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Review

The influence of omega-3 fatty acids in the refinement of subcortical visual pathways and critical periods of plasticity

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ABSTRACT

In sensory systems most of the precise wiring of visual connections occurs during a postnatal time window of brain development known as the critical period. During this time window, brain connections become highly specified through the selective elimination of ineffective synapses and the maintenance of the correct ones. Omega-3 fatty acids are exclusively acquired through the diet, and thus blood levels are directly influenced by their dietary availability. These essential fatty acids are transferred through the placenta and are also present in human milk. Therefore, these fatty acids are substantially accumulated in the brain and retina during the fetal period and early postnatal development. Studies have shown that the deprivation of omega-3 fatty acids results in deficits not only in visual acuity but also in cognition. We discuss the role of omega-3 fatty acids in the development of sensory connections, the consequences of its nutritional restriction in animal models and the impact of such nutritional imbalance in the development of motor and cognitive skills.

KEYWORDS: essential fatty acids, omega-3, docosahexaenoic acid, retinal ganglion cells, retinofugal connections, visual system development, synapse elimination, topographical maps, critical period

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INTRODUCTION

Appropriate neural circuits develop through the selective elimination of misplaced axons and the maintenance of correct ones and their synapses [1]. These processes will determine the specificity of brain connections responsible for sensory perception and coordination of motor and cognitive systems that characterize a mature nervous system [2, 3]. Nutrition is a major factor that affects central nervous system functioning, especially in the light of the existence of critical periods for the formation and differentiation of neural circuitry during embryonic and postnatal life [4, 5].

The development of topographical maps: the visual system as a biological model

Synaptic specification and the importance of topographical maps have been recognized as major features of brain organization and neural processing since the pioneering studies of Roger Sperry [6]. Since then, the concept that sensory, as well as motor and cognitive abilities depend on the correct patterning of connections, has become part of our current knowledge about brain function [7]. In this way, a keystone feature of sensory visual processing relies on the correct patterning of visual connections that allow the proper development of various visual attributes of form, color and motion, that directly influence visual acuity and the same is true for all other sensory systems [8].

The development of organized and specific connections found among mammalian species

depends on two general strategies: an initial over production of neurons and synaptic contacts followed by the death of excess neurons, and the elimination of misplaced and ineffective axons/ synapses [2, 9]. During the last trimester of human gestation and the first two postnatal weeks of the rodent development, about the time when neuronal contacts begin to emerge, nearly 50% of the immature neuronal population undergoes a process of natural neuronal death. However, natural neuronal death seems to play only a marginal role in the development of topographical maps [10, 11].

The topographical specificity of visual pathways has been extensively studied in rodents. In those species as in other mammals including humans, the connections between retinal ganglion cell axons and target neurons at the superior colliculus (SC) and at the dorsal lateral geniculate nucleus (dLGN), develop within the first three postnatal weeks forming highly specific circuits [12-14]. This form of developmental plasticity occurs mainly through axonal elimination and synaptic growth at appropriate territories [3] (Figure 1). The initial development of retinocollicular topography is strongly influenced by repulsive/ attractive molecules between retinal axons and target neurons. Retinal ganglion cell axons and target cells in the SC express Ephrins and Eph receptors in complementary gradients that vary along the main retinal axis (dorsal to ventral/ temporal to nasal) [15]. A later step of topographical refinement is achieved by activity-dependent mechanisms that are required to ensure the fine-tuning of the correct synaptic distribution of retinal axons over postsynaptic sites leading to the development of functionally mature circuits [16]. The activity-dependent mechanisms include both the spontaneous (prior to eye opening) and the evoked (after eye opening) activity of retinal ganglion cells [17].

Critical periods for brain development

Neuronal connections in the mammalian brain become highly specified during a time window known as the critical period. The duration of the critical period is highly variable between mammalian species and is inversely related to the species longevity; rodents display a three/four-week critical period while humans develop protracted critical periods that extend up to 5-12 years and possibly beyond [18, 19]. The critical period

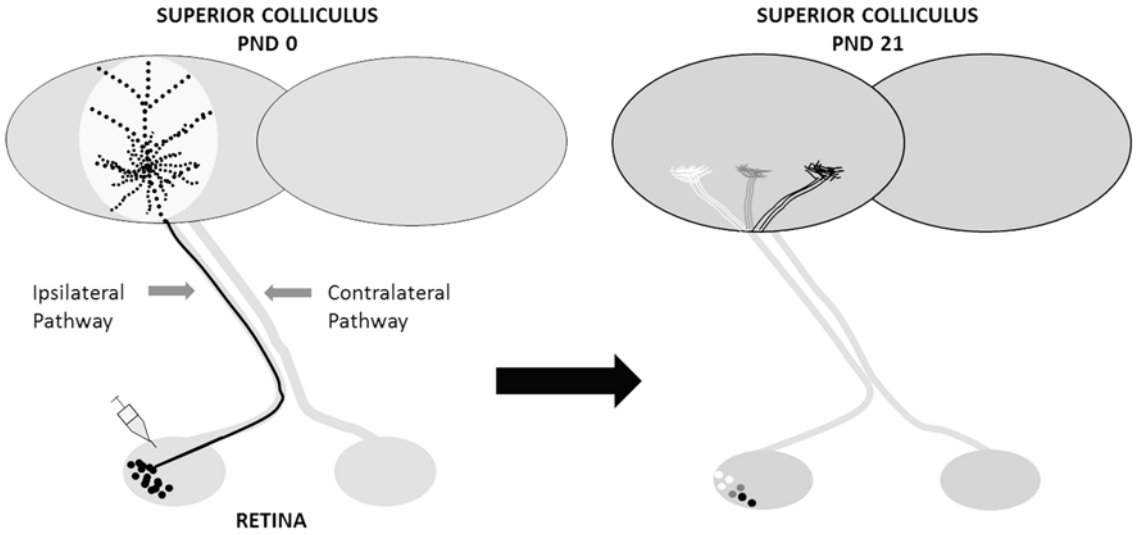

Figure 1. Development of the ipsilateral retinocollicular pathway as a model of topographical specification. At postnatal day 0, ipsilateral axons labeled by the anterograde transport of neuronal tracers are found dispersed throughout the collicular visual layers, both in the medio-lateral and rostro-caudal axis. By the end of the second and third postnatal weeks, an adult topography develops in which specific groups of neighboring retinal ganglion cells project their axons to adjacent post-synaptic sites.

corresponds to a developmental stage in which environmental cues provide rapid plasticity of neuronal circuits, necessary for the acquisition of appropriate sensory, motor as well as cognitive skills. Indeed critical periods have been described in many brain systems and in a large variety of species, for example, song learning in birds, auditory localization in barn owls and, in humans, the development of sensory acuity, motor and language skills [20]. The end of the critical period considerably reduces use-dependent plasticity of visual, auditory and somatosensory cortical areas [19, 21] as well as plasticity in subcortical visual nuclei such as the superior colliculus [3]. Although the end of the critical period affects plasticity in cortical and subcortical primary sensory areas it does not limit plasticity in other associative regions, which are still able to undergo use-dependent modifications even in adulthood [22-24]. One important question is how use-dependent activation of primary sensory areas during early postnatal development affects development and plasticity of other brain areas later on. It has been shown that early visual experience directly influences plasticity in the adult visual cortex [25] and early musical training (before the age of 7) influences sensory motor integration and thus, performance of musicians [26]. Therefore, the experiences acquired during this developmental window may directly affect the emergence of several other brain abilities and influence the outcome of our individuality. Importantly, those use-dependent modifications in neuronal connectivity ultimately result in certain behaviors or capabilities, which would not be revealed/developed otherwise [18, 20, 26, 27].

Furthermore, it has been suggested that various forms of mental retardation/autism are related to errors in the selective elimination of synapses that takes place during initial stages of post-natal development [28, 29]. It is worth mentioning that critical periods have different time courses in different sensory, motor and cognitive systems, and the correct timing of such partially overlapping periods may be of fundamental importance for the progressive gain in the complexity of the brain [18, 26, 30]. Therefore it has been proposed that the pathological conditions of brain development such as those found in Autism Spectrum Disorders and Fetal Alcohol Spectrum Disorder may result from disturbances in duration and/or timing of critical periods [31-33].

The influence of critical periods on the development of sensory brain connections was originally defined after the experiments made by Wiesel & Hubel (1963) in kittens. These investigators showed that a visual deprivation of one eye causes a dramatic change in the ocular dominance distribution, in favor of the open eye, between the fourth and the eighth postnatal weeks [34, 35]. In humans, neonatal strabismus can also result in similar loss of visual acuity; eye misalignment, if not appropriately treated before the age of 5, produces a permanent loss of visual acuity, a condition known as amblyopia [36]. This acuity loss results from the weakening of synapses originating from the non-aligned eye. Furthermore, cats raised under visually biased environments (e.g. exposed to visually stereotyped patterns of horizontal or vertical lines) do not develop accurate discrimination of visual stimuli (except for those horizontal or vertical stimuli), as well as the proper binocular representation of the visual field [37].

In the visual cortex, the critical period has been correlated with mechanisms involving neurotrophin signaling, especially brain-derived neurotrophic factor (BDNF), which aids the differentiation of inhibitory gamma-aminobutyric acid (GABA) circuits [20]. The development of GABAergic innervation seems to be crucial for the onset of the critical period [38] and inhibitory circuits are under the control of both visual experience and BDNF [39]. Also insulin-like growth factor 1 (IGF-1) has been shown to facilitate the development of inhibitory innervation and increase visual acuity [40]. The closure of the critical period in the primary visual cortex involves extracellular matrix (ECM) molecules that develop an environment that inhibits axonal and dendritic remodeling. Such molecules include chondroitin sulphate proteoglycans (CSPGs) [41], tissue plasminogen activator (tPA) [42] and growth inhibitory proteins like Nogo, MAG, and OMgp [43].

In visual subcortical nuclei such as the superior colliculus, the critical period overlaps with the period of fine-tuning of topographical maps [2, 44]. Lesion studies, either monocular enucleation

or restricted retinal lesions, have been used to induce reorganization of axons originating from the intact eye [3, 45, 46]. Those experiments revealed that the plastic capacity of retinocollicular connections during the critical period is characterized by a rapid reactive growth of axons from the non-lesioned eye in response to lesions during the first three postnatal weeks. After the third postnatal week, a single retinal lesion was still able to elicit a certain amount of reorganization of the intact pathway, which took, however, several weeks to develop. Therefore, a second slow stage of plasticity does occur even after the end of the critical period [3].

Nutrition and the impact of omega-3 fatty acids on brain development

Nutritional deficiencies are related to structural changes in the brain, such as alterations in overall size, decrease in hippocampal volume, modifications in developmental processes such as neurogenesis and gliogenesis, synthesis and release of neurotransmitters, the onset of neural activity including excitatory and inhibitory circuits, and finally behavioral and cognitive aspects [47, 48]. The consequences of malnutrition will depend on the nature and severity of malnutrition, including the type, level and duration of the nutritional deficiency [49].

Essential nutrients are exclusively acquired through diet [50]. Therefore, social and cultural factors that influence nutritional habits could lead to functional changes in neurochemical aspects of synaptic organization, with serious consequences for neural circuitry maturation [51-53]. Lipids are responsible for about 50-60% of brain dry weight of an adult, about 35% of which are long chain polyunsaturated fatty acids (LCPUFA). α-Linolenic acid (omega-3 fatty acid) and linoleic acid (omega-6 fatty acid) are considered essential fatty acids (EFAs), as they cannot be endogenously synthetized [54, 55]. Docosahexaenoic acid (DHA/ omega-3) and arachidonic acid (AA/omega-6) derived from their respective precursors, are the main LCPUFA found in the brain [56-58]. These lipids, highly sensitive to dietary changes, participate in the formation and physiology of neural membrane and may thus regulate signaling events that depend on membrane functional integrity [59].

Adequate supplies of EFAs are required during development and in adulthood, in order to ensure appropriate brain function [60-62]. Numerous studies on the deficiency of omega-3 fatty acids mention the initial stages of development as a critical period of brain modeling [12, 63, 64]. During pre-natal development, DHA is transported from mother to the offspring through the placenta. After birth, omega-3 acquisition is achieved by breast milk consumption [60, 65, 66]. Thus, the fetus and the newborn are completely dependent on maternal supply of essential fatty acids. Several factors can interfere with the conversion of EFAs into their specific compounds. These factors include: intake of saturated fatty acids and hydrogenated lipids, deficiency of vitamins and minerals that act as cofactors (mainly zinc deficiency) [67], excessive alcohol consumption and stress related hormones [68, 69]. Those conditions indicate that even with an adequate dietary intake of EFAs, deficiency of AA and DHA may still occur. Therefore, differences in the metabolism of essential fatty acids have been recognized as possible risk factors for neuro-developmental disorders [70].

The balance of omega-3/omega-6 fatty acids is an important determinant in maintaining homeostasis and normal brain development [71, 72]. The ratio of omega-3/omega-6 has decreased in the modern Western human diets in comparison to a higher ratio observed prior to industrialization in the XIX century [73, 74]. This change has been attributed to an increase in omega-6 intake due to high protein diets and also to an increased intake of saturated fat found in industrialized food. Both habits have been associated to DHA deficiencies even in breast fed infants [57, 75]. The main food sources of α-Linolenic acid (ALA) are flaxseed and some nuts such as cashew nuts. DHA is also primarily available from fish and seafood [59, 76, 77].

Randomized clinical studies with children pointed out the importance of the introduction of omega-3 fatty acids in infant formulas as a requirement to reach children's growing and developing needs [78]. A study reported a persistent effect of DHA in visual acuity in the first year of life of children fed with breast milk as opposed to infants fed with DHA supplemented formula, indicating that the

blood levels of DHA are directly related to changes in visual acuity [66, 79]. It has been demonstrated in a clinical trial study that infants at 12 months of age that received a formula supplemented with different concentrations of DHA increased visually evoked potentials and acuity when compared with control subjects fed with a formula lacking DHA [80].

Thus, an adequate DHA supply is necessary for the correct shaping of brain circuitry. DHA levels in the brain seem to be strictly controlled, since any disturbance leads to severe impairment in brain development and maturation [81-83]. Most of the incorporation of DHA in the brain and retina occurs throughout the last trimester of gestation and continues up to the first four years in humans [79, 84]. This time-course overlaps with major landmarks of visual system development, from neurogenesis to axonal elimination and the critical period of use-dependent plasticity, when visual circuits acquire their ultimate functionality.

Omega-3 fatty acids have been shown to modulate the levels of neuronal synaptic proteins [12, 85, 86]. It has been reported that rats that received a supplementation with DHA and uridine during gestational period until post natal day 21 (PND21) enhanced synapsin-1, mGluR1 and PSD-95, suggesting that DHA is involved in synaptic stabilization [87].

DHA also increases the number of dendritic spines and synapses probably in hippocampal neurons, particularly at excitatory synapses [88]. DHA is highly concentrated in synaptic membranes that facilitate exocytosis of neurotransmitter-containing vesicles, indicating an important role in regulating neurotransmitter release [89]. Moreover, it not only modulates the physical properties of the neuronal membranes [90], but also promotes the formation of second messengers that can function in signaling processes [91].

DHA as a free form, or by way of bioactive derivatives such as neuroprotectin D1 (NPD1), can be released by calcium-independent phospholipase A2 (iPLA2) activity in neurons, glial cells, endothelial cells and cerebral blood vessels by the stimulation of neurotransmitters, neurotrophic factors, cytokines, membrane depolarization, and activation of ion channels [92, 93]. Those lipid messengers can regulate and interact with multiple signaling cascades, contributing to the development, differentiation, synaptic function, protection, and repair of cells in the nervous system [94].

DHA has also been described as a trophic molecule since it is able to directly influence the expression of genes related to signal transduction mechanisms, synaptic plasticity, energy metabolism, and traffic through membrane receptors [95]. DHA has its role as an endogenous ligand for retinoid X receptors (RXR) [96]. The receptors RXRα and RXRβ together as peroxisome proliferator-activated receptor (PPAR) gamma can be activated by DHA, leading to dimerization of these receptors and their insertion into the nucleus, where they can act as transcription factors inducing differentiation and synaptic stability [97]. Studies have shown that DHA can regulate the expression of BDNF mRNA, the neurotrophic factor directly related to processes of neuronal survival and synaptic strengthening [98-100].

Role of omega-3 on development of central visual connections

DHA has been shown to exert several roles in the visual system from photoreceptor differentiation to synaptic plasticity in a series of events that has a direct influence on visual acuity [101, 102]. In order to address a more specific role for omega-3 in the developing visual system, we used a nutritional approach in which female rats were given an isocaloric diet containing coconut oil as a lipid source [12]. This diet protocol started 5 weeks before mating in order to deplete omega-3 fatty acids. Females were kept under this nutritional restriction during mating, pregnancy and after delivery until the litters reached postnatal day 42 (PND42). Lipid levels were measured in samples from the collicular visual layers of rats at PND28. Those samples revealed a 53% reduction in the levels of DHA without any changes in arachidonic acid (AA) content [12].

The topographical distribution of uncrossed retinocollicular terminal fields was determined by the anterograde transport of horseradish peroxidase (HRP). It was shown that this chronic form of malnutrition was able to disrupt the topographical development as early as the second postnatal

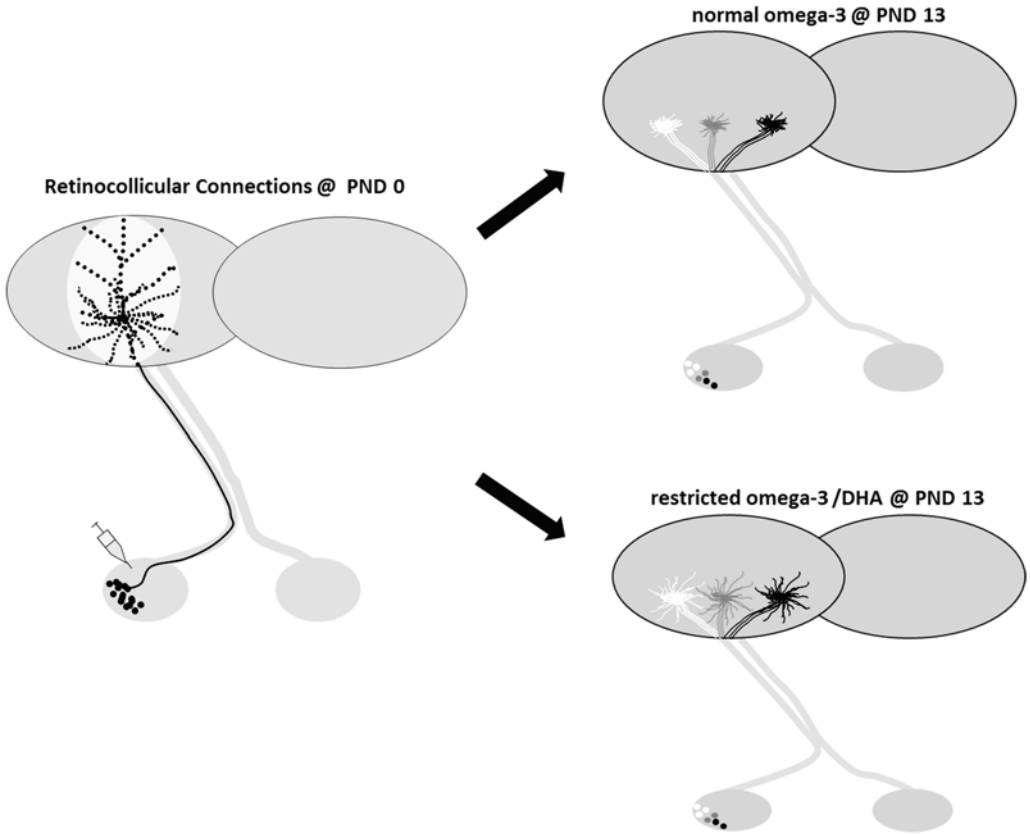

Figure 2. Nutritional restriction of omega-3/DHA induces abnormal terminal fields of visual axons in the superior colliculus, which are expanded relative to control individuals. This effect could be due to either a reduced elimination of misplaced synapses or to an increased abnormal sprouting outside the mains terminal zones. In either case, a developmental delay in topographical maturation is evident.

week (PND13) when terminal fields displayed a 2-fold increase in label density when compared to the control, soy oil fed-animals (Figure 1). Coconut-fed litters also revealed topographically expanded terminal fields at PND28 and PND42 strongly suggesting that an omega-3 restriction, and the subsequent reduction of DHA levels, produced abnormal connections in the rodent visual system [12] (Figure 2). This could be due either to a slowdown in axonal elimination of transitory synapses or to an unspecific sprouting as a result of a decrease in DHA-induced synaptic stabilization mechanisms. The latter mechanism was in part confirmed by a decrease in phopho-GAP43 (pGAP-43) content observed in the visual layers of the SC [12]. The phosphorylated form of GAP-43 (pGAP-43) protein has been involved in hippocampal synaptic plasticity and in the stabilization of developing synapses [45, 103].

The disturbance on visual system development induced by omega-3/DHA reduction was not confined to the ipsilateral retinocollicular pathway. During normal development, most of the development of retinogeniculate segregation has finished by PND28 and terminal zones from each become restricted to eye-specific layers of the dorsal lateral geniculate nucleus [104]. However, under omega-3/DHA restriction, the ipsilateral and contralateral eye specific zones were still expanded at PND 28 in relation to control animals suggesting that the disturbance in the fine-tuning of the visual system topography is a common finding in visual system development [12].

The results described by de Velasco and colleagues are consistent with a general delay in development which results in errors in topographical fine-tuning of retinal connections [12]. To directly address whether other aspects of development

could also exhibit a similar delay, we made a series of retinal lesion experiments which are suitable to access the critical period limits. As described earlier [3], restricted retinal lesions to one eye induce a rapid sprouting of axons from the intact eye that converge to the same aspect of the superior colliculus contralateral to the lesioned eye. It has been shown that after the third postnatal week, a slow plasticity is observed only within weeks or months [3]. Under normal conditions virtually no sprouting of intact axons can be detected one week after a retinal lesion made at PND21, which characterizes the end of collicular critical period [105, 106]. However, animals depleted of DHA still displayed a vigorous plastic response to a retinal lesion at PND21 suggesting, therefore, that DHA restriction altered the duration of the critical period [12].

CONCLUSION

In conclusion, omega-3 nutritional restriction directly impacts DHA availability within visual nuclei and dramatically alters the time course of topographical refinement and critical period-windows. The consequences of those influences on such a precisely regulated time-course may explain the dysfunctions observed in DHA deficient children, who display reduced visual acuity [107] and impaired cognitive performance [88, 101]. Thus, an improved understanding of the role of essential fatty acids in brain development is, thus, mandatory for the establishment of adequate dietary requirements for these essential lipids during early postnatal life.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

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