and for shorter durations [23], scanning exclusively at night is often more successful. However, this requires a dedicated research team and an imaging facility designed with sleeping rooms to accommodate children [22, 24]. An example of such a facility is illustrated in Figure 1.

To help facilitate scanning during natural sleep, consideration must be given to peripheral nerve stimulation, energy deposition (SAR or specific absorption rate), and the level of acoustic noise. Both peripheral nerve stimulation and scanner noise are associated with gradient switching, and reducing the slew rate from typical values of 100–200 mT/m/s by 25–50% can effectively eliminate peripheral nerve stimulation and significantly reduce noise levels [22], though at the expense of lengthened scan times. This,
however, can be mitigated through parallel or reduced k-space (i.e., partial Fourier) acquisition techniques. Reducing gradient switching times can also help reduce time-averaged SAR levels, as can the reduction in acquisition flip angle, which can be a concern given the smaller size of an infant and their reduced ability to dissipate heat. In all cases, the use of pediatric ear protectors, such as MiniMuff protectors, together with pediatric headphones is advised both to protect the infant’s hearing and to minimize the chance of waking them up during scanning. Soundproof foam bore liners can also be used to minimize acoustic noise further.

Whilst data acquisition during sleep allows for collection of structural, spectroscopic, diffusion, and resting-state functional connectivity data, it does preclude acquisition of task-based functional imaging information. However, auditory stimuli [25] and, to a lesser extent, visual and motor stimuli can be presented to a sleeping infant.

For older children, acclimation in a 0-T or “mock” scanner, coupled with feedback and training, can help them remain still whilst awake for at least short periods, allowing scanning to be scheduled throughout the day. Children can also be trained for specific tasks and games, allowing more specific functional imaging paradigms to be investigated.

**Measures of Brain Development**

From MRI data, a number of quantitative and semiquantitative metrics can be obtained that inform on structure, function, and connectivity. These include measures of total and regional brain volumes, cortical morphometry (thickness, surface area, and curvature), tissue architecture and fiber coherence (diffusion anisotropy and diffusivity), microstructure and composition (myelin content), connectivity, functional activity and connectivity, and metabolite concentrations. Special care must be taken when performing this analysis using software packages developed for adult populations. For example, cortical analysis via FreeSurfer [26] is not intended for use in children under 2 years of age due to its use of brain atlases developed and validated in older adults that may not be representative of infants and toddlers. Further, the changing tissue contrast in infant im-

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**Fig. 1.** Examples of imaging facilities designed for pediatric imaging studies. Nursery rooms (a) are located adjacent to the scanner so that children can fall asleep and then be moved (b) into the scanner suite. The scanner is lined with noise-cancelling foam to help minimize noise (c). For older children, a rocket or castle theme (d) is used to help reduce anxiety for awake scanning.
ages often poses a challenge to image registration and segmentation tools that rely on tissue signal boundaries and gradients.

With the increasing interest in the developing brain, newer pediatric-specific atlases and analytic tools designed specifically for the low and changing tissue contrast characteristics of infant and toddler MRIs have begun to be developed and validated. For example, 3D and 4D atlases of the neonatal, infant, and toddler brain have been presented by previous studies [27, 28]. Accompanying these atlases, image alignment and segmentation methods have also been developed that utilize longitudinal data [27].

The Influence of Nutrition on Brain Structure and Function

While many nutrients play important roles in the developing brain, some, including iron, zinc, copper, choline, vitamins A, B and D, LC-PUFA, cholesterol, and lipids, play prominent roles in myelin synthesis, composition, and maintenance [29–33]. Many of these same nutrients, including zinc and folic acid, are important to neurogenesis and differentiation [34]. Beyond structural development, micronutrients, proteins, minerals, and lipids are also involved in functional brain processes, including neurotransmitter and hormone metabolism [20, 35, 36]. Unlike many of the known factors that shape brain development, such as specific genes, the prenatal in utero environment, or other environmental factors that are beyond easy control, nutrition may be readily modifiable. Thus, there is significant public interest in understanding how specific nutrients may be involved in optimal brain development.

Much of our knowledge regarding the role of nutrition on the developing human brain derives from epidemiological studies performed in sensitive populations, including malnourished children in developing or impoverished settings. These studies, therefore, predominately focus on the effect of nutrient deficiency and cognitive and physical outcomes, with the obvious caveat that confounding latent variables associated with these settings and populations may mask or amplify potential nutrient-driven deficits. Studies of nutrient supplementation also expand our knowledge, with these studies also typically performed in sensitive populations, such as preterm or low-birth-weight infants. A third theme of knowledge derives from a focus on cognitive differences and outcomes in children fed breast milk or formula milk. Supporting these human studies, however, is a large literature from small animal studies, in which individual nutrients and environmental conditions can be carefully regulated. While the outcomes from most human infant studies are indirect measures of brain structure (i.e., cognition, head circumference, or linear growth), histological analysis of animal brain specimens allows more direct investigation of brain structure and composition.

The earliest studies specifically exploring brain structure in relation to nutrition utilized EEG and evoked event-related potentials to measure processing. Changes in the magnitude, polarity, latency, and spatial location of EEG signals recorded before, during, and after stimuli (including auditory, visual, or somatosensory stimuli) can be used to explore neural systems and cognitive processing differences in infants and young children. More recently, functional near-infrared spectroscopy (fNIRS) can also be used to probe neural system development and changes in response to verbal, visual, or other stimuli. The relative mobility of EEG and fNIRS allows them to be used in lower-income or developing settings were other neuroimaging modalities may not be possible.

While EEG and fNIRS provide important functional information, they do not provide morphological or structural information related to neural regions, pathways, or systems. Further, since they are primarily sensitive to cortical signals, they provide little
information regarding deep brain or brain stem function. The primary advantage of MRI is its ability to measure both brain structure and function throughout the brain, with the signal sensitized to structural aspects (morphometry, microstructure, and fiber architecture), chemical species and metabolites (spectroscopy), function (blood oxygen and perfusion), and connectivity. As a result of this versatility, and despite limited mobility and poor temporal resolution, MRI has become the dominant method for investigating brain structure and growth, their relationship with evolving cognitive function, and the primary factors that influence these brain-cognitive relationships.

**Results**

**Structural and Functional Brain Development**

Relative to many other species, the human brain has a long postnatal developmental timeline, with many regions and systems not achieving maturity until the 2nd or 3rd decade of life [8, 37]. However, a significant degree of this development occurs over the first 5 years of life (Fig. 2, 3). Throughout early childhood, white matter volume increases more than 4-fold due to axonal changes and myelination [38]. Changes in white matter microstructure are associated with changing brain and cognitive function [3, 5, 39–41], and alterations are commonly associated with behavioral, neurological, and psychiatric disorders [42–47]. Beyond white matter volume, microstructural integrity, and myelin content, the relationship between myelin thickness (t) and axon diameter (d) is defined by the myelin g-ratio (d/d + t), a quantitative parameter that informs on the relative efficiency and conduction velocity of an axon. Significant g-ratio variation is observed along a single axon, between different brain regions, throughout development, and in association with psychopathology.

Changes in synaptic density and cortical myeloarchitecture also play important roles in defining and facilitating function [48]. The number and density of synapses changes dramatically through late gestation and early infancy [9] in association with developing brain function. In older children, changes in cortical thickness (a neuroimaging marker of synaptic density) have consistently been linked with differences in behavioral and cognitive performance; and differential trajectories of thickness changes are predictive of cognitive (IQ) outcomes [49]. While division of the cortex into structurally and functionally distinct regions has traditionally been based on cytoarchitecture [50], work by Campbell [51], Cecile and Oskar Vogt [52], and other early anatomists have demonstrated functionally specific divisions based on myeloarchitecture. Recent work has shown the importance of the cortical myeloarchitecture in developing brain function [6] and myeloarchitectural changes
(absent neuronal changes or axonal loss) in neurodegenerative disorders [53, 54].

With respect to network connectivity, resting-state functional and diffusion tractography data have shown a dynamically reorganizing brain, with developmental trends of reduced intrahemisphere and increasing interhemisphere connectivity with age (Fig. 4) [55–57]. Overall, the brain appears to move from a local to a distributed organizational structure, allowing it to incorporate and integrate multiple disparate streams of information as required for higher-order cognitive, emotional, and social processing and functioning.
Controlled animal models, where individual nutrients can be regulated, have provided the foundation for our understanding of how early nutrition impacts brain and cognitive growth, as well as the roles of specific nutrients. As a brief overview, rat pups weaned early and without fatty acid (docosahexaenoic acid, DHA) supplementation, for example, show reduced myelination in frontal and hippocampal areas [58]. Iron deficiency before and after weaning significantly alters oligodendrocyte functioning, reducing myelin production [59] as well as its structure and morphology [60]. Importantly, these changes are not corrected even with supplementation. Rat pups fed L-cycloserine, which reduces sphingolipid synthesis, show significant alterations in myelin morphology (specifically content and thickness) that is partially reversed by sphingomyelin supplementation [61]. Other nutrient deficiencies, including vitamins A, B₆, B₁₂, and C, and micronutrients, including copper and zinc, have also been associated with hypomyelination or aberrant myelin morphology [17, 62, 63]. With respect to neurogenesis, reducing the amount of folate, choline, and vitamin B₁₂ in nursing rat pups resulted in decreased neuronal density throughout the brain and, specifically, the hippocampus, cerebellum, and striatum. Early postnatal protein deprivation can also lead to reduced synaptogenesis as well as changes in synapse structure [64, 65]; and ω-3 (DHA) deficiency can delay critical synaptic pruning in the visual system [66]. Finally, micronutrient deficiencies, such as in iodine and zinc, affect synaptic density and synapse function, and reduce myelination [34, 67–69].

**Fig. 3.** Multi-MRI contrast visualization of neurodevelopment from birth to 5 years of age. Rows correspond to (from top to bottom) myelin water fraction (MWF); quantitative T₁ relaxation (qT₁); quantitative T₂ relaxation (qT₂); diffusion fractional anisotropy (FA); and qualitative T₁-weighted imaging (T₁w).
Beyond specific changes in myelination, neuronal density, and synaptogenesis, animal studies have shown corresponding changes in behavior and cognitive outcomes associated with malnutrition and nutritional deficiencies. For example, vitamin B deficiency has been associated with deficits in exploratory behaviors and learning as well as memory capabilities in nursing rats. Iron deficiency has been associated with long-term impairments in motor development, visual acuity, and attention, memory, and executive functioning [70–74]. Inadequate intake of essential fatty acids, including DHA, is associated with impaired learning [75] and long-term cognitive decline [76, 77].

**Fig. 4.** Overview of changing functional connectivity with age from 1 to 5 years of age (a), with decreasing short-range and intrahemisphere connections, and increasing longer-range and interhemisphere connectivity. Functional connections with significant associations, corrected for age, with cognitive scores for visual reception and fine motor function (b). All statistical associations were corrected for multiple comparisons (FWE) using a cluster based technique.
Studies in human infants suggest many of these same cognitive and behavioral deficits are present and, thus, may be related to similar brain changes. Here, we overview neurodevelopmental deficits in humans associated with some of the more common nutritional deficiencies that have been studied using both cognitive measures and neuroimaging.

Human Milk and Long-Chain Polyunsaturated Fatty Acids

Human milk provides not only the rich complement of nutrients, hormones, and bioactive factors necessary to support healthy infant growth, but does so in an evolving and dynamic fashion that meets the infant’s changing health and nutritional needs. Within human milk, the amounts of LC-PUFA and, in particular, DHA and ARA have been associated with physical growth and brain development in infants. DHA and ARA are by far the most abundant LC-PUFA in the human brain, making up approximately 20% of the brain’s total lipid content. Throughout the last trimester of pregnancy and up to 2 years of age, DHA is rapidly accumulated within the brain, coinciding with both physical growth (i.e., brain volume and weight) \[78, 79\] and myelination \[80\]. In particular, DHA appears to preferentially accumulate within the frontal and prefrontal cortices, brain regions involved in executive functions, including attention, planning, emotion, and problem solving \[81\]. Unfortunately, as de novo synthesis of DHA and other LC-PUFA is limited in infants \[82\], these fatty acids must be obtained from dietary sources \[83\].

The general consensus across observational studies that have examined the influence of fatty acid intake on cognitive development \[84\] is that LC-PUFA are important to overall cognitive maturation, including general cognitive performance (IQ), executive functioning, motor control, language development, and visual acuity. With respect to DHA alone, the most noted developmental outcome is improved visual acuity and function \[77\].

As levels of DHA, ARA, and other LC-PUFA vary significantly between human milk and infant formula, it has been hypothesized that these fatty acids may be responsible for the cognitive differences generally seen between breastfed and formula-fed children \[85\]. Though DHA blood levels have consistently been found to be lower in formula-fed than breast-fed children \[82\], differences in brain DHA concentrations are small \[86\], and clinical trials comparing formulas with DHA to those without DHA supplementation do not provide, on average, convincing evidence that DHA supplementation benefits term-born children \[87\]. The notable exception to this, however, are preterm and low-birth-weight infants, who do show improved long-term motor development and cognitive outcomes with DHA-supplemented formulas, on a par with breastfed infants \[88–90\].
Though not specific to DHA, ARA, or other LC-PUFA, neuroimaging (both EEG and MRI) has been used to investigate potential neuroanatomical differences associated with human versus formula milk. From EEG studies, formula-fed infants (without DHA) have increased response latencies to auditory and visual stimuli, and slower changes in these measures with age [91–93]. Infants receiving DHA-supplemented formula, however, had similar response times as exclusively breastfed infants [94, 95]. More recent studies of gray and white matter using MRI [96–98] have revealed differences in white matter volume, subcortical gray matter volume, parietal lobe cortical thickness, and rate of myelination between formula- and breast-fed infants (Fig. 5). Without controlled studies of DHA intake, however, it is not possible to ascribe observed brain differences to milk LC-PUFA content versus other nutrients that differ between breast milk and formula, including choline, specific glycoproteins, cholesterol, or latent environmental conditions (e.g., maternal-child interaction).

Iron and Zinc
Iron is one of the most thoroughly studied nutrients, as well as one of the common nutritional deficiencies in developed and developing countries. Within the developing brain, iron facilitates the development and normative functioning of the monoaminergic neurotransmitter systems, and it helps to maintain neuronal energy metabolism [59, 60, 99]. In human children, antenatal and/or infant iron deficiency has been further associated with neurocognitive and behavioral deficits, specifically impaired motor development [70, 71], reduced cognitive performance [100], worsened memory performance [72], attention problems [74], and decreased language [101], visual acuity [60], and executive functioning [73]. Perhaps more troubling, these effects have been found to persist into later child- and adulthood even when infants are adequately treated with iron supplementation [72, 102].
Though few neuroimaging studies have been performed to examine the neuroanatomical correlates of early iron deficiency, electrophysiology (EEG) studies have revealed altered cognitive processing associated with attention and memory recognition tasks [103]. More recently, pre- and postnatal iron deficiency has been associated with right frontal EEG asymmetry [104]. More broadly, measurements of auditory brain stem responses and central conduction times provide objective measures of central nervous system development and myelination. Iron-deficient infants show increased auditory brain stem response latency and longer central conduction times, suggesting decreased myelination throughout the central nervous system [105], which may be related to abnormalities in iron homeostasis, availability, storage, and transport [106].

Like iron, zinc deficiency is similarly widespread, potentially affecting up to 40% of the world’s population [34, 107, 108]. Biophysically, zinc helps to maintain the binding of myelin basic protein to the surface of the myelin sheath, thereby playing an important role in the maintenance of myelin sheath integrity. Within the brain, the highest concentrations of zinc are found in the hippocampus, a critical structure for memory and learning [109]. Zinc deficiency has been associated with neurological and psychiatric disorders, with prolonged deficiency leading to symptoms such as emotional instability, irritability, and depression [107], and it has been implicated in disorders such as the attention-deficit hyperactivity disorder [110].

Within children, there have been no neuroimaging studies that have directly investigated the impact of zinc deficiency on brain function or development. However, zinc supplementation in schizophrenic patients resulted in a shift in EEG measures towards normal [111].

Choline, Phospholipids, and Sphingolipids
Phospholipids and sphingolipids comprise more than 35% of the lipid weight of myelin [112] and play critical roles in maintaining the structure and function of the myelin sheath [31]. The effect of dietary sphingomyelin on neurodevelopment has been observed in low-birth-weight infants [113], in whom a sphingomyelin-fortified infant formula (20 vs. 13% total milk phospholipids) resulted in improved performance on the Bayley Scales of Infant Development (BSID-III) and other measures of cognitive performance and processing speed at 18 months of age.

Within the myelin structure, phospholipids are in relatively fast exchange with other subcellular membrane lipids [114]. As a class of phospholipids, phosphatidylcholine is a major and important component of biological membranes, including myelin. As choline is a necessary precursor for phosphatidylcholine, choline deficiency can significantly reduce phosphatidylcholine concentration.
Following a 3-week choline-deficient diet, a 30% reduction in free circulating phosphatidylcholine levels was observed and reduced processing speed was noted [115]. Cytidine-5′-diphospho-choline supplementation has been shown to promote oligodendrocyte activity, influencing myelination and remyelination [116, 117]. Evidence for altered neurodevelopment in response to choline deficiency stems principally from animal studies, which consistently suggest the influence of antenatal choline on fetal hippocampal development [118], with associated lifelong enhancements in visuospatial and auditory memory [119, 120]. However, it remains unclear if similar enhancements occur in humans [121].

Beyond its roles in cell membranes and gray matter development, choline, acting in concert with folate, is necessary for normal neural tube closure. In a retrospective case-control study of periconceptional dietary choline intake, children born to women in the lowest quartile for daily choline intake had a 4-fold increased risk of neural tube defects compared with those born to women in the highest quartile [122].

**Conclusions**

While neuroimaging methods, including EEG, fNIRS, and MRI, provide direct information related to brain function, structure, and chemistry, their application to the study of nutrition effects and nutrient deficiency remains in its infancy. Hence, despite well-established findings of altered cognitive outcomes associated with deficiencies in vitamins B₉, B₁₂, D, and K, as well as other minerals, proteins, and micronutrients [19, 36, 123–126], direct evidence for altered infant brain structure and/or function from neuroimaging is lacking. However, a primary limitation of current imaging technology is that it does not directly inform on the molecular mechanisms and pathways by which specific nutrients may influence brain structure and function. This, unfortunately, remains the domain of invasive and destructive histological and histochemical analyses.

Perhaps one of the primary advantages of neuroimaging is that it provides information that can be related to cognitive outcomes that is culturally and language ‘agnostic.’ That is, unlike traditional cognitive and behavioral assessment tools, which need to be translated and renormed for different populations and languages [127], EEG, NIRS, and MRI provide objective measures independent of the cultural context. For example, fNIRS data acquired in Gambian infants show similar patterns of activation as seen in UK children in response to social cues [128], despite obvious differences in environment and demographic upbringing. EEG is seeing similar increased use to investigate brain maturation in response to malnutrition in developing and rural areas [128]. The relative ex-
Pense and immobility of MRI may limit its application in rural areas; however, it remains an indispensable tool in more developed and clinical settings.

The ability for neuroimaging to provide objective and consistent longitudinal measures of both prenatal fetal and postnatal infant and child neurodevelopment ideally lend it to studies of malnutrition and nutritional supplementation before and following pregnancy. Such information will be critical for understanding the relative importance of different nutrients and combinations, as well as maternal health and fetal programming on long-term child health and cognitive outcomes.

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