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Young Brain Big Appetite

Brain Fuel Utilization in the Developing Brain

Nutritional Factors in Fetal and Infant Brain Development

Critical and Sensitive Periods in Development and Nutrition

Sleep and Early Brain Development

Editor: Weili Lin

Karger

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Young Brain – Big Appetite

Editor

Weili Lin, Chapel Hill, NC

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Policy Statement

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Editorial

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Young Brain – Big Appetite

Weili Lin

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The first few years of life represent one of the most dynamic and critical time periods in brain development. The total brain volume of a 2-week-old is roughly 35% of the adult brain volume, and it increases by ~101% and 15% during the first and second year of life, respectively. By the age of 2 years, brain volume reaches about 80% of the adult brain volume. In addition to the rapid increase in brain size, critical brain functions also emerge during the first years of life and continue to mature into adulthood. Underlying these morphological changes and functional development are complex cellular and molecular processes, which require an extraordinarily high demand for energy (food) to ensure adequate maturation of our brains during early infancy. Although the "young brain" is relatively small when compared to the entire body, it has a "big appetite" for energy (food) to support these cellular and physiological processes underpinning the rapid increase in brain size and the emergence of brain functions. Specifically, an infant brain consumes about 60–75% of the total daily intake of calories, which is in marked contrast to an adult brain consuming roughly 20–25% of the total energy intake. Therefore, it is not surprising that malnutrition during pregnancy as well as in early postnatal life could lead to a cascade of negative impacts on the long-term health of our brains.

Dr. Steiner's chapter offers insights into the underlying cellular and physiological processes of brain structural and functional development. The critical metabolic pathways to meet the energy demands for supporting these important developments are introduced. In particular, in order to meet the extraordinarily high energy demands to support early brain development, glucose and ketone bodies work synergistically to support not only the energetic, but also anabolic demands and provide the carbon backbones used to synthesize lipids, nucleic acid, and cholesterol, which are indispensable building blocks of neuronal cell proliferation during early brain development.

Following Dr. Steiner's chapter, Dr. Cheatham's chapter describes how different nutrients, providing energy to the brain, may play different roles during preconception, pregnancy, and after birth. Reviewing the effects of different nutrients at different stages is clearly important since cellular processes of early brain development vary throughout pregnancy and postnatal life. Thus, important nutrients are likely to vary depending on the stage of brain development. The importance of 6 nutrients that have been studied extensively with respect to maternal nutrition and subsequent offspring brain development, namely folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA; 22:6n-3), are comprehensively discussed. More importantly, the timing, doses, and duration of different nutrients along with the sequelae of nutrient deficiencies on brain development are provided. For example, vitamin D deficiency during pregnancy could potentially lead to morphological differences in brain size. Children

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of mothers who were diagnosed with anemia in the first 30 weeks of pregnancy exhibited a higher incidence of autism spectrum disorder, attention deficit hyperactivity disorder, and intellectual disability relative to children of mothers who were diagnosed later in pregnancy, or not diagnosed. Postnatally, iron deficiency at 9 months of age has been related to concurrent delays in memory and attention development. Together, it should be noted that the effects of nutrients on brain development depend on timing, dose, and duration.

In addition to the "big" appetite for energy/food to support early brain development, a young brain also exhibits a craving for learning. Learning through interacting with the external environment is one of the keys to ensuring proper maturation of cognition. Similar to the importance of tailoring nutrients at different stages of early brain development, brain functional development is also age dependent, with the basic brain functions maturing earlier, while higher-order brain functions follow a protracted developmental process. The chapter by Colombo et al. links the notion of fetal/neonatal programming – a common concept within the nutrition field – to the notion of "critical period" of brain development, a topic that has been extensively studied in biobehavioral and developmental sciences. Specifically, the history of and criteria for critical periods are first provided with important distinctions between "critical" and "sensitive" periods. Subsequently, the links between the fetal/neonatal programming within the framework of critical periods and developmental science are discussed. Finally, building on the understanding of the critical/sensitive periods, the implications of these time periods for the design of future preclinical research and clinical trials are offered.

An infant spends most of the time sleeping during early infancy; that is, a "young brain" has a "big appetite" for sleep. Therefore, it is not surprising that the quality of sleep can greatly impact the development of the young brain. Dr. Jiang's chapter first reviews the architectural organization of sleep, including non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and wakefulness. The transition from early infancy to a more adult-like sleep pattern is also discussed. In particular, early childhood could be an important time period to establish a healthy sleep rhythm. Interestingly, through a systematical review of 102 studies with 167,886 children aged 0–3 years from 26 different countries across the world, Dr. Jiang's team revealed an apparent cross-cultural disparity in the sleep parameters in early childhood. More importantly, it appears that parental sleep-setting behaviors may be one of the main contributors to the observed cultural disparity of the sleep parameters, underscoring the potential parental influence on establishing a healthy sleep pattern for children. The potential links between sleep and cognition are extensively reviewed by Dr. Jiang. It has been widely implicated that sleep plays a critical role in memory functions of the adult brain. In contrast, current evidence on the links between memory functions and sleep in infants is inconclusive and warrants additional studies. Furthermore, sleep appears to also play a key role in mental health, psychosocial adjustment, general cognitive development, and language development. Imaging studies further elucidate the potential interplay between sleep and brain structures, although more studies are needed to further determine the neural substrates underpinning the observed relations.

In summary, the first years of life, undoubtedly, are an important time period of brain development. While the "young brain" is relatively small when compared to the entire body, it has a "big appetite" for food, learning, and sleep. The chapters included in this volume provide some insights into the complex cellular processes and the neural substrates underpinning the highly dynamic processes of early brain development. Nevertheless, we have only seen the tip of the iceberg of these complex processes and their implications for how one could potentially enrich the development of a healthy brain. Future studies integrating noninvasive imaging methods, such as magnetic resonance imaging, during early infancy could further shed new light on how these complex factors work synergistically to improve the total health of our brain.

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Focus

The ability of humans to perform complex mental activities, including thinking, reasoning, remembering, problem-solving, decision-making, and learning new information, depends on the ability of the brain to adapt to its environment and alter its functional and structural organization

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Brain Fuel Utilization in the Developing Brain

Pascal Steiner

Key Insight

In humans, the brain is the single organ with the most protracted development and maturation time and the highest energetic needs. Glucose is the primary metabolic substrate used by the brain. During early brain development and maturation, however, the energetic demands exceed the availability of blood glucose. This energetic challenge is solved in part through the mobilization of ketone bodies (KBs) as fuel. Glucose and KBs are not only the main sources of energy, but are also used for the biosynthesis of macromolecules essential for neuronal cell proliferation, synapse formation, and myelination. Thus, besides meeting energy demands, glucose and other fuel substrates, including KBs, may play a broader role in brain development.

Current knowledge

Brain development is characterized by a period of rapid growth beginning in utero up to 3 years of age, followed by a slower pace of reorganization and development that continue up to the third decade of life. During the latter period, the growth rate slows, and the maturing brain undergoes significant reorganization, dominated by synaptic pruning and myelination. While the adult human brain requires up to 20–25% of total energy provided by basal metabolism, the energy demands of the newborn human brain are around 50% of the body's daily energy consumption. Not surprisingly, the brain energy requirement mirrors its development and maturation, with peak energy demands reached during the first 3 postnatal years when the rates of synapse formation and myelination are at their highest.

Stage	Brain energy requirements (% of total daily energy)
Newborn	60%
10 years	50%
Adult	20–25%

Comparison of the brain energy requirements of newborns, children, and adults.

Practical implications

Under normal conditions, glucose is used for generation of energy from glycolysis or oxidative phosphorylation. In the newborn, glycolysis seems to be particularly important to support the generation of macromolecules involved in brain structural changes. Moreover, ketones (i.e., β-hydroxybutyrate and acetoacetate) are derived from oxidation of body fat by the liver. In addition to serving as an extra fuel substrate, ketones may also play a role in the synthesis of macromolecules, such as cholesterol and fatty acids (which represent around 50% of brain gray matter). Ketones can also act as signaling and epigenetic mediators that regulate brain plasticity and reorganization. The nutrients required to support brain development are found in complex food matrices, such as breast milk. Understanding how these nutrients interact to affect brain metabolism is a key to defining the nutritional requirements for supporting optimal brain development

Recommended reading

Goyal MS, Iannotti LL, Raichle ME. Brain Nutrition: A Life Span Approach. Annu Rev Nutr. 2018 Aug;38(1):381–99.

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Brain Fuel Utilization in the Developing Brain

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Key Messages

- The brain consumes up to 60% of the total energy available to the body during development.
- While glucose is the main source of energy for the brain in adults, ketone bodies are essential to complement glucose to fulfill the metabolic and energy needs of the brain during its development.
- During brain development, glucose and ketone bodies are not only the main sources of energy but are also utilized for the biosynthesis of macromolecules indispensable for neuronal cell proliferation, synapse formation, and myelination.

Keywords

Brain development · Brain metabolism · Neurogenesis · Synapse · Myelin · Glucose · Ketone bodies · Aerobic glycolysis · Oxidative phosphorylation · Metabolism · Energetic and anabolic needs

Abstract

During pregnancy and infancy, the human brain is growing extremely fast; the brain volume increases significantly, reaching 36, 72, and 83% of the volume of adults at 2–4 weeks, 1 year, and 2 years of age, respectively, which is essential to establish the neuronal networks and capacity for the development of cognitive, motor, social, and emotional skills that will be continually refined throughout childhood and adulthood. Such dramatic changes in brain structure and function are associated with very large energetic demands exceeding by far those of other organs of the body. It has been estimated that during childhood the brain may account for up to 60% of the body basal energetic requirements. While the main source of energy for the adult brain is glucose, it appears that it is not sufficient to sustain the dramatic metabolic demands of the brain during its development. Recently, it has been proposed that this energetic challenge is solved by the ability of the brain to use ketone bodies (KBs), produced from fatty acid oxidation, as a complement source of energy. Here, we first describe the main cellular and physiological processes that drive brain development along time and how different brain metabolic pathways are engaged to support them. It has been assumed that the majority of energetic substrates are used to support neuronal activity and signal transmission. We discuss how glucose and KBs are metabolized to provide the carbon backbones used to synthesize lipids, nucleic acid, and cholesterol, which are indispensable building blocks of neuronal cell proliferation and are also used to establish and refine brain connectivity through synapse formation/elimination and myelination. We conclude that glucose and KBs are not only important to support the energy needs of the brain under development, but

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they are also essential substrates for the biosynthesis of macromolecules underlying structural brain growth and reorganization. We emphasize that glucose and fatty acids supporting the production of KBs are provided in complex food matrices, such as breast milk, and understanding how their availability impacts the brain will be key to promote adequate nutrition to support brain metabolism and, therefore, optimal brain development.

Introduction

The ability of humans to perform complex mental activities, including thinking, reasoning, remembering, problem-solving, decision-making, and learning new information, depends on the ability of the brain to adapt to its environment and alter its functional and structural organization [1–4]. This is often referred to as brain, neuron, or synapse plasticity [5]. Moreover, the brain organization is incredibly complex: it is estimated that the human brain contains more than 200 billion neurons and non-neuron cells, 1 quadrillion of connections, 100 km of nerve fibers, and 600 km of blood vessels [6, 7]. In order to maintain such dynamic abilities and sustain the functioning of this complex architecture, outstanding energy supply is required. Indeed, the adult brain, accounting for a mere 2% of body weight, is estimated to be responsible for 20% of oxygen (O_2) consumption and 20–25% of glucose utilization [8, 9]. In comparison, adult vertebrate brains, with the exception of primates, use 2–8% of total energy at resting state [10]. While adult brain energy demands are astonishing, the energy requisite during early life is even higher and essential to support the rapid development of the brain with a growth burst starting around the 5th gestational month and continuing postnatally, increasing the brain's weight from ~27% of its adult weight at birth to ~80% by age 2 years [11, 12]. In addition to its enormous demand of energy, the dramatic brain size expansion that happens during the first years of life requires specific nutrients, such as lipids, proteins, and micronutrients, which are not only the building blocks of brain structures but also support brain and cognitive functions during the rest of the lifespan [3, 13, 14].

In normal conditions, the main source of energy for the brain is glucose that is utilized for the generation of energy in the form of adenosine triphosphate (ATP) from either glycolysis or oxidative phosphorylation, the latter being 15 times more efficient to generate energy [15–17]. Nevertheless, the particularly high energy needs of the developing human brain seem not to be supported by the sole consumption of glucose. Indeed, it has recently been suggested that ketones (β-hydroxybutyrate, acetoacetate, and acetone) derived from the oxidation of newborn body fat by the liver, may provide an important additional fuel substrate for the developing brain through oxidative phosphorylation as well [2, 17].

The adult brain, accounting for a mere 2% of body weight, is estimated to be responsible for 20% of oxygen (O_2) consumption and 20–25% of glucose utilization

While glucose and ketones have been traditionally considered for their canonical role in mammalian energy metabolism, recent studies showed that they play additional roles associated with brain structure development and function [12, 17–20]. For example, in an adult brain, 10–12% of glucose is metabolized through glycolysis to produce lactate, despite oxygen being available for oxidative phosphorylation, a phenomenon called "aerobic" glycolysis or the "Warburg effect" [21]. Aerobic glycolysis remains a prevalent metabolic pathway in the brain all along the lifespan and especially during brain development. It is especially crucial for the biosynthesis of cell constituents (e.g., lipids) that support key developmental processes, including synapse formation/elimination and myelination [19, 22]. On the other hand, ketones seem to be the substrate for the synthesis of certain macromolecules, such as cholesterol and fatty acids, which represent around 50% of the gray matter of the brain [17]. Recent observations also underline the importance of ketones as key signaling and epigenetic mediators, suggesting that they may influence gene expression involved in brain plasticity and reorganization during brain development [23–25]. Therefore, glucose and other fuel substrates including ketone bodies (KBs) may be used for other purposes than to fulfill the energy demands only and may play a broader role during brain development.

In this chapter, we first describe the key physiological processes underlying brain development and how brain metabolism may be necessary to support them. We will especially focus on describing how glucose and KBs support not only the energetic but also anabolic demands of the brain during development. Of course, the brain relies on many other nutrients for its proper development, function, and mainte-

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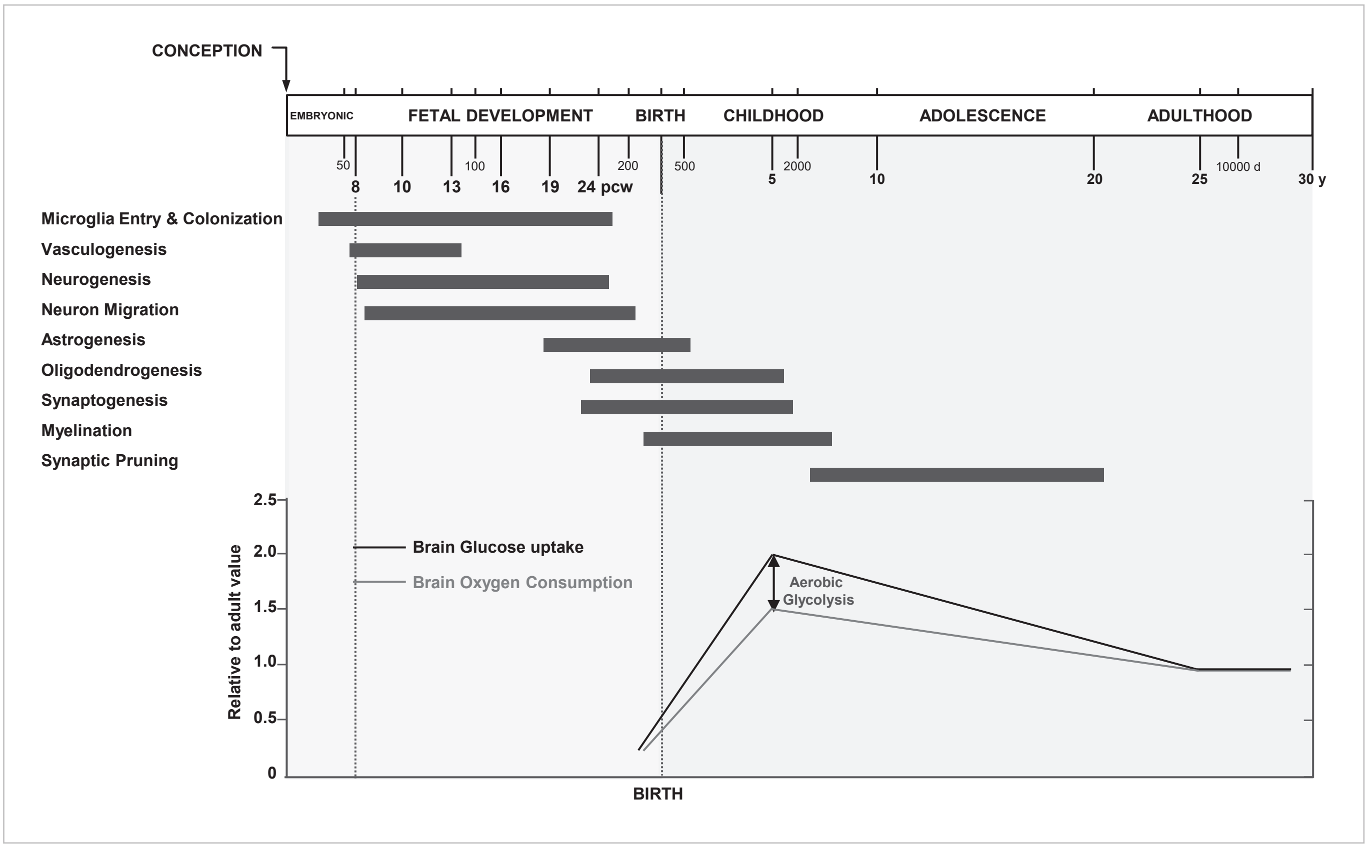

Fig. 1. Timelines of neurodevelopment processes and glucose metabolism changes from conception to adulthood. The figure represents the key neurodevelopmental processes that are occurring during brain development and the changes in glucose metabolism associated with them. The top of the figure represents the major periods of human development expressed in days (d), postconceptional weeks (pcw), and years (y). The bars associated with each neurodevelopmental cellular process represent the approximative peak of the developmental period for each of them. The bottom of the figure represents the changes in glucose uptake (black line) and oxygen consumption (gray line) along time that peak around postnatal day 5. The glucose uptake is higher than the oxygen consumption, suggesting that a significant amount of glucose is metabolized via aerobic glycolysis (arrow) and parallels the rise in synapse formation and myelination. The figure has been adapted from [3, 12, 43].

nance, which will be discussed by a subsequent chapter in this volume and has been previously discussed in excellent reviews [3, 13, 17, 26].

Main Physiological and Cellular Processes Underpinning Brain Development

The brain is one of the organs of the human body to develop the earliest, starting in utero during the 3rd gestational week, and it completes its development during the second and third decades of life, therefore being the organ with the longest development and maturation time [7, 22]. Once the primary organization of the brain is achieved, consisting of defining its main different regions during the embryonic period, key cellular processes emerge and proceed in developmentally overlapping waves (Fig. 1). The generation of neurons (neurogenesis) and their migration are initiated during the 8th gestational week, and the repertoire of neurons found in the adult neocortex is largely established before birth. Glia cell proliferation that follows neurogenesis peaks around birth, and it includes the generation of oligodendrocytes, supporting myelination and astrocytes, which have been shown to be involved in many physiological processes in the brain, especially in the modulation of information processing, synaptic transmission, and energy dynamics [27–29]. While regional variation exists, proliferation, migration, and differentiation of oligodendrocytes and astrocytes continue throughout the first 3 postnatal years, which coincides with the peak of synapse formation and neural network reorganization [7]. This

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reinforces the idea that oligodendrocytes and astrocytes play a crucial role in brain connectivity development and maturation all along childhood and adolescence.

While astrocytes and oligodendrocytes are generated and differentiated from neural progenitor cells, microglia, which are the resident macrophages of the brain involved in innate immunity, neuroprotection, synaptic pruning, and phagocytosis of cellular debris, originate from macrophages present in the yolk sac and migrate and colonize the brain during gestational week 4.5 [30, 31]. Interestingly, while neural progenitors are actively dividing and generate the first neurons early during embryogenesis, astrocytes and oligodendrocytes will appear only at late embryonic time points, as mentioned earlier. Consequently, early microglia colonization not only precedes the peak of neurogenesis and neuronal migration but constitutes the main glial population during a large part of fetal life, suggesting that microglia are involved in early brain development. Indeed, recent studies demonstrate that microglia contribute to the regulation of neuronal numbers and migrations and actively contribute to activity-dependent synaptic reorganization during neural network establishment [32].

Development of neuron arborization consisting of axon and dendrite outgrowth followed by synapse formation is the key cellular process associated with the functional maturation of the brain after neuron migration. Indeed, from mid-gestation until the third postnatal year, immature neurons are initiating a protracted period of axon outgrowth and dendrite arborization, accompanied by the formation of synaptic junctions that ensure connectivity between neurons and lead to the formation of neuronal networks [33, 34]. Importantly, an overproduction of synapses will take place during the first 2 postnatal years with a burst of synapse growth between 3 and 15 months, depending on the brain areas, followed by a discrete period of synaptic pruning that typically starts during childhood and persists towards adolescence [35–37], although the visual area has been reported to undergo pruning as early as 3 months of age.

While neuronal networks are being built, oligodendrocytes-generated myelin sheets are wrapped around axons, which act as insulators and lead to a dramatic increase in axonal conduction velocity and, therefore, information transmission [29]. Myelination starts during mid-gestation in the human brain, is a long process that dramatically accelerates during the first 2 postnatal years, and reaches its full maturity during the second to third decade of life [29, 38]. It also plays a key role in the maturation of brain networks, coordinated information processing, and ultimately cognitive performance in infants, children, and adults.

The high energy requirement of the brain is fulfilled by a constant transport of nutrients into the brain through the blood-brain barrier (BBB). The BBB tightly controls the passage of selected substances in and out of the brain, provides protection against external potentially toxic agents, and is critical to maintain brain homeostasis and, thus, proper brain function [39, 40]. The BBB includes 3 major cellular components: endothelial cells constituting the wall of blood vessels, pericytes that stabilize the BBB and are critical to maintain its integrity, and astrocytes that extend cellular processes whose endfeet ensheath the blood vessels and play a vital role in the transport of nutrients into neuronal cells [39]. The development and differentiation of the BBB is supposed to start in the very young embryo [41, 42]. Formation of blood vessels by endothelial cells is quickly accompanied by the recruitment of pericytes and astrocytes that will "seal" the BBB in order to isolate the brain from the external environment and control transport of substances. At the time of birth, the pattern of brain vasculature is very similar to what it will become in the adult brain [40].

The high energy requirement of the brain is fulfilled by a constant transport of nutrients into the brain through the blood-brain barrier

Recently, significant efforts have been made to understand how genes orchestrate the physiological and cellular processes described above. Gene expression analysis revealed that the brain transcriptome is segregated in clusters that are spatially and temporally organized and parallel the structural and functional developmental aspects of the brain. For example, clusters of genes associated with neuronal fate specification are mainly expressed embryonically and early fetally, while genetic clusters controlling synapse formation and function are highly expressed during early childhood [7]. Interestingly, it has also been shown that gene expression associated with mitochondria closely follows synapse density, suggesting that the proper development and maturation of brain connectivity is highly linked to energy availability [12, 43].

In summary, the human brain undergoes a rapid growth from the 4th gestational week to the 3rd postnatal year. Subsequently, the rate of growth slows down and the brain

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is subjected to a significant reorganization, which is dominated by synaptic pruning and myelination that extends throughout the third decade of life. It is important to keep in mind that brain development is not structurally and functionally homogeneous with age. Indeed, associative regions of the neocortex and especially prefrontal cortex are slower to mature than motor and sensory cortices, for example. Therefore, while being less important than during the prenatal or early postnatal periods, brain growth and especially brain reorganization at cellular and molecular levels continue beyond childhood to early adulthood. Refinement of neuronal networks is indeed thought to be critical for the functional specification of brain regions and crucial for the development of higher cognitive functions and behavior.

Energetic and Anabolic Demands during Human Brain Development

As briefly mentioned earlier, energy demands for vertebrate species correspond to 2–8% of the total energy provided by basal metabolism, while the human adult brain requires as much as 20–25% of it [10]. The energy demand during brain development is even more striking; it has been estimated that the newborn human brain, which represents about 13% of lean body weight, is consuming around 60% of the body's daily requirement [12, 15, 17, 19, 20, 44]. This dramatic energetic demand persists and is even increased during childhood; while a child brain at age 10 years accounts for 5–10% of the body mass, it approximately consumes 50% of the total basal metabolic rate of the human body [3, 12].

Why are the energetic costs associated with brain function so high in humans and especially during brain development? In order to understand this, it is first necessary to identify the brain components and processes that cost energy. From an evolutionary point of view, a comparison of glucose and oxygen metabolic rates of the adult brain in awake mammals (rodents, macaque, baboon) suggests that the total metabolic cost is a simple linear function of the number of neurons present in the brain [45]. This is in agreement with a recent approximation of neural cellular energy demands which estimates that neurons consume 75–80% of the energy produced, whereas the rest is used for glia-based processes [15, 46, 47]. Two main reasons may explain why neurons have high energetic demands: first, the generation of action potentials along the axons and synaptic transmission from neuron to neuron are based on electrochemical and cellular processes, such as ion fluxes, neurotransmitter release and reuptake, and vesicle cycling, which are energetically costly [15, 44, 46]. A signaling mechanism at the synapse has been suggested to be especially energy consuming; for example, it has been estimated that 80% of the energy in myelinated hippocampal axons is expended by postsynaptic potentials [48]. Second, the ability of the brain to change and adapt continuously along the lifespan is due to the constant remodeling of its architecture that culminates by the addition or the elimination of synapses to strengthen or weaken neuronal network activities accordingly. Constant synthesis of proteins, lipids, and amino acids is necessary to support the molecular modifications that underlie brain plasticity, which contributes to increasing brain energy expenditure [19, 46, 49, 50]. Rapid turnover of proteins and lipids is crucial to support dendritic spines and synapse modification, which are essential for learning and memory processes [51]. Nevertheless, it has been widely recognized that the majority of the energy in the adult brain is used to maintain its physiological baseline activity, including neuron and synaptic resting membrane potential, while changes in brain activity required to sustain specific cognitive tasks linked to synaptic plasticity result in an increase of energy demands by only 5% [18, 46, 52]. Importantly, brain development has significant additional energetic needs that are essential to support the constant and sustained synthesis of the molecular building blocks (proteins, lipids, and nucleic acids) underlying the rapid development and maturation of neuronal networks. In particular, at birth, the brain is about 25% of the weight of an adult brain, by age 2 years it is about 75% of its adult size, and around the age of 7 years, the human brain has reached its maximal size. Therefore, postnatal growth, especially during early childhood, happens rapidly and is not the result of the addition of new neurons, since neurogenesis mainly happens prenatally. Instead, it is the development and the maturation of neurons already present at birth that account for the increase in brain biomass and energy demands, including axon growth, dendritic arborization elaboration, synaptic formation/elimination, and axon myelination [7, 18, 36, 37]. Interestingly, brain energy metabolism requirement follows the development and maturation of the brain, reaching its peak in energy demand per gram of tissue during postnatal year 2 and 3, especially when the rates of synapse formation and myelination are reaching their maximal intensity [3, 53]. Indeed, metabolic and especially anabolic demands are expected to increase with the addition of new synaptic connections and myelin wraps around axons. Therefore, there is a very close temporal and spatial relationship between the brain metabolic and anabolic needs and the cellular and physiological changes of the neural tissue through development and adulthood.

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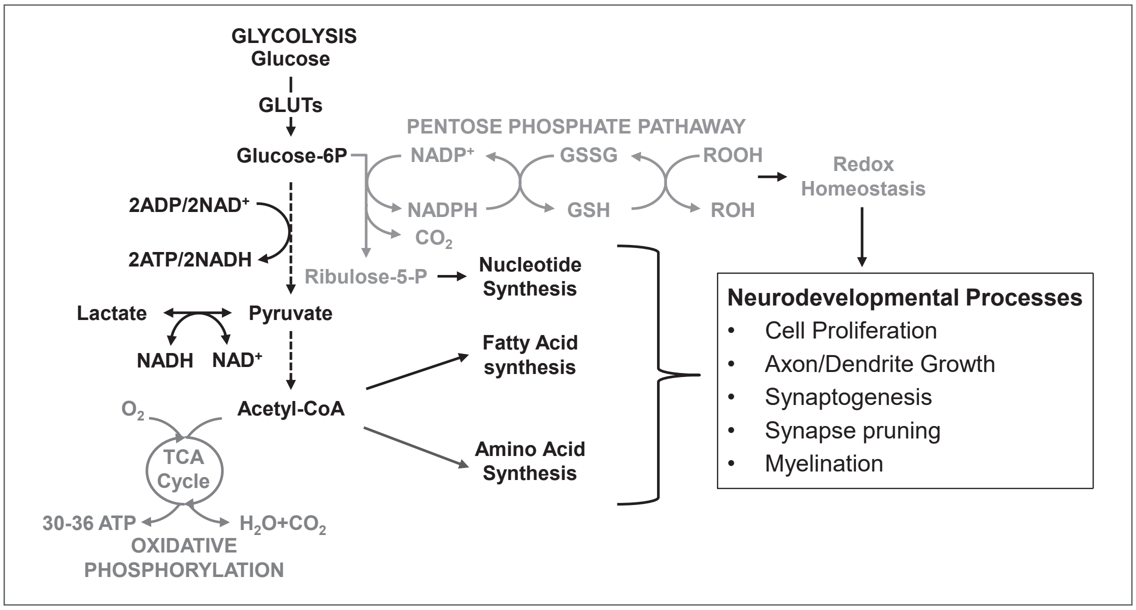

Fig. 2. Key biochemical pathway involved in glucose metabolism. Blood glucose is crossing the BBB in order to enter the brain. Glucose enters cells through glucose transporters (GLUTs) and is immediately phosphorylated to generate glucose-6-phosphate (glucose-6P). Glucose-6P is used as the metabolic substrate for different biochemical pathways. First, it is converted into 2 molecules of pyruvate through glycolysis that generate ATP and NADH. Pyruvate is then either reduced in lactate, consuming one molecule of NADH, or is metabolized in acetyl-CoA. Lactate can be released in the extracellular space through monocarboxylate transporters and is used as a source of energy or as a biosynthetic substrate by neurons and oligodendrocytes. Second, acetyl-CoA is metabolized through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation that produce ATP and CO_2 while consuming oxygen. The complete oxidation of glucose produces larger amounts of energy in the form of ATP in the mitochondria (30–36 ATPs) compared to glycolysis (2 ATPs). Alternatively, acetyl-CoA is used for the synthesis of fatty acid and amino acids. Glucose-6P can also be metabolized along the pentose phosphate pathway (PPP) and leads to the generation of ribulose-5-phosphate (ribulose-5-P, use in the synthesis of nucleic acid) and NADPH. NADPH is important to support fatty acid synthesis but also for the regulation of glutathione metabolism. Glutathione exists in the reduced form (GSH) or as a disulfide from (GSSG). The reduced form GSH is a source of reducing equivalent that can neutralize reactive oxygen species (ROS), such as hydroxyperoxides (ROOH). GSH is converted into GSSG, which is then recycled back to GSH by using NADPH as an electron donor. Glutathione is, therefore, a key antioxidant that protects cells against oxidative stress and is also critically involved in the control of cell redox homeostasis. Ultimately, nucleic acid, fatty acid, amino acid synthesis, and the control of redox homeostasis are providing the necessary energy and source of macromolecules that support neurodevelopment processes in brain development. The figure has been modified from [15].

Glucose Requirements to Support Energy and Anabolic Demands during Brain Development

Measurements of cerebral metabolic rate for glucose (CMRGlc) and for oxygen ($CMRO_2$), which is a measure of glucose and oxygen utilization in the brain, show a constant increase in their values during the first 2 years of life, reach approximately 2 and 1.5 times the adult value around 3–5 years of life, respectively, and then gradually decrease to the average adult value during the second decade of life (Fig. 1) [3, 54]. These observations suggest that energy demand increases during brain development, presumably due to an increase in synaptic transmission. Intriguingly, glucose utilization is increased to a greater extent compared to brain oxygen utilization. Indeed, at birth, CMRGlc and $CMRO_2$ measurement showed that the glucose consumption rate exceeds oxidative phosphorylation by around 34% [54, 55]. Moreover, Goyal et al. [20] reported that oxygen utilization during childhood accounts for approximately 70% of the total glucose consumption in a child brain. Since oxygen in the brain is utilized almost entirely for the oxidation of carbohydrate through oxidative phosphorylation to generate ATP, these results suggest that glucose may play additional functions to being an energetic substrate (Fig. 2) [3, 18, 56]. The preference of converting the glucose metabolite pyruvate produced through glycolysis into lactate or using it as a source of carbon for biosynthetic processes instead of converting it to ATP despite the availability of oxygen has been named aerobic glycolysis or the War-

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burg effect [21]. Aerobic glycolysis has been well described in tumor tissues that metabolize approximately 10-fold more glucose to lactate than normal tissues, to provide substrates for biosynthesis of cell constituents and support cancer cell proliferation [57]. Nevertheless, since neurogenesis at birth is limited and restricted to specific brain areas, metabolic and anabolic demands supported by glucose are presumably due to the maturation of preexisting neurons, refinement of synaptic connectivity, glia proliferation, and rapid rise in axon myelination.

Glycolytic byproducts are a crucial source of carbons to produce glutathione, NADPH, and riboses along the pentose phosphate pathway (PPP), which are themselves essential for the synthesis of fatty acids and nucleotide sensitive, respectively, and to maintain oxidative stress homeostasis (Fig. 2) [58]. Biosynthesis of macromolecules from glucose metabolites is critical to support key physiological processes behind proper brain growth and maturation; it has been shown, for example, that axon growth, synapse formation, and myelination rely critically on aerobic glycolysis [20, 59, 60]. Interestingly, aerobic glycolysis is predominant in the white matter compared to the gray matter, and it has been shown that glycolytic byproducts, such as lactate, are especially important for myelin production by oligodendrocytes [61, 62]. While it has been assumed that most of the glucose is used for ion pumping to maintain synaptic activity, these findings highlight that glucose is critically involved in anabolic requirements beyond energetic demands during neurodevelopment [18, 63, 64].

As discussed, aerobic glycolysis varies through the lifespan depending on regional and temporal metabolic and anabolic demands and seems to be critical as well during early fetal brain development; measurement of glucose uptake in 12- to 21-week previable human fetuses demonstrated that around one-third of the total body glucose was consumed by the brain and only half of it was presumably oxidized [65]. Studies performed in preterm infants, when neurogenesis is still active, demonstrated a very low rate of oxygen consumption and suggested that 90% of glucose is dedicated to aerobic glycolysis [66, 67]. While studies during early stages of brain development are limited, these data indicate that the fetal brain is highly dependent on aerobic glycolysis, possibly due to the large requirement of de novo biosynthesis of lipids, amino and nucleic acids that are associated with neuron generation and proliferation (Fig. 2).

The peak of CMRGlc happens around postnatal year 5 and stays elevated until 10 years of age [3, 54, 55]. While aging, glucose consumption slightly declines before reaching its adult life level during the second decade of life, and aerobic glycolysis decreases to one-third of its value in adulthood, representing 8–10% of glucose utilization [55]. Nevertheless, aerobic glycolysis in some areas of the brain, such as the medial and lateral parietal and prefrontal cortices, can contribute to as much as 20–25% of glucose utilization [68, 69]. These brain areas integrate multimodal sensory information and participate in complex cognitive functions, such as executive function and self-awareness, that necessitate a high level of synaptic plasticity and, therefore, a significantly high biomolecular turnover. It is, therefore, possible that during brain development glucose utilization is the key to not only provide energy through oxidative phosphorylation but also to support increase in biomass and macromolecule biosynthesis through aerobic glycolysis. Importantly, aerobic glycolysis seems to be especially crucial prenatally to support neurogenesis and then postnatally to support mainly neuronal growth, synapse formation, and myelination and eventually the proper development of neuronal networks underlying cognitive function. During brain maturation, a gradual metabolic switch between aerobic glycolysis and oxidative phosphorylation is happening. As neuronal networks mature, oxidative phosphorylation is predominant and maintains basal synaptic activity, while aerobic glycolysis is prevalent in areas where brain plasticity is engaged to sustain experience-dependent structural and functional changes that accompany higher cognitive functions (Fig. 2).

While aging, glucose consumption slightly declines before reaching its adult life level during the second decade of life, and aerobic glycolysis decreases to one-third of its value in adulthood

Ketones as a Source of Energy for the Brain during Development

Glucose is the primary metabolic substrate used by the brain to generate ATP in the central nervous system of adult mammals [8]. However, during brain development and maturation, the demand of energy and the high rate of macromolecular biosynthesis exceed the availability of blood glucose. The most relevant additional fuels to support extra energetic

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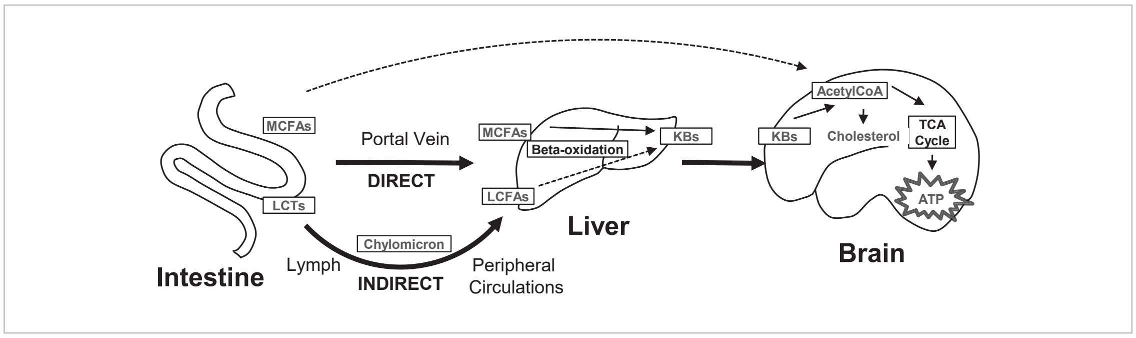

Fig. 3. Comparison of the absorption of medium-chain fatty acids (MCFAs) and long-chain fatty acid (LCFAs). MCFAs are rapidly absorbed from the gut and directly reach the liver through the portal vein. LCFAs are first integrated into chylomicrons and are primarily absorbed through the lymphatic system before reaching the target organs, including the liver, from the peripheral circulation. In the liver, MCFAs and LCFAs are converted into ketone bodies (KBs) (see Fig. 4) that are then released in the peripheral circulation before reaching the brain through the BBB. KBs are then converted to acetyl-CoA that is metabolized to produce either cholesterol in the smooth endoplasmic reticulum or energy in the form of ATP through the TCA cycle. The figure has been modified from [75].

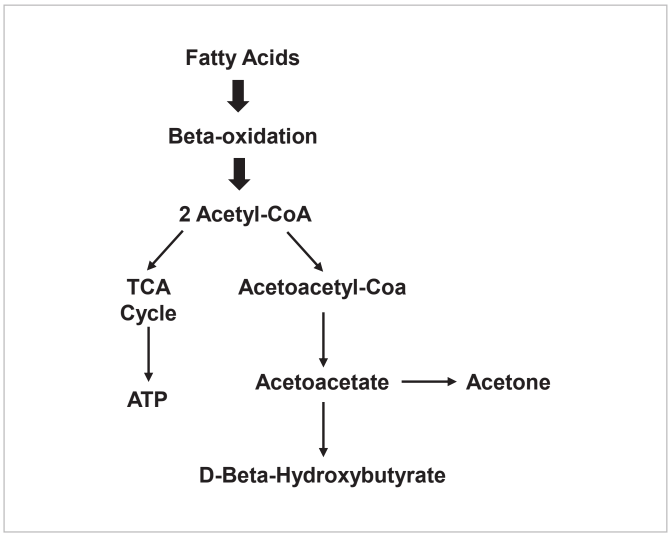

Fig. 4. Ketone body synthesis. Fatty acids are converted to acetyl-CoA through β-oxidation. Acetyl-CoA can then either enter the TCA cycle to generate ATP, or 2 molecules of acetyl-CoA are condensed in acetoacetyl-CoA. Acetoacetyl-CoA is then used to produce acetoacetate that can be used to produce either acetone or D-β-hydroxybutyrate. The figure has been adapted from [17].

needs of brain development are KBs, especially β-hydroxybutyrate and acetoacetate [17, 70–72]. KBs are short-chain fatty acids (SCFAs) derived mainly from liver β-oxidation of fatty acids that are available for the brain in direct proportion to their concentration in the blood [17, 73]. KBs are then oxidized through oxidative phosphorylation in the mitochondria of neuronal cells to generate ATP [17]. While the use of KBs for brain development is starting in utero, postnatal brain development also highly depends on KBs [65]. An interruption of continuous transplacental nutrient and energy supplies at birth necessitates the newborn to adapt quickly to the new metabolic environment and, especially, to move from continuous feeding to alternate periods of feeding and fasting [71]. This leads to a rapid metabolization of available substrates to produce energy, first, acutely from newborn reserve and, second, from alimentation in the form of milk from the mother [71, 74]. At birth, brain glucose reserves are very limited and could support brain needs for a few hours only. Metabolization and utilization of glucose from other organs, such as muscle, or tissue breakdown are not a viable long-term solution to support growth development. Interestingly, at birth, newborns are in a state of permanent mild ketosis (0.1–0.5 mM β-hydroxybutyrate), which is independent of feeding status or hypoglycemia [75]. Moreover, the brain uptake of KBs is 4–5 times faster in infants and children than in adults, which means that infant and child metabolism is programmed to actively produce KBs from liver β-oxidation and that the brain is dependent on KBs to support its metabolic and anabolic needs. Indeed, it has been estimated that KBs may be able to replace for up to two-third of brain energy demands when glucose availability is low [17].

It has now been recognized that fatty acids, especially medium-chain fatty acids (MCFAs) that constitute up to 10–20% of fatty acids contained in breast milk, are one of the main substrates used to produce SCFAs and maintain sustained ketosis in infants [72]. MCFAs are either directly converted into KBs by β-oxidation in the liver that will be taken

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up by the brain or they can be stored in adipose tissues and can be used later to support energy demands during a fasting period (Fig. 3, 4). Moreover, it is estimated that human milk contains around 15–17% SCFAs, which are highly ketogenic and may support brain energy and anabolic needs immediately [72, 76, 77]. Interestingly, body fat deposition during development is unique in humans; the human fetus starts to accumulate fat in subcutaneous adipose tissues during midgestation and has 500–600 g of subcutaneous fat at birth, while most mammals have a very limited amount of adipose tissues and, therefore, inability to store either MCFAs or SCFAs [17].

What are the main advantages for the brain to use KBs during development? First, SCFAs are either immediately available through the milk, or MCFAs stored within subcutaneous adipose tissues can be mobilized and metabolized to KBs. Second, the use of KBs as an alternative source of energy preserves glucose utilization for additional key metabolic pathways, such as the PPP, as described earlier. Third, KBs are not only a high energetic substrate but are also used as anabolic metabolites. For example, cholesterol is the main carbon source for the synthesis of cholesterol, which represents 20% of total brain lipids. Cholesterol is not only indispensable to properly build the cell membrane, but it is also crucial to build axon myelination [78, 79]. Finally, the generation of KBs from MCFAs and SCFAs is very fast compared to other fatty acids, since they directly reach the liver through the portal vein, bypassing the lymphatic system, and are β-oxidized into the mitochondria without the usual activation of the enzyme carnitine palmitoyltransferase (Fig. 3).

Therefore, contrary to the adult brain, it appears that KBs are essential for brain development and maturation as they are not only an essential source of energy to complement glucose to entirely fulfill the brain metabolic needs but also, similar to glucose, to support the anabolic demands associated with cell proliferation, growth, and maturation.

Conclusion

From conception to the third year of life, brain size increases dramatically, leading to the formation and expansion of neuronal networks that will eventually be reorganized and reshaped according to a variety of genetic and environmental factors [3]. Amongst the latter, nutrition is important for optimal brain development, since it provides glucose, KBs, and ketogenic fatty acids, which are the main metabolic substrates of the brain, during its development and maturation. Aerobic glycolysis and biosynthesis of macromolecules from glucose seems to be particularly important to support the establishment and maintenance of synaptic plasticity associated with higher cognitive functions. Utilization of KBs may, therefore, be used to "free" glucose for aerobic glycolysis, while supporting energy demands for synaptic transmission. In addition, KBs are also necessary for the synthesis of specific macromolecules, such as cholesterol, as discussed earlier. Nevertheless, many questions remain: first, it is still unknown what are the intrinsic and extrinsic factors that trigger aerobic glycolysis and oxidative phosphorylation in the brain, depending on its stage of development; second, it is not well understood how the balance between the use of glucose and KBs as energetic versus anabolic substrates is regulated. It will, therefore, be crucial to elucidate the genetic, metabolic, and physiological processes during brain development that dictate brain metabolism changes. Such nutrients are normally provided in complex food matrices, such as breast milk. Understanding fully how specific nutrients, especially in the context of food intake, interact together and affect brain metabolism (please see the chapter in this issue focusing on essential nutrients for early brain development: "Nutritional Factors in Fetal and Infant Brain Development" by Cheatham) will help us to better define the minimal requirements to support it and promote brain development.

Disclosure Statement

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Focus

Nutrients do not appear in nature in isolation. Thus, it is safe to assume that they do not work in isolation

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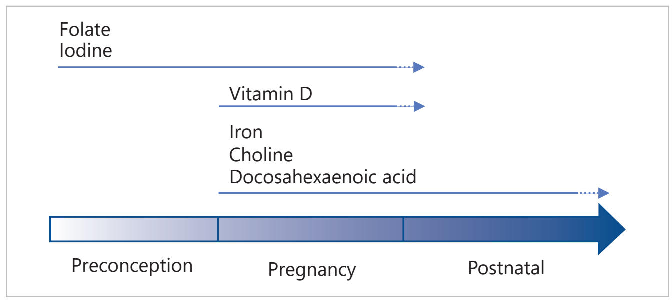
Nutritional Factors in Fetal and Infant Brain Development

Carol L. Cheatham

Key Insights

Optimal maternal and infant nutrition during the period of early brain development is critical to the integrity and functioning of brain tissues. We are only beginning to understand the importance of the timing, dose, and duration of specific nutrients in human early brain development. Each nutrient has its own critical/sensitive time period when deficiency can lead to a cascade of negative impacts on early brain functional development, also known as the sensitive period. This article reviews the available data on the importance of folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA) on early brain development during preconception, pregnancy, and the first years of life.



Key nutrients that support fetal and infant brain development from preconception to pregnancy and after birth.

Current knowledge

As one of the most important organs in the body, the brain requires a high level of nutrition for optimal function. After birth, brain development continues well into the second decade of life (then, optimal nutrition is needed to protect against the onset of aging), highlighting the need to support the brain throughout an individual's lifespan. Classic examples to illustrate the importance of pre-conceptional maternal nutrition in fetal brain development are folate and iodine. During infancy and early childhood, iron deficiency has been shown to cause long-lasting, irreversible damage to neural tissue function. Emerging data suggest that DHA and choline act synergistically with other nutritional factors (such as uridine) to support neuronal plasticity during pregnancy and after birth.

Practical implications

New evidence indicates that folate may not be the only B vitamin critical for preventing neural tube defects in the fetus. The greatest impact on reducing the risk of neural tube defects comes from intake of methionine, choline, and betaine in combination with folate, rather than folate alone, before conception, underscoring the importance of overall optimal nutrition. During pregnancy, the fetus is entirely reliant on maternal provision of key nutrients, such as vitamin D and iron. Fetal demand for DHA is highest in the third trimester. The need for many of these nutrients, including iron, DHA, and choline, persists after birth. Therefore, women of child-bearing age should understand that optimal nutrition is a continuum that spans the preconception period, pregnancy, and across the early years of a child's life.

Recommended reading

Cheatham CL, Sheppard KW. Synergistic effects of human milk nutrients in the support of infant recognition memory: an observational study. Nutrients. 2015 Nov;7(11):9079–95.

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Nutritional Factors in Fetal and Infant Brain Development

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Key Messages

- Maternal nutrition is integral to fetal and, if breastfeeding, infant brain development.
- Nutrition effects are governed by the timing, severity, and duration of a deficiency or a sufficiency.
- Genetics and epigenetics determine the individual needs for and metabolism of nutrients.
- Nutrients work together in a synergistic manner for the benefit of the organism.

Keywords

Brain development · Fetal nutrition · Infant nutrition · Maternal nutrition

Abstract

Fetal and infant brain development determine the trajectory of the organism across the lifespan. Optimal maternal and infant nutrition during the period of rapid brain development is vital to the integrity of the neural substrate for subsequent lifelong functions. The goal of this review is to educate the reader on the effects of fetal and infant nutrition on the developing human brain. A review of the literature reveals 6 nutrients that have been studied with respect to maternal nutrition and subsequent offspring brain development: folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA; 22:6n-3). The research is discussed with a focus on the timing of nutrient needs (preconception, prenatally, and postnatally) as well as potential confounding and unobserved variables.

Introduction

Arguably one of the most important organs in the body, the brain requires a high level of nutrition to function optimally. In fact, glucose utilization is 60% of the total in the body. During development, proper maternal and infant nutrition are needed to ensure that the neural substrates are lain down with integrity. As detailed elsewhere [1], the sequelae of nutrient deficiencies depend on timing, dose, and duration: at what point in development did the deficiency occur; how severe was it; and how long did it last? Each nutrient has its own period when its lack can cause developmental issues; this period is

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Table 1. Examples of natural sources of select nutrients

Nutrient	Examples of sources
Folate	Dark leafy greens Legumes Dairy products Grains Poultry Eggs
Iodine	Seaweed Seafood Oysters Legumes Strawberries Iodized salt
Vitamin D	Sunshine Fatty fish Beef liver Egg yolks Mushrooms
Iron	Red meat Spinach Liver Shellfish Legumes
Docosahexaenoic acid	Free-range eggs Grass-fed beef Fatty fish Algae
Choline	Eggs Red meat Liver Peanuts Dark leafy greens

known as a sensitive period. That is, the organism is especially sensitive to a deficiency of a specific nutrient at a specific time. If the deficiency is severe and long lasting, the issues can be devastating and irreversible. In this review, the known important aspects of maternal and infant nutrition that contribute to brain development and function will be discussed. It should be noted that maternal nutrition is integral to other important aspects of human development, such as length of gestation, intrauterine growth restriction, and other birth outcomes that will not be covered here. The goal of this review is to educate the reader on the effects of fetal and infant nutrition on the developing human brain.

A review of the literature reveals 6 nutrients that have been studied with respect to maternal nutrition and subsequent offspring brain development: folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA; 22:6n-3). See Table 1 for example sources of these nutrients. The research surrounding these nutrients will be summarized here, as will a few underlying concepts, but the coverage will not be exhaustive.

Importance of Maternal Nutrition before Conception

Women of child-bearing age who are sexually active should be aware that nutrition is important *before* conception. As mentioned, timing is imperative. In the first few weeks of gestation when most women do not know that they are pregnant, the zygote is growing at an incredible rate. Proper nutrition supports the rapid cell division, development of supporting structures such as the placenta, implantation, and neural tube closure that occur in those first few weeks. Therefore, it is important for women of child-bearing age to have the proper nutrients on board in the event of unanticipated pregnancy. Research foci in preconception nutritional needs were suggested by developmental issues. In particular, work has been done to document the effects of folate in the prevention of issues during neurulation and iodine in the prevention of cretinism.

It is important for women of child-bearing age to have the proper nutrients on board in the event of unanticipated pregnancy

Folate

The prevalence of neural tube defects (NTD) is 1–10 per 1,000 live births with a higher prevalence in nonviable pregnancies [2]. The severity of effects ranges from anencephaly, which is usually fatal, to asymptomatic closed spinal lesions. In 1964, it was proposed that folate might be involved [3], in part, due to the higher prevalence in low-income, potentially undernourished populations. Supplementation with a multivitamin containing folic acid starting 28 days before conception proved to lower the incidence of NTD relative to the unsupplemented control group [4], and similarly, recurrence was significantly diminished with preconception supplements [5]. Importantly, when classifying women by the quality of their diets, only those with inadequate diets gave birth to infants

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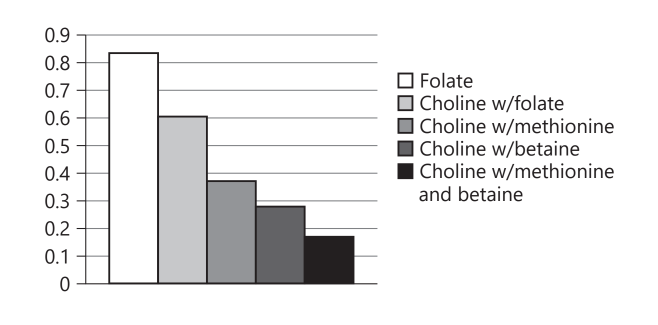

Fig. 1. Data from Shaw et al. [7] on the risk of giving birth to an infant with neural tube disorders when preconception dietary intake is in the highest quartile for folate, folate with choline, choline with methionine, choline with betaine, and choline with methionine and betaine.

with NTD [6]. Based on the growing body of evidence, policy makers established a requirement for folic acid in women of child-bearing age, and in the United States, folic acid was added to the food supply in 1998. New evidence suggests that folate may not be the primary B vitamin in the amelioration of NTD [7]. Data collected by Shaw et al. [7] suggest that the risk of NTD is furthest reduced by a high preconception intake of methionine, choline, and betaine in combination rather than intake of folate alone (Fig. 1). Thus, although folic acid supplementation has reduced the incidence of NTD, overall optimal nutrition is important before conception.

Iodine

A major cause of childhood cognitive issues worldwide is maternal iodine deficiency. Iodine is essential (meaning that it needs to be acquired from the diet) and is used in the production of thyroid hormones. During pregnancy, iodine requirements increase because there is an increased need for thyroid hormones (the fetal thyroid does not start working until the second trimester), for transfer of maternal iodine to the fetus throughout gestation, and for renal clearance of iodine. If a woman is severely deficient in the first few days or weeks of gestation, the result is cretinism in the child, which is characterized by mental deficiencies, deaf mutism, and motor spasms of the arms and legs. The severity of the problem is dependent on the severity of the deficiency. It is thought that cretinism is due to the inability of the mother to produce enough thyroid hormone in those crucial first few weeks when the fetal thyroid is not yet functioning. Because thyroid hormones are involved in neurogenesis and neuronal migration as well as several other neuronal processes, the effects of iodine deficiency can be globally pervasive in the brain.

Several iodine supplementation studies have been implemented in developing countries. In a study in Ecuador, one village was treated with iodine and another acted as a control. Mean IQs of the children born in the treated village were higher relative to the control village, but interestingly, if the treatment occurred before pregnancy or in the 1st trimester, the difference in IQ was a full 11 points [8]. Scientists working in New Guinea gave injections of saline or iodine [9]. The untreated group had a cretinism rate of 9% and the treated group had a rate of just 2%. Analyses showed that 6 of the 7 cretins in the treated group were born to mothers who were treated late in pregnancy. So, treatment must be done early in pregnancy, and since most women do not know that they are pregnant in the first few weeks, it is imperative that iodine sufficiency is achieved *before* conception. Salt iodization programs are in place globally, but due to the cost of iodized salt, results have not been as pervasive as expected.

Summary

Folate and iodine are the quintessential examples of the need for good maternal nutrition before conception. Most likely, other nutrients will be found to have just as many profound effects. Thus, women of child-bearing age who are sexually active should be counseled to establish heathy dietary habits such that their nutrition levels are stable and optimal. Importantly, folate and iodine are needed throughout gestation. The next section details other nutrients that have been researched for their utility in fetal development.

Importance of Maternal Nutrition during Gestation

Fetal neural development is dependent on the nutritional environment in utero. A fetus developing in a suboptimal environment will compensate by adapting metabolic systems to the anticipated external world. This adaptation is known as "fetal programming" and is thought to be partially responsible for the progression of disease into adulthood [10]. For example, maternal obesity during gestation has been related to insulin resistance and, thus, metabolic disorder in adulthood [11]. Even though a complete review of the developmental origins of health and disease (DOHaD) hypothesis is beyond the scope of this paper, the concept is important to its thesis: early nutritional programming effectively prepares the fetus and infant for the world to come based on a prediction of the nutrients that will be available. The seminal example comes from the Dutch famine of 1944. Offspring of women who were pregnant during the famine and, thus, were unable to provide sufficient nutrients to their fetuses in utero went on

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as adults to develop significantly higher levels of cardiovascular disease, obesity, and adult-onset diabetes relative to offspring of mothers who were sufficiently nourished during pregnancy [12]. Fetal programming in this example would have prepared the fetus epigenetically for a world with little nutrition. Then, with the famine resolved, the previously famine-programmed child would have had access to plentiful food, and the system would have experienced a mismatch between prenatal and postnatal nutrition environment. DOHaD predicts that this mismatch can result in a progression to disease. Thus, maternal nutrition can have a profound and long-lasting effect on the developing fetus. In what follows, the importance of maternal vitamin D, iron, DHA, and choline will be detailed.

Vitamin D

Maternal vitamin D deficiency has been studied extensively for its effect on the developing fetal brain as those born in winter have a higher risk of developing schizophrenia [e.g., 13]. The fetus is wholly dependent on maternal provision of vitamin D [14]. When the mother is deficient, the fetus is deficient. Scientists utilizing animal models revealed that vitamin D deficiency results in morphologically different brains in the offspring: vitamin D has a role in brain size, ventricle size, cell proliferation, and growth factor signaling [15]. To date, all the research in humans has been correlational; it would not be ethical to randomize women to remain deficient throughout pregnancy.

Effects of maternal vitamin D deficiency on IQ have been mixed. Whereas better scores at 7 years of age on the Wechsler Intelligence Scale for Children (WISC) were related to better maternal vitamin D status and cord blood vitamin D [16], better vitamin D status during pregnancy did not predict better scores on the Kaufman Brief Intelligence Test (KBIT) at 5 years of age [17] or on the Wechsler Abbreviated Scale of Intelligence (WABI) at 9 years of age [18]. Better gestational vitamin D status has been related to better language abilities at 5 and 10 years of age [19]. In one of the few studies wherein toddler development was assessed, researchers reported a relation between both the psychomotor and mental subscales of the Bayley Scales of Infant Development (BSID): higher vitamin D status at week 13.5 of gestation was related to higher BSID scores in 14-month-olds [20]. Finally, maternal vitamin D status has been related to risk of attention deficit hyperactivity disorder (ADHD) with lower maternal vitamin D predicting higher risk of the child developing ADHD [21].

Certainly, the body of research suffers from a lack of consistency in assessments and study timepoints, as is often the case in epidemiological analyses of established datasets. In addition, and perhaps more importantly, women who are vitamin D deficient generally are of lower socioeconomic status, and as such, would be more susceptible to viruses, more likely to be consuming teratogenic substances (e.g., tobacco and alcohol), and would be more likely to be undernourished in general.

Iron

Iron deficiency is the number one nutrition issue in the world. The sequelae of iron deficiency result in a loss of billions in productivity annually. One can be iron deficient without being anemic, but iron deficiency with anemia (IDA) rates can be quite high – as high as 77.2% among children 1–3 years of age in rural India [22]. In the USA, the prevalence of iron deficiency in those 1–2 years of age is as high as 30.5% based on total body stores [23]. Finally, rates of deficiency among pregnant women worldwide reach as high as 50% [24]. Iron deficiency prenatally and in infancy can cause irreversible neural issues. Moreover, maternal hypertension and smoking during pregnancy are known to cause a decrease in materno-fetal transport of iron, and gestational diabetes results in a higher fetal need for iron. Thus, pathways to iron deficiency vary, and it is not known if supplementation can prevent subsequent neurobehavioral issues in the offspring.

Fetal iron sufficiency supports neural energy metabolism, the development of dendrites and synapses, the synthesis of neurotransmitters, and the onset of myelination [25]. As mentioned previously, timing, dose, and duration of the insufficiency determine the sequelae. In an analysis of over half a million of children in Sweden, it was shown that children of mothers who were diagnosed with anemia in the first 30 weeks of pregnancy had a higher incidence of autism spectrum disorder, ADHD, and intellectual disability relative to children of mothers who were diagnosed later in pregnancy or not diagnosed [26]. Thus, the earlier timing and longer duration of the insufficiency led to more severe and diagnosable issues.

Fetal iron needs increase in pregnancies complicated by gestational diabetes. A sample of infants of diabetic mothers (IDM) were followed longitudinally by a research group led by Nelson and Georgieff. These infants were first tested at 38–42 weeks' postmenstrual age in an electrophysiology paradigm known as event-related potentials or ERP to assess their ability to recognize their own mothers' voices [27]. The infants were divided into 2 groups defined as ferritin levels in cord serum above and below 34 μg/L. Neonates in the low-iron group were not able to differentiate their mothers' voices from strangers' voices, whereas those in the group with higher iron levels were able to perform this recognition memory task. A subset of this sample was tested at 12 months of age on a behavioral task designed to test declarative (explicit)

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memory [28]. The IDM group was compared, in this case, to the non-IDM group rather than dividing them by ferritin levels. The IDM group had lower scores on the mental scale of the BSID-II and on the memory task relative to the controls (Fig. 2). It is important to note that these infants were not iron deficient at 9 months of age [29], and thus, the cognitive outcomes can be directly attributed to prenatal and neonatal iron status.

Iron is currently the quintessential nutrient for the discussion of timing, dose, and duration of deficiency. When a fetus is iron deficient for extended periods of time, brain development does not proceed on a typical trajectory and the suboptimal outcomes are most likely irreversible even when iron is replete. That said, iron accretion by the fetus in the third trimester is quite high, and once iron accumulates in the fetal brain, it does not deplete. Importantly, in the third trimester, the system pulls on maternal iron reserves that are acquired before conception. Women of child-bearing age need to consume appropriate amounts of bioavailable iron if they are to have the stores needed to support fetal development, especially if they plan to have another child before the stores have a chance to rebuild.

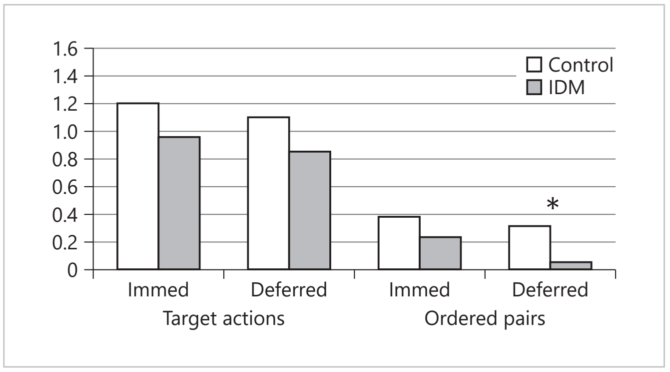

Fig. 2. Data from DeBoer et al. [28] on explicit memory performance for IDM at 12 months of age. Infants were tested on performance immediately after the researcher-modeled 2-step events and after a 10-min delay. Participants were scored on whether they performed the actions (n = 2) and whether they performed the actions in the proper order after a 10-min delay (n = 1). Performance was significantly different on the most difficult part of the task – getting the actions in the proper order after the delay (* $p < 0.05$). Immed, immediately; IDM, infants of diabetic mothers.

Docosahexaenoic Acid

The omega-3 fatty acid DHA (22:6n-3) is integral to cellular and neural function as it and other fatty acids comprise the phospholipid bilayer. The fetus requires high amounts of maternal fatty acids [30]. The demand is highest in the 3rd trimester, and multiple maternal pathways are upregulated to insure sufficient supply [31, 32]. Maternal DHA stores are mobilized in the 3rd trimester of pregnancy; maternal circulating levels of DHA decline progressively across pregnancy such that toward the end of pregnancy, maternal plasma levels of DHA are very low [33]. At birth, DHA levels in the infant are typically higher than in the mother [34], suggesting preferential transfer of DHA to the fetus. Materno-fetal transfer takes precedence over the maintenance of maternal DHA levels.

Whether there are any effects of maternal supplementation with fatty acids on infant cognition has been called into question by systematic reviews [35, 36]. Maternal DHA studies (supplementation or associative designs) have been completed with mixed results. Positive effects have been found on infant problem-solving [37], preschool-age processing [38], elementary-age verbal abilities [39] and full scale IQ [40], whereas no effects were found on global cognitive function [41–46], recognition memory [37], visual acuity [47], language [42, 43], attention [48], or working memory/inhibitory control [48]. Negative effects have been reported on mathematical abilities [39]. However, positive effects have been found in the reduction in risk of neurological disorders [49], language disorders [50], autism spectrum disorder [51], and developmental delays [42]. Taken together, no definitive conclusions can be drawn from the maternal supplementation literature.

There are potential confounding variables that may help explain the lack of consistency in the results of fatty acid supplementation studies. First and foremost, positive effects of gestational supplementation have been found longitudinally when the offspring reach school age [38, 52]. It is possible that the effects of DHA on the fetal brain do not become apparent until the higher-order cognitive abilities known as executive functions (i.e., working memory, inhibitory control, planning, etc.) begin to come online. In addition, the seeming lack of discernable effects in the early months of life could be because the researchers utilize global assessments [41–46] rather than assessing specific cognitive effects, such as hippocampal function. Indeed, Levitsky and Strupp [53], in a meta-analysis, found that nutrition deficiencies do not result in whole-brain issues, but rather have very specific effects in the hippocampus, cerebellum, and neurotransmitter function. Thus, trials should be conducted based on hypotheses of specific effects on cognition.

Another confounder in the trials is the significant genetic component, which has historically been an unobserved variable in fatty acid studies. Mammals have the ability to metabolize DHA from the fatty acids found in plants (see Fig. 3 for pathways). The enzymes for the metabolic steps are coded by the *FADS* gene complex. Certain single nucleotide polymorphisms have been related to less than optimal action of this

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metabolic pathway. Review of the genetics behind the conversion from α-linolenic acid (LNA; 18:3n-3) to DHA and the implications for subsequent brain function has been done [54] and, thus, it will not be covered here. In a related issue, the balance between the n-6 and n-3 pathways determines the metabolic progression as the pathways compete for enzymes. We have shown that cognitive abilities are compromised in the individual when the n-6:n-3 balance is off [55, 56]. Importantly, placental metabolism of fatty acids is differentially affected by imbalances between the n-6 and n-3 pathways [57, 58]. A correlational study was undertaken to explore the balance hypothesis in pregnant women and their subsequent children [59]. A higher n-6:n-3 ratio was found to be negatively correlated with language at 2 years of age and neurodevelopment in general at 3 years of age. Together, the evidence indicates that study design, background diet, and background genetics are integral in the consideration of the effects of fatty acids on cognition. With attention to these confounders, the effects of maternal supplementation with DHA on the cognitive abilities of the subsequent infants may become clear.

Choline

Choline is a micronutrient that is found in, for example, meat, legumes, and eggs. It is needed during pregnancy as it is the seminal source of its metabolites that are used in the development of all tissues, the synthesis of the neurotransmitter acetylcholine, the methylation of genes (epigenetics), and, in general, the one-carbon metabolic pathway. Phosphatidylcholine is a phospholipid that is used in the development of the brain and other tissues and as such is in high demand during gestation. There is a large body of animal work in support of maternal supplementation during fetal development, but the effects are not apparent until older age in the rodent models. Clinical trials in humans are few due to ethical concerns surrounding the choline status of women who would be randomly assigned to the control group. Supplementation with twice the recommended amount of choline (930 mg/day) during the third trimester resulted in improved speed of processing in infants [60], whereas supplementation with a lesser amount (750 mg/day) did not improve memory [61]. In the former study [60], background choline was carefully controlled. In the latter [61], background choline was already adequate. Estrogen up-regulates the metabolism of choline via the *PEMT* gene, and thus, when background choline is adequate, the system is poised through up-regulation to provide for the needs of the fetus. Alternatively, and as would be predicted by the thrifty hypothesis, fetal programming may have set the fetus to expect extra choline in the environment, and in the absence of that, a mismatch occurred resulting in suboptimal cognitive abilities.

Summary

As mentioned, all nutrients are no doubt important during pregnancy. It is important that women of child-bearing age understand that optimal nutrition during pregnancy will set their infants on a trajectory of health for the lifespan. Just as important is postnatal nutrition. Brain development does not stop until into the second decade of life (at which point optimal nutrition is then needed to protect against the onset of aging). Moreover, as mentioned, it is possible that a match between pre- and postnatal nutrition is important to development. We now move to a discussion of the evidence for postnatal nutrients that support brain development and function.

It is important that women of child-bearing age understand that optimal nutrition during pregnancy will set their infants on a trajectory of health for the lifespan

Importance of Postnatal Nutrition

Brain development continues into the second decade of life, and arguably, optimal nutrition is needed to support the brain not only during that period of time, but across the lifespan. That said, postnatally, the brain is most rapidly developing and most plastic during infancy and toddlerhood. Optimal nutrition in the fetal period and the first few years of life is central to the development of neural substrate on which a lifetime of cognition is based. There are sensitive periods in which certain nutrients may be more salient than at other times. For the most part, the same nutrients that have been studied in relation to prenatal development are integral to postnatal brain development. Thus, in this section, the utility of iron, choline, and DHA for postnatal brain development and function will be summarized.

Iron

As has been discussed, the timing, dose, and duration of deficiencies in relation to sensitive periods determines the extent and severity of the effects [1]. Iron deficiency during infancy appears to cause long-lasting and irreparable damage to neural tissue and neurotransmitter function. Iron deficiency at 9 months of age has been related to concurrent delays

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in memory and attention development [62, 63]. Scientists following up a cohort in Chile have shown that infants who were identified as iron deficient with anemia (IDA) in infancy and were subsequently supplemented with iron for a minimum of 6 months [64] evidenced issues with inhibitory control and reaction time at 10 years of age [65] relative to a non-IDA comparison group. Similarly, in a sample from Costa Rica [66], those who had experienced IDA in infancy evidenced issues with executive functions and memory at 19 years of age relative to the controls [67]. In the latter study, interim follow-up sessions had documented that the IDA from infancy was no longer evident at 5, 11–14, and 19 years of age. With all appropriate covariates controlled, the source of the documented cognitive issues is most likely the IDA in infancy. As evidenced, timing of the deficiency is, therefore, important.

The background environment cannot be dismissed when considering iron deficiencies. Whereas it is true that those who are iron deficient more often than not are also living in less-than-optimal conditions, the statistical inclusion of replete comparison groups from similar environments in the described studies lends validity to the conclusions. Children adopted into the United States from other countries experience sudden and complete change in their environments. In a sample of international adoptees [68], it has been shown that regardless of country of origin (Ethiopia, China, post-Soviet) or length of institutionalization before adoption (52–91 months), those who were iron deficient on arrival in the United States performed less well on a battery of neurodevelopmental tests at baseline (arrival) and 6 months later relative to a comparison group matched for post-adoption socio-economic status. Importantly, the deficiencies were not completely remediated after 6 months even though they were in stable homes with proper nutrition. Two and a half to five years after adoption, another sample [69] evidenced a higher incidence of ADHD relative to controls that had not resolved in the post-adoption phase, whereas IQ scores had improved. Importantly, in this sample, longer periods of institutionalization and more severe iron deficiency predicted lower IQ [70].

Because preference is afforded the red blood cells when ferritin is low, the brain is already severely iron deficient before a diagnosis of anemia is warranted [71]. Therefore, prevention is key. Supplementation of at-risk mothers, delayed clamping of the umbilical cord, and supplementation from birth of at-risk infants are suggested strategies [72]. However, it should be noted that supplementation of replete individuals or of children who live in areas where malaria is an issue is not advised [72].

Docosahexaenoic Acid

As has been described, DHA is integral to synaptic transmission and neuronal fluidity, which underlie all cognition. DHA is found in wild fatty fish, free-range eggs, and grass-fed meat. Intake country to country varies based mostly on whether the country's culture is fish focused. Results of studies conducted early on were mixed [73]. There was evidence of effects of exogenous DHA on visual acuity in early infancy [74–76], but the effects leveled off after 4 months of age [75], and reviewers of the literature did not find sufficient evidence of an effect [e.g., 77, 78]. Moreover, scientists conducting randomized controlled trials (RCTs) of the effects of exogenous DHA on the cognitive development of infants born full term reported inconsistent results [for review, see 73, 78]; fewer than 40% of RCT results showed an effect of DHA supplementation on cognition.

A decade later, the story is still the same: there is little concrete evidence that DHA or DHA supplementation positively affects brain development and function [79–81]. Recent reports are mixed. For example, in an RCT designed to supplement women pre- and postnatally with fish oil or a placebo, an effect was reported in communicative abilities at 4 months of age [82]. Conversely, DHA status at 9 months of age has been reported to be inversely related to communicative abilities at 3 years of age in females [83]. As another example, in a fish-eating country (Norway), naturally occurring maternal DHA levels in the 28th week of gestation and infant DHA levels at 3 months of age were related to infant problem-solving abilities at 12 months of age [84]. These women were presumably eating DHA foods throughout gestation and lactation. However, supplementation in pregnancy and lactation with DHA in another fish-eating country (the Netherlands) did not result in any differences between supplemented and controls when the children were 18 months of age [45]. It is possible that the background consumption of fish weekly was sufficient, and further supplementation of DHA was a redundancy.

However, importantly, an effect was seen when the analyses were completed on continuous data (rather than grouped) relating cord blood DHA to cognitive abilities at 18 months of age [45]. This result illustrates that the lack of a clear consensus in the field is most likely due to unobserved variables. Whereas it is true that heterogeneity in designs and inappropriate cognitive assessments (global vs. specific) are a pervasive issue in this literature [73], maternal and infant DHA status differ with respect to placental control of fatty acid conversion and transfer. As mentioned previously, there is a genetic component to fatty acid status that has proven to be very complex. Until recently, scientists have discounted the fact that humans can synthesize endogenous DHA from its precursor, LNA (Fig. 3). Conventional thought was that this conversion rate

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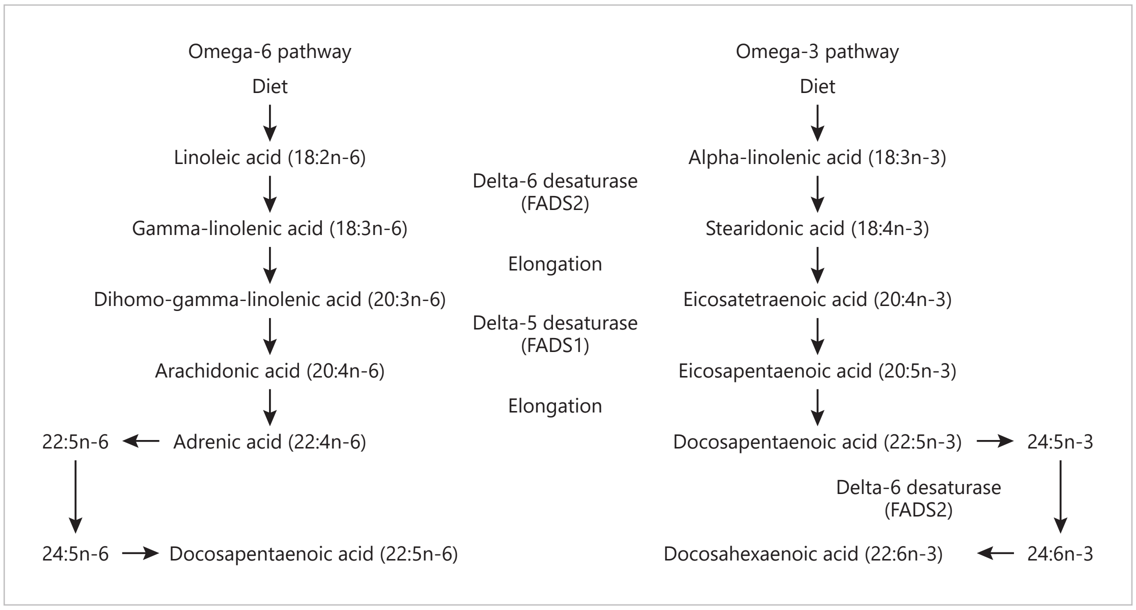

Fig. 3. Metabolic pathways of the omega-6 (left) and omega-3 (right) fatty acids. Figure used with permission [56].

was so low that it was of little consequence (mean LNA:DHA rate ~0.047%; [85]). Nonetheless, if control groups include participants who are endogenously producing their own DHA, they are confounding the results. In non-fish-eating countries such as the United States and Australia, the ability to metabolically improve one's own DHA status is optimal in over 90% of the population. In a study where genetic status was controlled [86], it was shown that background genetics were related to maternal levels of fatty acids. No effect was noted on offspring cognitive abilities, but the study was conducted in a fish-eating country. In a study designed to assess both maternal genetics and infant methylation (fetal programming), we did find that maternal genetic status for a single nucleotide polymorphism (*FADS2* rs174575) and infant methylation on the promoter region of that gene predicted toddler cognitive performance [87]. Thus, genetics and epigenetics are important considerations in the characterization of participants in fatty acid studies, especially in relation to brain development.

Choline

Choline supplementation is most often investigated during gestation as the animal models suggest sensitive periods for fetal neural development. Supplementation studies in infants and toddlers are rare even though they are not achieving the recommended intake [88]. Higher betaine (choline metabolite) levels are related to better visuomotor development in toddlers [88]. Infant choline supplementation is beneficial in neural inhibition development (presumably by improving acetylcholine receptor activation) that has been noted as a risk factor for schizophrenia [89]. Supplementation with phosphatidylcholine did not help with suspected cerebral palsy [90], and 2 years' choline with uridine supplementation did not remediate the sequelae of neonatal brain bleeds [91]. Attempts to rectify the damage exacted by fetal alcohol exposure have met with challenges, but with proper timing, choline supplementation may be useful. Again, supplementation during pregnancy has been shown to prevent effects of fetal alcohol exposure [92, 93]. Postnatal supplementation appears to mitigate symptomology, but only in the younger participants (2.5- to 4-year-olds) [94] and not in those 5–10 years old [94, 95]. Thus, there may be distinct sensitive, even critical, periods for choline supplementation.

Importantly, DHA, choline, and uridine appear to work synergistically in the support of plasticity in the brain. Animal models have shown that the improved plasticity results in increases in synapses, dendrites, and neurotransmitter activity when all 3 are supplemented [96]. The incremental improvement of plasticity is not sufficient to overcome brain damage [90, 91] but may be of import in at-risk infants. In a study of the effects of human milk nutrients on the brain development and subsequent cognitive function of 6-month-olds, we showed that DHA and choline work together in support of recognition memory [97]. Infants whose milk contained higher levels of both choline and DHA exhibited better recognition

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Table 2. Documented utility in humans for nutrient intake that will support fetal and infant brain development and subsequent function

Developmental period	Nutrient	References on positive effects	References on null finding
Preconception	Choline and metabolites Iodine	[4–7] [8]	
Prenatal	Vitamin D Iron Docosahexaenoic acid Choline	[16, 19, 20, 21] [26–29] [37–40, 42, 49–51] [60]	[17, 18] [37, 41–48] [61]
Postnatal	Iron Docosahexaenoic acid Choline	[62–69] [74–76, 82, 84, 97] [88, 94, 97]	 [45, 83] [94, 95]

memory relative to those whose mothers were producing milk that had lower levels of the 2 nutrients. With DHA dependent on phosphatidylcholine for transport to the brain, it stands to reason that the 2 are needed together in support of the development of neural structures. The mixed results in the RCT of DHA supplementation could be the result, in part, of unobserved background diet.

Summary

Most certainly, all nutrients are important in the construction and maintenance of a human. That said, a few common concepts have emerged from the few that have been studied extensively and reviewed here.

Timing, dose, and duration of nutrient intake is important. Sensitive periods for nutritive action exist, and some may even reach the level of critical periods, the latter meaning that if a certain nutrient is not received at a particular time (critical period), the results will be profound and irreversible.

Background genetics and epigenetics determine the individual's level of need and ability to metabolize a given nutrient. Not only should background genetics always be considered, but also, full consideration should be given to the prenatal nutritional environment. Prenatal and postnatal nutrition should match as the fetus is most likely (and ideally) programmed epigenetically for a world that will provide a similar nutritional experience.

Nutrients do not appear in nature in isolation. Thus, it is safe to assume that they do not work in isolation. Nutrients are working synergistically and, as such, should be studied together. Reductionism has its place in research. Once the basics of a particular nutrient's mechanistic actions have been established, synergisms should be explored.

When considering the mixed results that seem to be the hallmark of nutrition research (see Table 2 for summary), it will be important to keep these concepts in mind.

Disclosure Statement

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Focus

Biological systems are broadly malleable very early in life, and as the organism matures, these systems become settled in form and function and become less vulnerable to environmental insult

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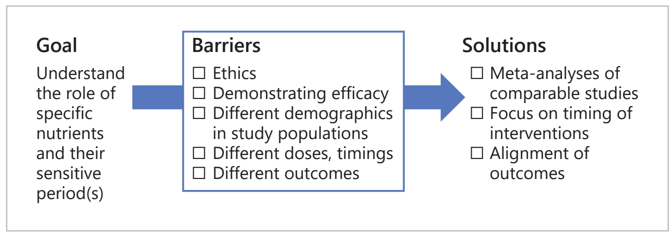
Critical and Sensitive Periods in Development and Nutrition

John Colombo et al.

Key Insight

The concept of "critical" or "sensitive periods" has been known in developmental science for more than a century and has held special relevance for studies on brain plasticity. This notion of critical/sensitive periods in developmental sciences has been widely invoked in the context of the concept of nutritional programming: the prenatal period is a time when various metabolic systems are malleable and can be influenced by conditions of maternal physiology and environmental exposures, including nutrient intake. Currently, the term "sensitive period" is used to refer to these early periods of malleability. Nevertheless, it is very difficult to conclusively establish sensitive periods for particular nutrients.



Overcoming the barriers to understanding the role of micronutrients and the sensitive period.

Current knowledge

Some of the earliest data arose from observing the effects of toxic substances on embryos. Toxic exposures occurring during the embryonic period had severe effects across multiple systems; interestingly, the same exposure later in development resulted in milder and more restricted effects. Behavioral studies on imprinting in birds not only reinforced the concept of the critical period, but emphasized several key points. First, there was a brief period of great learning plasticity, during which imprinting could occur. Second, exposure during this critical period was largely irreversible. We now understand that some degree of recovery is possible under special conditions. These concepts have been extended across different fields, including language, food imprinting, and nutritional programming.

Practical implications

How can we determine the sensitive period for a specific nutrient (i.e., a particular vitamin or micronutrient) in human development? Future trials must not only overcome the hurdles of ethics but also face the great challenge of demonstrating efficacy for isolated nutrients within a complex system. One way to overcome this is to insist that meta-analyses of those trials include the age group of their interventions and where outcomes are comparable. Comparison of the DIAMOND and KUDOS trials provides a starting point for such efforts. Although the comparisons cannot be considered definitive, this paves the way for future trials to harmonize outcomes and brings us one step closer to understanding whether the effects of nutrition are mediated by sensitive periods of human development.

Recommended reading

Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr. 2013 Aug;98(2):403–12.

Annales Nestlé

Young Brain – Big Appetite

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Critical and Sensitive Periods in Development and Nutrition

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Key Messages

- The concept of *critical period* is often invoked with reference to phenomena in the field of nutrition. The history and evolution of the critical period concept in development is briefly reviewed.
- A critical period (or its less restrictive form, a *sensitive period*) carries with it a number of methodological criteria that are typically not met in the literature on early nutrition.
- The phenomenon of *programming* is placed within this developmental concept.
- Implications of these developmental phenomena for the design of preclinical research and clinical trials that seek to demonstrate true programming or critical/sensitive period effects are described.

Keywords

Critical period · Sensitive period · Nutritional programming

Abstract

Critical or sensitive periods in the life of an organism during which certain experiences or conditions may exert disproportionate influence (either for harm or benefit) on long-term developmental outcomes have been the subject of investigation for over a century. This chapter reviews research in the context of the development of social preferences and sensory systems, with a summary of the criteria for defining such a period and the evidence necessary to establish its existence. The notion of nutritional programming, central to the Barker/Developmental Origins hypotheses of health and disease, represents a variant of the critical/sensitive period concept. It is implicit in these hypotheses that the fetal period is a time during which metabolic and physiological systems are malleable and thus susceptible to either insult or enhancement by nutrient intake. Evidence for critical/sensitive periods or nutritional programming requires a systematic manipulation of the age at which nutritional conditions or supplements are implemented. While common in research using animal models, the approach is difficult to establish in epidemiological studies and virtually nonexistent in human clinical trials. Future work seeking to establish definitive evidence for critical/sensitive periods or programming may be advanced by harmonized outcome measures in experimental trials across which the timing, duration, and dose of nutrients is varied.

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Critical and Sensitive Periods in Development

The idea that early nutritional status is critical to lifelong health is pervasive in the scientific literature [1]. Although much of the writing on this topic has been focused on the potential early-life determinants of adult obesity [2–5], much has also been written about the importance of nutrition in the first 1,000 days following conception [6] and the potential impact of nutrition and nutritional status on both biological [7] and behavioral [8] systems later in life.

In many of these papers, authors make direct reference to *critical periods* as a developmental basis for these proposals [9, 10]. While the critical period phenomenon has been a topic of extensive discussion in the biobehavioral and developmental sciences, there have been few detailed expositions of the concept and its implications within the nutrition literature. One objective of this chapter is to provide a background on the history of and criteria for critical periods for nutrition researchers. A second objective is to integrate the notion of fetal/neonatal programming – a common concept within the nutrition field – within the framework of critical periods and developmental science. Finally, the chapter seeks to delineate the implications of critical/sensitive periods for the design of future preclinical research and clinical trials.

The effect of exposures to toxic substances on developing embryos was observed to vary systematically with the timing of the exposure

History of the Concept of Critical Periods

As noted above, the concept of critical periods has a long history in the field of developmental psychology [11–13]. The basic phenomenon was first identified from research in embryology [14], where the effect of exposures to toxic substances on developing embryos was observed to vary systematically with the timing of the exposure. Toxic exposures occurring in the embryonic period produced pervasive and severe effects across multiple biological systems; however, the same exposure or dose later in development resulted in somewhat milder effects, which were constrained more narrowly to particular or specific systems. Indeed, the same exposure applied even later in development might have no demonstrable effects or result in effects evident only upon systemic challenges or stressors. These common sequelae led investigators to the logical conclusion that the biological systems were broadly malleable very early in life, and that as the organism matured and those systems became settled in form and function, they became less vulnerable to environmental insult.

Imprinting and Critical Periods

The extension of this work to the behavioral sciences came with Lorenz's [15] exposition of *imprinting* in birds. In this phenomenon, precocial bird species developed strong social preferences for objects to which they were exposed immediately after hatching; young birds would then attach emotionally and maintain proximity to such objects until fledging. The evolutionary adaptiveness of this phenomenon is obvious, as hatchlings are typically exposed immediately after hatching to their own mother (or at least, a conspecific from the same species), and a neural mechanism that promoted hatchlings' emotional and physical affiliation with their mother very likely increased the probability of their survival. Indeed, this framework was adapted for use in the early evolutionary-based accounts for explaining human infants' attachment to their own mothers [16].

Of critical importance to the current discussion, however, two points shaped future thinking about the nature of critical periods in development. First, the nature of the objects to which hatchlings could be imprinted was extremely general; during this period young birds could be manipulated to form social preferences for nearly any object, whether it was Lorenz [17] himself or a moving tennis ball [18]. The other points were derived from Lorenz's claim that the development of these strong social affiliations could only be formed during a very brief period of time during the hatchlings' development – once imprinting had occurred, it could not be undone [19] – and that nonimprinted organisms were not able to imprint beyond the hatchling period [20]. Thus, the effects of exposure during this early period of life were claimed to be both irreversible and unrecoverable, thus bringing about the label of the period as *critical*. However, much of the literature that emerged immediately after these initial claims demonstrated substantial reversibility and flexibility [21] in imprinting. Thus, while the early period of life might represent heightened malleability or plasticity, the period might not be as rigidly bound or essential as it had originally been designated, making the term *sensitive period* more appropriate. The phenomenon was later generalized to the notion of *food imprinting*

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[22–25] in several species, where the food preferences typically exhibited by certain animals could be substantially altered by early exposure to alternate foods.

Critical Periods in the Development of the Visual System

The 1960s and 1970s produced the most comprehensive descriptions of critical periods in mammalian biology and behavior in Hubel and Wiesel's program of research on the development of the visual system in the cat [26–28]. Briefly, these investigators used techniques for measuring the activity of single neurons in the cat visual cortex, mapped the responsiveness of these neurons to different visual stimuli, and then sought to map the maturation of this neuronal activity from birth to adulthood. While some neurons in the visual cortex were dedicated from birth to processing specific types of input (e.g., accepting from one or both eyes, or responding to horizontal vs. vertical bars), they also determined through careful experimentation that the fate of many cells in the cortex was determined by both the quantity and quality of postnatal input [29, 30] and that the period during which that input was received was limited to the first 4–7 weeks of life. Similar to imprinting, recovery of normal vision after deprivation of input during that period of life was initially reported to be limited [31], suggesting that this was another clear manifestation of a true "critical" period. These findings from the cat were largely confirmed in primates [32, 33], and observational studies of humans deprived of various visual input were found to be generally consistent with the principles outlined in this work [34–36].

Since the emergence of this seminal line of research in biobehavioral development, numerous refinements have been explored in isolating the specific mechanisms underlying the early plasticity of the system and the processes which bring that plasticity to an end [37]. For example, it is clear that this is a sensitive period, rather than a critical period, as some level of recovery of visual function can be attained after the end of the period [38, 39]. In addition, eye movements play a major role in the neural processing that contributes to the dedication of neurons to visual inputs [30], and both the onset and the eventual end of the sensitive period is triggered by the initiation of visual input [40]. In keeping with the general principles of early plasticity, early disruptions in the normal course of sensory exposure have been found to alter the order in which sensory systems develop and in which sensory preferences or priorities are expressed in postnatal life [41, 42].

Summary

The phenomenon of critical/sensitive periods in biobehavioral development has been explored in domains beyond that of imprinting and sensory systems; for example, there is also a substantial literature on a critical/sensitive period for language development [43–45]. Several generalities can be drawn from this brief and admittedly perfunctory review, however. First, the principles regarding early vulnerabilities of organisms to frank environmental insult or compromise appear to be reliable and robust; early damage will yield severe and widespread effects, while later damage will tend to be less severe and more specifically localized. Second, in the behavioral realm, wherever a "critical" period has initially been described, including claims of absolute irreversibility or inability to recover from deprivation, subsequent work has generally shown that some degree of recovery is possible under special conditions or with targeted remedial actions. Organisms may be both *relatively more vulnerable* to environmental deprivation and *relatively better able to benefit* from environmental enhancement early in life, but it is likely better to characterize these early periods of malleability as *sensitive periods* rather than truly critical periods [13]. Figure 1 schematically represents the difference between "critical" and "sensitive" periods and their interaction with both positive (beneficial) and negative (harmful) events. That said, given that evidence suggests that early interventions will be relatively (rather than absolutely) more effective than later interventions, there is clear economic value in understanding these developmental principles.

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Scott et al. [46] have offered one characterization of these phenomena in development, noting that critical/sensitive periods merely represent periods of rapid development within systems, such that enhancement or deprivation during these periods of emergent and rapid maturation can respectively bring either substantial benefit or wreak substantial havoc on the systems involved. As has been summarized previously [11], if there are qualitatively distinct stages of malleability in development, then one must define them in terms of the specific system involved, as well as by the onset and terminus of the period and the specific inputs that are presumed to enhance or disrupt normal development.

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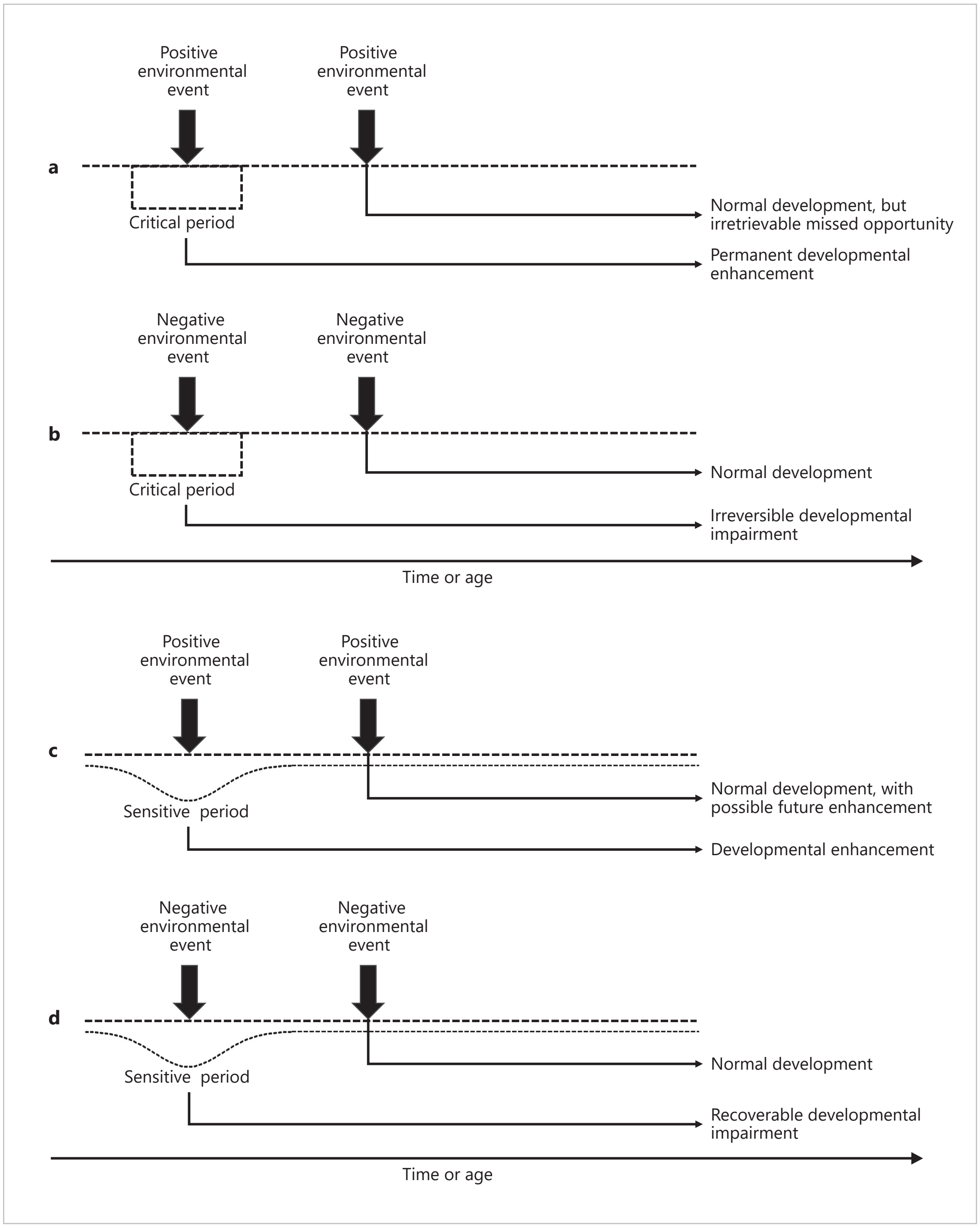

Fig. 1. Schematic representation of the difference between a critical period (**a**, **b**) and a sensitive period (**c**, **d**). Time/age moves from left to right. Note that, in a critical period, the period of malleability or plasticity is sharply defined as a box, with a clear beginning and end, and no gradient over time. In a sensitive period, the degree of plasticity is relatively higher, but plasticity never ends. As a result, the end states from a critical period are irreversible or irretrievable, while in a sensitive period some degree of future enhancement or future recovery from harm is possible.

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At this point, we turn to discuss *programming*, a phenomenon similar to the critical/sensitive period as referenced in the nutrition literature.

Early Programming and Critical Periods

The notion of *nutritional programming* [47] is a popular one among the nutrition science community; a search on the phrase in Google Scholar™ in late 2019 generated over 190,000 entries. This notion emerged from a comprehensive epidemiological study of the Dutch hunger winter [48] in which food shortages precipitated by weather, bad crops, war, and a Nazi embargo of food transport to parts of the Netherlands limited pregnant women's nutritional intake to only 400–800 calories per day. This restricted intake resulted in a remarkable increase in the incidence of coronary heart disease in the offspring whose mothers' were exposed to restricted food intake early in gestation, markers of reduced renal function among those exposed in mid-gestation, and lifetime growth restriction among those exposed late in gestation [48]. The *Barker hypothesis* was derived from observations in the UK that disproportionate fetal growth in middle to late gestation programmed later coronary heart disease in the offspring. The hypothesis regarding the fetal origins of adult disease expanded to the *Developmental Origins hypothesis* [49–52], the notion that, by influencing epigenetic processes, metabolic set points, or early inflammatory status, prenatal nutrition in some way "programs" the fetus or maladaptively prepares the fetus for an environment that will induce adiposity/obesity [53, 54] or other metabolic-based diseases [55]. It is a clear implication of the Barker/Developmental Origins hypothesis that the early part of life is in some way special in its malleability or capacity for enacting long-term changes in the organism. Such studies would presume to reveal a critical-period phenomenon in that it is the early stages of the organism's development that serves as a causal vehicle for the efficacy of the exposure. Furthermore, the notion that the organism is "programmed" comes from the fact that the outcomes associated with fetal conditions reach far into the future and represent health and neurodevelopmental status in adulthood.

A key point about the original Barker study was that, for an observational study, it controlled fairly well for the timing of the deprivation. For example, subsequent secondary analyses noted that the effects varied as a function of the gestational state of the fetus [56]; malnutrition in early pregnancy was associated with a higher risk of coronary heart disease and accelerated cognitive aging [57], mid-gestation exposure had an increased prevalence of bronchial disease, and late/mid-gestation exposure was related to poorer glucose metabolism. It is not a far reach to extrapolate this to the idea that early nutrition extending into the postnatal period may also bring about programming effects; indeed, this case has been made for a number of different functions [58–60], and this argument takes on immediate weight given what is known about the postnatal development of the central nervous system and the potential effects of certain nutrients on brain and behavioral function [61–63].

Age and Timing in Nutritional Studies

Like much of the critical/sensitive-period research, studies lending support to early nutritional programming have largely been conducted with animal models [64]. While it has been argued that the animal data coupled with human clinical trials showing the effects of early nutritional manipulations are compelling [65], in the absence of systematic experimental data in which the age of exposure is manipulated, claims about early nutritional programming remain largely speculative.

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In order to definitively establish a true critical/sensitive period or programming effects, one must manipulate the timing of the early intervention [11]. That is, it must be shown that vulnerability to risk or ability to benefit from enhanced conditions at a particular time during development is either absolutely or relatively higher at one time during development over others. Of course, human studies to experimentally vary the timing of adverse interventions to demonstrate the critical/sensitive period-programming effects are unethical, but it is possible and ethical to focus on timing in clinical trials that purport to provide interventions that benefit to their participants; indeed, from an economic point of view, one could argue that such a focus is necessary. Furthermore, going back to the original point in the critical period phenomenon about

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the dose of exposure interacting with timing [11], one might further argue that designs featuring dose × timing interactions would be ideal.

Even a quick perusal of the literature, however, shows that the extant nutrition clinical trials almost entirely exclude the timing or age at which manipulations are implemented. For the most part, nutritional interventions are implemented as early as possible in infancy, and if they show efficacy that persists, as has been established in some cases [66], it is tempting to propose that an early programming effect has taken hold. However, in the absence of exposure to a nutrient for an equivalent duration at a later age, it is by no means clear that this programming effect is endemic to early prenatal or postnatal life. Those who design such trials likely understand the potential importance of timing well, but the conduct of such trials obviously requires tremendous resources to simply establish efficacy; establishing that a nutrient's efficacy is greater at one age than at another may seem like a luxury. However, until there is evidence that benefit varies with the age at which a nutrient is provided, one cannot have evidence for a critical/sensitive period or for an age-specific programming effect.

In the absence of clinical trials that comprehensively address the issue of age and timing in their designs, one way to examine the relative efficacy across ages is to compare completed trials that have varied the age of their interventions, but where outcome measures were more or less harmonized. This has been done to some degree for the examination of differences in outcome as a function of dose [67], although dose still remains an understudied factor in much of the literature on early nutrition. One potential example approximating this approach is represented by 2 trials conducted in our laboratory over the last 2 decades. The DIAMOND trial [66, 68] involved postnatal supplementation with 4 doses of docosahexaenoic acid (DHA) but with a constant level of arachidonic acid (ARA) compared to a placebo. The KUDOS trial [69–71] involved prenatal supplementation with 1 dose of DHA, again compared to a placebo. While the trials are too different in their manipulation and in their fundamental sample demographics to compare directly here, they do share a fair number of harmonized outcome variables in the domain of postnatal cognitive development to invite a putative inference that postnatal supplementation might produce more pervasive long-term positive effects on infant child neurocognition [72] than prenatal supplementation. On the other hand, the prenatal supplementation produced clear metabolic effects [73] that were not evident from the postnatal trial. While these outcomes and comparisons cannot be considered definitive, they do invite a vision of what might be possible with broadly harmonized outcomes for clinical trials in the future in the field of nutrition.

Summary and Conclusions

Critical and sensitive developmental periods have been key concepts in developmental science for over a century; they have a long history for biobehavioral development and have particularly special importance with respect to the plasticity of the brain. In such developmental periods, certain experiences, exposures, or conditions are thought to exert disproportionate influence over the long-term development of the organism due to the fact that the organism is in a particularly malleable state. Examples of putative critical/sensitive periods in biobehavioral development include the establishment of social and food preferences (imprinting), shaping the structure and function of sensory systems, and possibly the area of language and language acquisition. There is still considerable debate over the nature of critical/sensitive periods, but one hypothesis is that such phases are simply the epiphenomenon of systems that are undergoing rapid maturation or change.

While critical- and sensitive-period concepts have often been used with respect to studies of early nutrition, they also underlie the concept of nutritional programming, as the implication of programming (particularly within the context of the Fetal/Developmental Origins hypothesis) is that the prenatal period is presumably a time when various metabolic systems are malleable and can be influenced by conditions of maternal physiology and environmental exposures, including nutrient intake.

Critical to the establishment of any critical/sensitive period (and by extension, to any claim for prenatal programming) is the demonstration that an intervention shows improved efficacy when implemented at one age relative to other ages. For example, in order to establish the existence of a critical period for omega-3 effects on neurodevelopment, one would have to show that supplementation at, say, birth to 6 months of age, would have far more influence on outcome measures than supplementation from 6 to 12 months; obviously, from a design standpoint, this would necessitate feeding 2 age groups for an equivalent duration. While parametric manipulation of the age of nutritional interventions is relatively commonplace in animal models, the results of preclinical studies do not necessarily translate to human trials [74], and so, any conclusion about the critical/sensitive periods in nutrition or nutrition programming must be viewed as speculative. It may be that if enough trials have harmonized outcomes, meta-analyses that include age of feeding, duration of feeding, and dose would advance the field as close as possible to answering this question.

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Focus

Sleep does not only play important roles in learning and memory, but it can also stimulate creative thinking

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Sleep and Early Brain Development

Fan Jiang

Key Insight

Sleep is one of the primary activities of the brain during development and plays an important role in healthy cognitive and psychosocial development in early life. However, little is known about how sleep benefits children's memory or learning. Some of the differences between how children and adults process newly acquired information have been attributed to age-dependent differences in the types of sleep-related processing applied to memory and learning. Compared to adults, children have increased slow-wave sleep (deep sleep). The time spent in deep sleep at night, as well as daytime napping, have beneficial effects on learning in children. Sleep also has an impact on a broad range of outcomes, such as emotional regulation and cortical maturation.

Practice	Description
Regular, consistent bedtime routine	A bedtime routine should involve the same 3 to 4 calming and relaxing activities every night in the same order, e.g., warm bath, reading stories, singing, and listening to soft music
Safe and comfortable sleeping environment	The sleep environment should be calm, quiet, dark and with cooler temperatures. Place babies to sleep on their backs and remove unnecessary objects
Appropriate sleep onset associations	Facilitate the sleep onset transition. Put infants to bed when they are drowsy but still awake, encourage them to fall asleep on their own without parental interventions
Avoid media exposure	Reduce media exposure, particularly in the evening. Remove electronic devices from the sleeping environment
Regular daily schedule of activities	Timing of daily activities consistent with the natural rhythm of day and night. Sun exposure, outdoor activities, and mealtimes should be coordinated to regulate the sleep-wake cycle

Positive sleep practices are essential for establishing a healthy sleep pattern during the first years of life.

Current knowledge

Sleep is characterized by reduced motor activity and decreased interaction with the external environment. It is also associated with a specific posture (e.g., lying down) and with easy reversibility. With respect to sleep, the neurophysiological systems have been classified into 3 functional states: non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and wakefulness. Each state is distinctly associated with a discrete pattern of brain electrical activity. Sleep patterns evolve with age, particularly during the first 5 years of life. Early childhood is a critical period for the transition to the normal pattern of sleep-wakefulness, characterized by nighttime sleep consolidation and daytime sleep discontinuation.

Practical implications

So, what is considered a healthy sleeping pattern for children? The National Sleep Foundation, the American Academy of Sleep Medicine, and the American Academy of Pediatrics have issued similar recommendations for sleep duration in the pediatric population. It is important to note, however, that these guidelines were created from a population-wide standpoint; in the clinical setting, these need to be individualized for each patient. Parental sleep-setting behaviors play an important role in establishing a healthy sleep pattern in infants. It is recommended that parents begin promoting good sleep hygiene by establishing a safe and comfortable sleep environment, a regular bedtime routine, and an appropriate sleep onset association starting from infancy and throughout childhood.

Recommended reading

Mindell JA, Williamson AA. Benefits of a bedtime routine in young children: Sleep, development, and beyond. Sleep Med Rev. 2018 Aug;40:93–108.

Annales Nestlé

Young Brain – Big Appetite

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Sleep and Early Brain Development

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Key Messages

- Sleep pattern changes dramatically in early childhood.
- Establishing a healthy sleep pattern in early life is very important for child development.
- Sleep plays a critical role in learning and memory, emotional regulation, and related brain structure development.

Keywords

Brain development · Early childhood · NREM and REM sleep

Abstract

The early years of life are characterized by dramatic developmental changes. Within this important time period lies the transition from newborn to childhood. Sleep is one of the primary activities of the brain during early development and plays an important role in healthy cognitive and psychosocial development in early life. This paper will first review the normal sleep characteristics and their development in neonates and children, including architecture of sleep, development of a healthy sleep rhythm in early childhood, sleep recommendations and cultural disparity, as well as important factors for establishing a healthy sleep pattern during the first years of life, such as regular and consistent bedtime routine, safe and comfortable sleep environment, and appropriate sleep onset associations. This paper then provides recent updates of evidence of the effects of sleep on early brain development, particularly on learning and memory, emotional regulation, and general cognitive development through behavioral and neurophysiological studies. As regards the mechanism, many experimental sleep deprivation studies in animals and adults have attempted to explain the underlying mechanisms of sleep on cognition and the emotional brain. Future studies are expected to delineate the effects of sleep on brain structural and functional networks in the developing brain with the marked development of image acquisition approaches and the novel analysis tools for infants and young children in recent years.

Sleep and Early Brain Development

The early years of life are characterized by dramatic developmental changes. Within this important time period lies the transition from newborn to childhood [1]. Sleep is one of the primary activities of the brain during early development and also plays an important role in healthy cognitive and psycho-

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social development in early life [2]. This paper will first review the normal sleep characteristics and their development in neonates and children, followed by recent updates of the evidences of the effects of sleep on early brain development, particularly on memory functions and emotional control.

Normal Sleep and Its Development in Neonates and Children

Definition and Architecture of Sleep

Sleep is defined as a behavioral state characterized by reduced motor activity, decreased interaction with the external environment, a specific posture (e.g., lying down, eyes closed), and easy reversibility. The architectural organization of sleep refers to the coordination of independent neurophysiologic systems into 3 distinct functional states: non-rapid eye movement (NREM) sleep, rapid eye movement (REM) sleep, and wakefulness. Each state is distinctly associated with a discrete pattern of brain electrical activity [3].

NREM sleep is believed to function primarily as a restful and restorative sleep phase. NREM sleep also represents a time period of relatively low brain activity during which the regulatory capacity of the brain continues to be active and body movements are preserved. Using electroencephalogram, NREM sleep is conventionally subdivided into 3 stages (stages 1, 2, and 3), which roughly parallel a depth of sleep continuum, with arousal thresholds generally the lowest in stage 1 and highest in stage 3 sleep (stage 3 sleep is also called slow-wave sleep [SWS] or deep sleep). NREM sleep is usually associated with minimal or fragmentary mental activity.

REM sleep, also called "dream" sleep, is characterized by desynchronized cortical activity with low-voltage and high-frequency electroencephalogram. REM is typically thought to play a role in consolidating and integrating memories as well as in the development of the central nervous system – both maintaining and establishing new connections particularly during the time period of early brain development [4]. The mental activity of human REM sleep is associated with dreaming. The other important characteristic of REM sleep is the absence of skeletal muscle tone, meaning that people cannot move their body and limbs when they have vivid dreams.

NREM and REM sleep alternate in cycles throughout the night, which is called ultradian rhythm [4]. The relative proportion of REM and NREM sleep per cycle changes over night, and stage 3 NREM sleep (known as deep sleep) dominates the first 1/3 of the night, while REM sleep dominates the last third. In other words, the percentage of deep sleep declines and REM sleep increases over the course of the night.

The Development of a Healthy Sleep Rhythm in Early Childhood

The sleep patterns change with age during the first years of life. The characteristics of sleep-wakefulness states during early development originate from the rest-activity cycles in the fetus and the early months after birth. Sleep states are categorized as active sleep, quiet sleep, and indeterminate sleep in very young babies. By the second half of the first year, quiet sleep gradually transitions into NREM sleep, which could be further divided into 3 stages as outlined above. Meanwhile, the active sleep characterized by frequent muscle twitches and grimaces turns into REM sleep. After 6 months of age, the electronical patterns of NREM and REM sleep progressively resemble those seen in adults [5].

After 6 months of age, the electronical patterns of NREM and REM sleep progressively resemble those seen in adults

Early childhood life is a critical time period when normative transition of sleep-wakefulness patterns occurs, which is characterized by nighttime sleep consolidation and daytime sleep discontinuation. Starting from newborn babies to preschool children, 24-h sleep duration declines dramatically by decreasing both daytime and nighttime sleep amounts. Particularly, diurnal sleep gradually declines, while the extent to which nighttime sleep decreases is less remarkable during this period of time. Newborns (0–3 months) do not have an established circadian rhythm, and day/night reversal is common in the first few weeks after birth [6]. The regular rhythm of periods of sleepiness and alertness emerges by 2–3 months of age and becomes more nocturnal between the age of 4 and 12 months [7]. While children continue to take daytime naps between 1 and 4 years of age, the number of naps decreases from 2 naps to 1 nap by 18 months on average, and this typically stops by the age of 5 years [8].

Not only sleep duration but also sleep architecture and sleep cycle change with age. The proportion of REM sleep dramatically decreases from birth (50% of sleep) through early childhood into adulthood (25%). The proportion of deep sleep peaks in early childhood and then decreases over the lifespan. The ultradian cycle, which means the nocturnal cycle of sleep stages, is about 50 min in infancy and gradually increases to an adult level, about 90–110 min, by school age [5].

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Table 1. The recommended amount of sleep and sleep quality for children under 5 years old by the National Sleep Foundation in the USA [10, 11, 15]

Age category	Sleep duration per 24 h			Sleep quality		
	recommended	may be appropriate	not recommended	sleep latency[a]	awakenings (>5 min)[b]	Sleep efficiency[c]
Infants (4–12 months)	12–15 h	10–11 h 16–18 h	less than 10 h, more than 18 h	less than 30 min	na	85%
Toddlers (1–2 years)	11–14 h	9–10 h 15–16 h	less than 9 h, more than 16 h	less than 30 min	less than 2 per night	85%
Preschool children (3–5 years)	10–13 h	8–9 h 14 h	less than 8 h, more than 14 h	less than 30 min	less than 2 per night	85%

[a] Sleep latency: length to time, in minutes, it takes to transition from wakefulness to sleep. [b] Awakenings (>5 min): number of episodes, per night, in which a child is awake for more than 5 min. [c] Sleep efficiency: ratio of total sleep to time in bed.

Sleep Recommendations and Cultural Disparity

In a clinical setting, one of the most common questions from parents is "what is healthy sleep for children?" Generally, healthy sleep requires adequate duration, appropriate timing, good quality, regularity, and absence of sleep disturbances or disorders [9]. Although genetics plays an important role in the individual variability of sleep need, many healthy sleep practices can help children to achieve age-appropriate amounts of sleep with good quality from the very beginning of their life. To develop scientifically sound and practical recommendations for sleep duration, the National Sleep Foundation (NSF) in the USA convened a multidisciplinary expert panel to evaluate the latest scientific evidence, including a consensus and voting process in 2015 [10, 11]. Later, the American Academy of Sleep Medicine and American Academy of Pediatrics (AAP) issued similar recommendations for sleep duration in the pediatric population [12, 13]. The only difference of the recent guideline is that the 2 organizations did not include recommendations for infants younger than 4 months old owing to a wide range of normal variations in duration and patterns of sleep and insufficient evidence of their associations with health outcomes. In 2017, the NSF published evidence-based recommendations and guidance to the public regarding indicators of good sleep quality for children under 5 years of age [14], which are summarized in Table 1. Nevertheless, it is worth noting that even though the normative sleep duration values are helpful and inform what constitutes the norm and what is considered outside the norm for a given age, these references provide norms at the population level standpoint and need to be individualized for each patient in the clinical setting [15].

The culture milieu is of importance for the understanding and evaluation of child sleep duration and patterns [16]. We recently systematically reviewed 102 studies with 167,886 children aged 0–3 years from 26 different countries across the world. Our results indicated that an apparent cross-cultural disparity of the sleep parameters already exists in early childhood [17]. Specifically, the predominantly-Asian (PA) toddlers had a shorter sleep duration and more frequent night wakings when compared to their predominantly-Caucasian (PC) peers under 3 years of age. But the cultural difference of total sleep duration is not exactly the same across age groups. The total sleep duration of the PA cohort was more than that of the PC samples in the first 3 months of life but dropped below the PC samples beyond 3 months of life. More importantly, it seems that the PA children are not born with a shorter sleep duration and the intersection of the sleep duration trajectories between the PA and PC children occurs around 3 months old (Fig. 1a, b). We believe that parental sleep-setting behaviors contribute largely to the observed disparity of the sleep parameters between the PA and PC children. For example, parental nighttime involvement and nightly bedtime routine will play a major role in a baby's sleep [18–20]. Mindell et al. [19, 20] studied cultural differences of parental sleep settings for many years and indicated that children from the PA regions were much more likely to be engaged with their parents, to partake in maladaptive activities (for example, inappropriate sleep associations including rocking, nursing, and swinging) and were less likely to have a consistent bedtime routine than those from the PC regions. Trends of nighttime sleep duration for the PC regions showed rapid changes over the first 3–6 months before stabilizing to a plateau, whereas nighttime sleep duration for the PA regions exhibited a slight change across different states in early life with an increase initially, followed by a decrease. The cross-cultural disparities of the age-related trends for sleep parameters over the first 3 years of life can be found in Figure 1.

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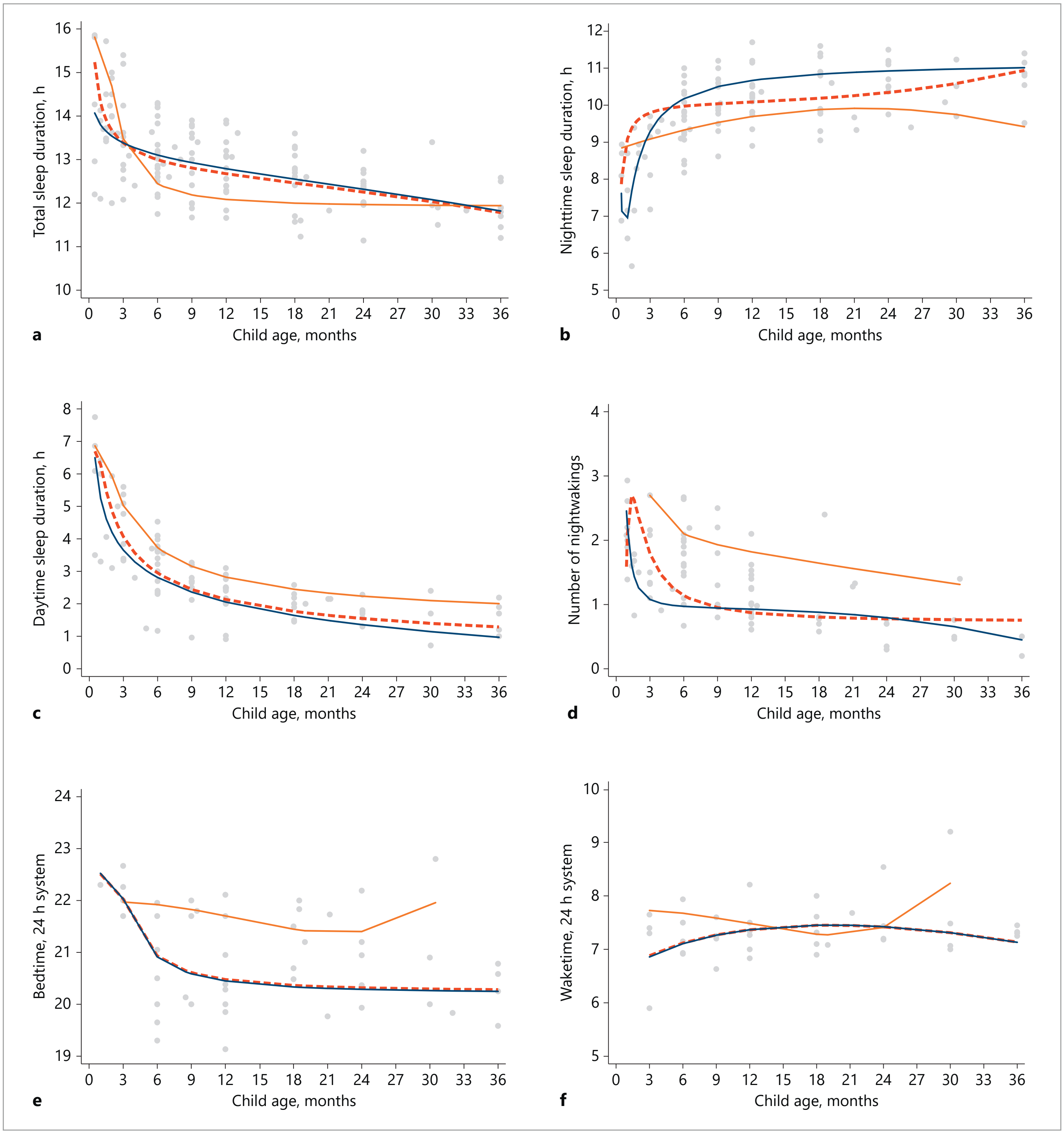

Fig. 1. Cross-cultural disparities of the developmental trajectory (weighted by sample size) for sleep parameters over the first 3 years of life. Grey dots represent the samples. The orange line represents the trajectory curve fitted by the data from the Asian region samples; the dark blue line represents the non-Asian region samples; and the red dashed line represents all samples. **a** Total sleep duration. **b** Nighttime sleep duration. **c** Daytime sleep duration. **d** Number of night wakings. **e** Bedtime in the evening. **f** Waketime in the morning [17].

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Important Factors for Establishing a Healthy Sleep Pattern during the First Years of Life
Positive sleep practices (known as "sleep hygiene") are essential for establishing a healthy sleep pattern during the first years of life. Thus, it is recommended that parents start promoting good sleep hygiene by establishing a safe and comfortable sleep environment, a regular bedtime routine, and an appropriate sleep onset association starting from infancy, and throughout childhood [21].

Regular and Consistent Bedtime Routine
Having a regular and consistent bedtime routine is one of the critical steps to achieve good sleep hygiene and yield health benefits to young children. It provides them a sense of predictability and security and helps with activity transitions. Bedtime routines deliver external clues to children that sleep is coming and assist them in preparing for sleep mentally by being both predicable and calming. A bedtime routine should involve the same 3–4 calming and relaxing activities every night in the same order, e.g., warm bath, reading stories, singing lullabies, and listening to soft music. A pictorial representation of the bedtime activities is recommended for children at a younger age or developmentally delayed.

A bedtime routine should involve the same 3–4 calming and relaxing activities every night in the same order

Safe and Comfortable Sleep Environment
Maintaining a safe and comfortable sleep environment could promote adequate sleep quantity and quality. Usually, a comfortable sleep environment should be calm, quiet, dark, and with cooler temperatures. Prevention of accidental suffocation and strangulation are key considerations, especially for young babies. The crib mattress should provide a firm sleeping surface and fit tightly in the crib. Removal of all pillows and stuffed toys from the crib is recommended. The AAP recommends that the baby should be placed on his or her back to sleep at night and during naptime as evidence has shown that sleeping in a prone position significantly reduces the risk of sudden infant death syndrome [21]. In addition, the sleep environment around babies should be a "smoke-free zone."

Appropriate Sleep Onset Associations
Sleep onset associations are those conditions that are present at the time of sleep onset as well as in the night following nighttime arousals. The "inappropriate" or problematic sleep onset associations refer to the conditions where infants require parental interventions, e.g., being rocked or fed. Infants with inappropriate sleep onset associations have been shown to be vulnerable to developing frequent night wakings. In order to avoid developing inappropriate sleep onset associations, the most important sleep behavior for a given infant to learn is the ability to self-soothe and fall asleep independently [22]. Specifically, putting infants to bed when they are drowsy but still awake and leaving them to go from drowsy to asleep on their own is a recommended approach for infants to develop appropriate sleep onset associations. Transition objects, such as blankets, dolls, and stuffed animals, could also help young children to foster independence and self-soothing to fall asleep.

Avoiding Media Exposure
It has been widely reported that young children have been exposed to significantly more media over the past few decades, and media exposure can negatively impact children's sleep duration and quality and may lead to sleep difficulties [23, 24]. Media (such as smartphones, iPad, and desktop and laptop computers) will not only interfere with a relaxed state required for sleep initiation, but also suppress the normal evening surge in melatonin and alter the sleep-wake cycle via light exposure. Parents are strongly encouraged to remove TVs and electronic devices from the child's sleeping environment.

Regular Daily Schedule of Activities with Appropriate Stimulations
Babies should be encouraged to develop a consistent age-appropriate schedule of sleep, outdoor activities, and mealtime to help regulating the internal clock and synchronize the sleep-wake cycle. For example, getting daily exposure to the sun especially in the morning and avoiding direct light exposure in the evening could appropriately regulate melatonin secretion to further promote sleep regulation. Evidence accumulated during recent years suggests that mealtimes can also affect the sleep-wake cycle [25].

Sleep and Early Brain Development

Learning and Memory
Sleep has been implicated to play a critical role in memory functions of the adult brain and is thought to favor the "off-

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line" processing of new memories [26]. Two types of sleep have been shown to be associated with different memory processing. The role of NREM sleep, especially SWS, is reactivation of the hippocampal-neocortical circuits activated during a waking learning period, while REM sleep is responsible for the consolidation of the new learning into long-term memory [27]. While the aforementioned information is informative about our understanding of the roles of sleep in adult memory function, how sleep benefits children's memory remains largely unknown.

It is explicit that the means through which children learn are very different from those of adults. Children rely more on rote learning other than knowledge-based learning, which is common in adults [28]. Wilhelm et al. [29] found that school-age children showed greater sleep-dependent extraction of explicit (or declarative) knowledge of the rules that govern an implicit procedural task than do adults. They further suggested that at least some of the differences in how children and adults process newly acquired information result from age-dependent differences in the forms of sleep-dependent processing applied to such memory. Pisch et al. [30] investigated whether the particularly high inter-individual differences in infant sleep duration and fragmentation are indicative of cognitive developmental trajectories examined by eye-tracking over a prolonged time period. They found that children spending less time awake during the night in early life were associated with better performance of a working memory task. Although several physiological explanations could account for the observed improved performance, it is highly plausible that the increased deep sleep (SWS) duration during the night in children is one of the main reasons.

Not only the whole night sleep but also daytime nap is related to declarative memory performance. The benefit of daytime nap on memory was also observed in infants and toddlers. Hupbach et al. [31] found that 15-month-old infants who had napped within 4 h of language exposure remembered the general grammatical pattern of the language 24 h later, while the infants without napping showed no evidence of remembering anything about language. More importantly, their results were confirmed by another research team which reported that nap facilitated generalization of word meanings, as indicated by event-related potentials [32]. Another study by Seehagen et al. [33] found that having an extended nap (≥30 min) within 4 h of learning a set of object-action pairings from a puppet toy enabled 6- and 12-month-old infants to retain their memories of new behaviors over a 4- and 24-h delay. These findings support the view that infants' frequent napping may play an essential role in establishing long-term memory.

Two studies examined the effects of daytime nap on recognition tasks and generalization of word meanings in preschoolers and confirmed the positive role of sleep in explicit memory consolidation [34, 35]. However, these results were not consistent with those reported by another study, which found that wakefulness (not sleep) promotes generalization of word meanings in children 2.5 years old [36]. Horváth et al. [35] speculated that the contrasting findings from these studies could be explained by 2 reasons. One possible reason is the developmental changes in the preferred sleep-dependent memory consolidation across early childhood. However, many studies in adults have also reported sleep-dependent generalization. Thus, it is plausible that other factors may have contributed to the observed inconsistent results, including, but not limited to, the change in background color and texture, the requirement of pointing in Werchan's task, or the circadian effects. Additional studies focusing on the potential benefits of daytime nap on cognitive development in children will be needed.

Sleep does not only play important roles in learning and memory, but it can also stimulate creative thinking. It is widely believed that sleep plays a role in the flashes of insight, for example. The Nobel Prize winner Loewi reported that he woke up with the essential idea for an experiment confirming the principle of chemical neurotransmission. The famous German chemist Kekule spoke of his great creation of ring-like structure of benzene and said that he had discovered the ring shape of the benzene molecule after having a daytime nap. Nevertheless, the hypothesis of sleep stimulating creative thinking was not proven until a well-designed study was conducted by a German group, which showed that sleep, by restructuring new memory representation, facilitates extraction of explicit knowledge and insightful behavior [37]. Since then, a few studies have further explored the association between sleep, especially REM sleep, and creative behaviors [38–40]. Nevertheless, in contrast to the ample evidence linking sleep and memory function, the relationship between sleep and creative thinking has not been widely studied and confirmed, most likely attributed to the challenges of a well-defined method of investigating insight/creative thinking [41], especially in young children.

Emotional Regulation

Sleep plays a critical role in mental health and psychosocial adjustment across the lifespan. A growing body of research has suggested that inadequate sleep leads to more negative and less positive emotions [42]. In addition, the impact of sleep on next-day mood/emotion is thought to be particularly affected by REM sleep [43]. During REM sleep, a hyper-limbic and hypoactive dorsolateral prefrontal activation and a normal function of the medial prefrontal cortex may explain its adaptive role in coping with emotional events [43].

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The impact of sleep on next-day mood/emotion is thought to be particularly affected by REM sleep

Actually, the effects of sleep on emotional regulation could be traced back to the neonatal period. It is noteworthy that active (or REM) sleep accounts for the biggest portion of a child's sleep, and it is likely to subserve crucial emotional function [44]. It was observed that the neonatal smiles, particularly Duchenne smiles, which involve lip corner raising with cheek raising, tend to predominate in active sleep compared to during wakefulness or other sleep states, suggesting a potential tie to early constituents of emotion [45]. An imaging study of 3- to 7-month-old infants revealed specific brain regions responding to emotional human vocalizations during sleep, including the orbitofrontal cortex and insula [46]. Not only REM sleep, but also sleep structure and quiet sleep (NREM sleep) contribute to children's emotional function. A longitudinal cohort study of premature infants found that premature infants with sleep state transitions characterized by shifts between quiet sleep and wakefulness at gestational age 37 weeks exhibited the best emotional and cognitive development in later childhood, contrary to other two-state transition patterns [47]. We recently used eye-tracking technology to study the association between sleep and circadian rhythm characteristics with waking social cognitions in 12-month-old infants, particularly face processing – an important predictor for social-emotional functions. We found that infants' face scanning patterns were related to several sleep- and circadian-related parameters, such as sleep quantity, sleep quality, circadian stability, circadian amplitude, and circadian phase [48].

A systematic review has examined the association between sleep duration and a broad range of health indicators in children aged 0–4 years, where emotional regulation was one of the important outcomes [2]. Overall, a shorter sleep duration was associated with poorer emotional regulations (13/25 studies), and among these studies, 2 randomized studies (both randomized cross-over trails with high quality of evidence) showed better self-regulation strategies and emotional responses in the routine sleep versus the sleep restriction conditions [44, 49].

Many experimental sleep deprivation studies in animals and adults have attempted to explain the underlying mechanisms of sleep on the emotional brain [42, 43, 50]. In particular, noninvasive imaging approaches have been widely employed to potentially shed light on our understanding of the underpinnings linking sleep and emotional control. Neuroimaging studies in adults reported that sleep deprivation was associated with a 60% greater magnitude of activation of the amygdala and a 3-fold greater amygdala activation volume between groups [51]. The diminished amygdala-prefrontal connectivity was also found after sleep deprivation, suggesting a lack of cognitive control over emotional brain areas [51]. Finally, a functional magnetic resonance imaging study investigating the effect of sleep loss on the emotional brain network found that sleep deprivation amplifies reactivity throughout the mesolimbic reward brain network in response to positive emotional pictures [52].

General Cognitive and Brain Structure Development in Children

Apart from the studies focusing on sleep and memory and emotional development in young children, several studies have examined the relationship between sleep and general cognitive development or language development in infants and toddlers. One study revealed that a greater number of awakenings after sleep onset measured via sleep actigraphy recordings amongst 10-month-old infants were negatively correlated with the scores of the Bayley Scales of Infant and Toddler Development second edition (BSID-II) Mental Development Index (MDI) [53]. Gibson et al. [54] also found that 11- to 13-month-old infants who had either greater sleep efficiency or longer proportions of sleep at night measured by sleep actigraphy data were associated with better cognitive problem-solving skills as measured by the Ages and Stages Questionnaire. Recently, we examined the association between nighttime awakenings and cognitive development in a large-scale community sample of infants and toddlers from 8 provinces across China and found that frequent nighttime awakenings reported by caregivers are associated with a lower MDI in BSID-I in toddlers between 12 and 30 months [55]. A longitudinal twin study assessed the association between sleep-wake consolidation at 6, 18, and 30 months and language skills at 18, 30, and 60 months and found that a poor sleep consolidation during the first 2 years of life may be a risk factor for language learning in later childhood [56].

In adults, many studies have reported that sleep patterns and problems are associated not only with brain functions but also with structural properties of the brain, especially the gray matter volumes [57–59]. But very little is known about how sleep affects the developing brain from the structure perspective, and the only few studies all collected imaging data from children older than 5 years old [60–64].

Recently, one study investigated the prospective associations between sleep disturbances throughout early childhood

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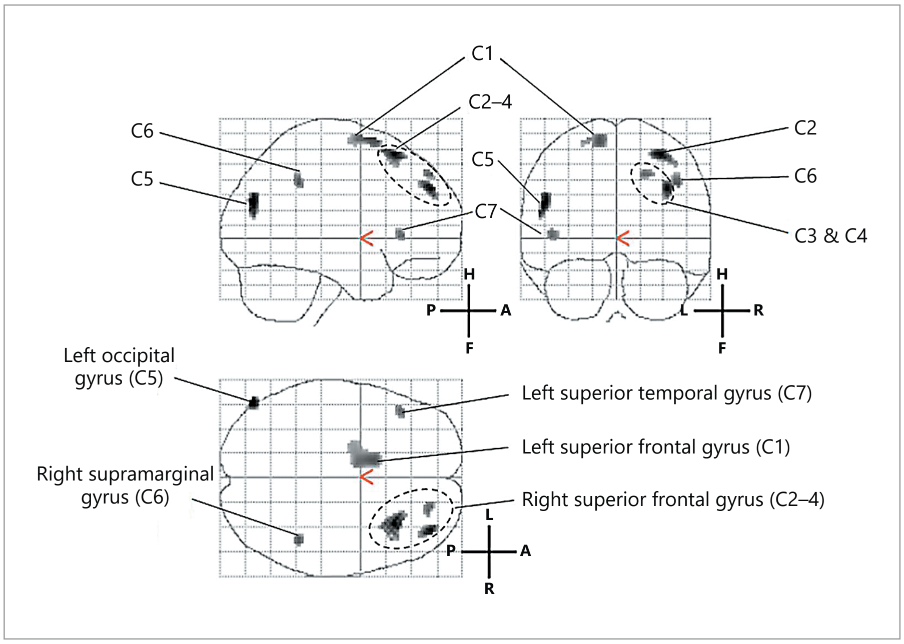

Fig. 2. Maximum intensity projection (MIP) of the statistical map showing areas of grey matter deficits in patients with moderate-to-severe obstructive sleep apnea. The MIP is projected on a glass brain in 3 orthogonal planes. Corresponding brain regions: C1, left superior frontal gyrus; C2–4, right superior frontal gyrus; C5, left occipital gyrus; C6, right supramarginal gyrus; C7, left superior temporal gyrus [61].

and brain morphology at 7 years of age [60]. They found that sleep disturbances from age 2 years onwards were associated with smaller grey matter volumes. The global trend of this phenomenon also showed meaningful regional specificity. Children with sleep disturbances were associated with thinner cortex in the dorsolateral prefrontal area, which may reflect effects of sleep disturbances on brain maturation [60]. However, one of the major limitations of this study is the use of a cross-sectional design, making it difficult to rule out reverse causality. That is, rather than being a consequence of sleep disturbances, brain morphology may underlie childhood sleep problems. Two studies explored the relationship between gray matter density and obstructive sleep apnea (OSA), which is one of the most common sleep disorders in childhood [61, 62]. Chan et al. [61] found that children with moderate-to-severe OSA had a significant grey matter volume deficit in the prefrontal and temporal regions (Fig. 2). A similar finding was also reported in Philby et al.'s [62] study where significant grey matter volume reductions were observed in OSA children throughout regions of the superior frontal and prefrontal, and superior and lateral parietal cortices. Even though these 2 studies of OSA children could further support the effects of sleep on brain structural development, the mechanisms of OSA and general sleep disturbance, for example dyssomnia, on cortical development might be very different. Reduction of grey matter volume in pediatric OSA children could be the result of sleep fragmentation as well as hypoxic damage to the brain [65].

Not only sleep problems but also sleep duration could impact cortical maturation. Taki et al. [64] analyzed the correlation between sleep duration and cortical development in 290 school-aged children and adolescents, which are the most vulnerable populations suffering from sleep deprivation. They found that the regional gray matter volumes of the bilateral hippocampal body as well as the right dorsolateral prefrontal cortex were positively correlated with sleep duration during weekdays. It has been speculated that children with more sleep problems could be delayed in reaching peak cortical thickness or advanced on the maturation curve of the prefrontal cortex [66].

Although there is abundant evidence from behavioral and neurophysiological studies suggesting that sleep affects infants' cognitive and emotional development, there is lack of evidence from imaging studies in this population, largely limited by the difficulties of imaging nonsedated children and the lack of analysis tools tailored to very young children. Nevertheless, with the marked development of image acquisition approaches and the novel analysis tools for infants and young children [1], we can expect more studies delineating the effects of sleep on brain structural and functional networks in young children.

Disclosure Statement

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