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REVIEW

Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: Mechanisms and implications for psychopathology

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Abstract

Accumulating translational evidence suggests that the long-chain omega-3 fatty acid docosahexaenoic acid (DHA) plays a role in the maturation and stability of cortical circuits that are impaired in different recurrent psychiatric disorders. Specifically, rodent and cell culture studies find that DHA preferentially accumulates in synaptic and growth cone membranes and promotes neurite outgrowth, dendritic spine stability, and synaptogenesis. Additional evidence suggests that DHA may play a role in microglia-mediated synaptic pruning, as well as myelin development and resilience. In non-human primates *n*-3 fatty acid insufficiency during perinatal development leads to widespread deficits in functional connectivity in adult frontal cortical networks compared to primates raised on DHA-fortified diet. Preterm delivery in non-human primates and humans is associated with early deficits in cortical DHA accrual. Human preterm birth is associated with long-standing deficits in myelin integrity and cortical circuit connectivity and increased risk for attention deficit/hyperactivity disorder (ADHD), mood, and psychotic disorders. In general, ADHD and mood and psychotic disorders initially emerge during rapid periods of cortical circuit maturation and are characterized by DHA deficits, myelin pathology, and impaired cortical circuit connectivity. Together these associations suggest that early and uncorrected deficits in fetal brain DHA accrual may represent a modifiable risk factor for cortical circuit maturation deficits in psychiatric disorders, and could therefore have significant implications for informing early intervention and prevention strategies.

Key words: Omega-3 fatty acids; Brain development; Prefrontal cortex; Docosahexaenoic acid; Connectivity; Attention deficit/hyperactivity disorder; Mood; Cognition; Bipolar disorder; Schizophrenia; Amygdala

Core tip: Although the role of perinatal brain omega-3

fatty acid (DHA) accrual on the maturation and long-term stability of cortical circuitry is only beginning to be fully understood, extant translational evidence suggests that DHA plays a role in the initial development and early maturation of cortical circuits. Emerging evidence from human neuroimaging studies further suggests that psychiatric disorders that initially emerge in childhood and adolescence and associated with low blood DHA levels are characterized by frontal circuit deficits compared with healthy developing youth. Based on existing evidence, these associations could have significant implications for informing novel early intervention strategies aimed at reducing the transmission of psychopathology.

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INTRODUCTION

Over the past 30 years evidence has emerged from both animal and clinical research implicating long-chain omega-3 (LC*n*-3) fatty acids in normal brain development and function. The principal LC*n*-3 fatty acid found in mammalian brain gray matter is docosahexaenoic acid (DHA), which comprises approximately 10%-20% of total fatty acid composition in the adult frontal cortex[1,2]. Although the omega-3 fatty acid precursors of DHA, including α-linolenic acid (ALA, 18:3*n*-3), eicosapentaenoic acid (EPA, 20:5*n*-3), and docosapentaenoic acid (22:5*n*-3), cross the blood-brain barrier, they are rapidly oxidized and consequently comprise < 1% of total brain fatty acid composition[3]. Mammals require a dietary source of *n*-3 fatty acids to procure and maintain adequate concentrations of DHA in peripheral and central tissues. Although DHA can be biosynthesized from the vegetable short-chain *n*-3 fatty acid precursor ALA *via* a series of microsomal desaturase, elongase, and peroxisomal reactions, preformed DHA is significantly more effective than ALA for increasing erythrocyte[4], breast milk[5,6], and cortical gray matter[7,8] DHA concentrations. Primary dietary sources of DHA include cold water fatty fish, milk and eggs fortified with DHA, and fish oil (FO) or algal supplements.

Human infant, childhood, and adolescence are critical developmental periods associated with the formation and establishment of structural and functional connectivity between frontal lobe regions that mediate attention and executive function and limbic structures that mediate emotion and mood[9-11]. During this perinatal period DHA concentrations increase sharply in the frontal cortex[1] and may therefore play an important role in cortical circuit maturation. This is supported in part by recently emerging neuroimaging data that suggests that DHA status is positively correlated with frontal cortex structural and functional integrity in human subjects across the lifespan[12]. Moreover, preterm delivery is associated with early deficits in cortical DHA accrual, long-standing deficits in cortical circuit maturation, and increased risk for developing psychiatric disorders. Lastly, psychiatric disorders which frequently initially emerge during rapid periods of cortical circuit maturation and are characterized by DHA deficits, myelin pathology, and impaired cortical circuit connectivity (see below). These associations support the hypothesis that LC*n*-3 fatty acids play a role in the early development of cortical circuits and that LC*n*-3 fatty acid insufficiency may represent a modifiable neurodevelopmental risk factor for psychiatric disorders. This review critically evaluates translational evidence implicating LC*n*-3 fatty acids in cortical circuit development, highlights plausible molecular and ultrastructural mechanisms, and explores potential relevance to the pathoetiology of recurrent neuropsychiatric disorders.

RODENT NEURODEVELOPMENT

During perinatal rodent brain development, cortical DHA concentrations increase sharply in conjunction with active periods of neurogenesis, neuroblast migration, and synaptogenesis[13]. For example, there is a 5-fold increase in cortical DHA levels during the late gestation compared with early gestation[13]. DHA preferentially accumulates in neuronal growth cone[14,15] and mature synaptic[16,17] membranes where it modulates membrane signaling dynamics and synaptogenesis[18,19]. DHA also increases neurotrophic factor expression including nerve growth factor (NGF) and brain-derived growth factor (BDNF)[20,21], and promotes neurite outgrowth[22-26]. Dietary-induced deficits in brain DHA accrual during perinatal maturation are associated with reductions in neurogenesis[27,28], delays in neuronal migration and embryonic cortical plate expansion[29,30], and reduced synaptic plasticity and connectivity[24]. Additionally, DHA and its bioactive metabolites are protective against a variety of neuronal insults associated with oxidative stress and lipid peroxidation in the fetal[31-33] and adult rat brain[34-39].

One consequence of changing the fatty acid composition of cellular membranes that is relevant to synaptic maturation and function is the alteration of phospholipid composition. Specifically, perinatal deficits in DHA accrual are associated with selective reductions in neuronal membrane phosphatidylserine concentrations[40,41], whereas perinatal FO supplementation selectively increases neuronal membrane phosphatidylserine concentrations[23,42]. Importantly, phosphatidylserine modulates the activity of signal transduction proteins including protein kinase C (PKC)[43]. PKC plays a pivotal role in filamentous actin (F-actin) cytoskeletal structural plasticity required for neurite outgrowth, growth cone motility, dendritic spine formation and stability, as well

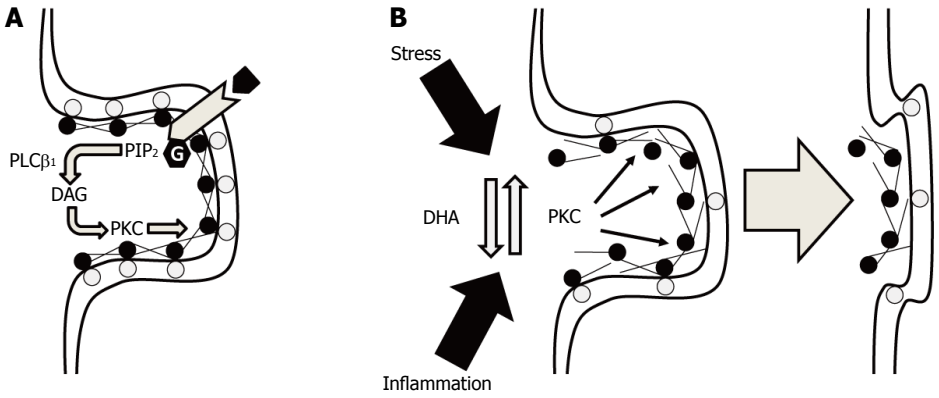

Figure 1 Potential ultrastructural mechanisms by which membrane DHA deficits could lead to a loss in synaptic connectivity. A: Under normal physiological conditions, synaptic membrane phosphatidylserine (gray circles) bind MARCKS (black circles) at the membrane which also cross-links and tethers F-actin to support dendritic spine cytoskeletal structural stability. Binding of MARCKS with membrane phosphatidylserine also inhibits phospholipase Cβ1-mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) into diacylglycerol (DAG) which increases PKC activity. PKC-mediated phosphorylation of MARCKS reduces the tensile strength of the F-actin cytoskeleton leading to the eventual collapse of the spine; B: Under conditions of membrane DHA deficits, reductions in membrane phosphatidylserine and membrane-bound MARCKS increase PKC activity and destabilizes the F-actin cytoskeleton leading to spine collapse. Elevated PKC activity secondary to membrane DHA deficits may also reduce the resilience of dendritic spines to other pathophysiological factors including chronic stress or inflammation. DHA: Docosahexaenoic acid; PKC: Protein kinase C; MARCKS: Myristoylated alanine-rich C kinase substrate.

as neurotransmitter release dynamics[44]. This response is mediated in part by PKC-mediated phosphorylation of substrate proteins including myristoylated alanine-rich C kinase substrate (MARCKS) which cross-links actin filaments in a phosphorylation-reversible manner[45]. Moreover, MARCKS binds membranes in part by electrostatic interactions between phosphatidylserine and the highly basic phosphorylation site domain in a phosphorylation-reversible manner[46]. Consistent with this mechanism, we demonstrated that perinatal deficits in DHA accrual were associated with a significant reduction in membrane-bound MARCKS, and an associated increase in cytosolic MARCKS, in the rat hippocampus[47]. These findings suggest that lower membrane phosphatidylserine content in response to reduced DHA levels are associated with a dysregulation in the signal transduction processes that regulate F-actin cytoskeletal structural plasticity.

Electrostatic binding of MARCKS with membrane phosphatidylserine also inhibits phospholipase Cβ1-mediated hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) by sequestering PIP_2 in lateral membrane domains[48]. Therefore, reductions in MARCKS membrane binding would also be predicted to increase Gqα-linked receptor-initiated hydrolysis of PIP_2 into diacylglycerol (DAG) and inositol triphosphate (IP_3) which increase PKC activity and intracellular calcium release, respectively. Moreover, free DHA inhibits PKC translocation and activity[49-52], and we previously demonstrated that perinatal deficits in DHA accrual were associated with significant alterations in the subcellular distribution PKC isozymes in the rat hippocampus[47]. Importantly, increases in PKC-mediated phosphorylation of MARCKS leads to a reduction in the tensile strength of the F-actin cytoskeleton and associated deficits in dendritic spine formation and stability[53]. Moreover, higher brain DHA levels are associated with elevated dendritic spine density and resilience[54-56], whereas perinatal deficits in DHA accrual are associated with reductions in synaptic connections[24]. It also relevant that elevations in PKC activity have been implicated in dendritic spine loss in response to chronic stress[57] and chronic inflammation[58,59]. Together, these findings suggest that DHA promotes synapse maturation and stability by decreasing PKC-mediated dismantlement of the F-actin cytoskeleton within synaptic terminals (Figure 1).

In addition to playing a role in the formation of new synapses, PKC, MARCKS, and the F-actin cytoskeleton also play a role in neurotransmitter vesicle trafficking and release efficacy within mature presynaptic terminals[60]. A role of DHA in this dynamic process is supported by findings of alterations in neurotransmitter vesicle distribution within presynaptic terminals[61,62] and abnormalities in the release, *i.e.,* increased basal release and deficits in stimulated release, of multiple neurotransmitter systems including dopamine[63-65], serotonin[66], and acetylcholine[67,68] in the DHA-deficient rat brain. It is relevant therefore that a dyregulation in dopamine[69-73], serotonin[74,75], and acetylcholine[76,77] have been implicated in the pathophysiology and treatment of mood and psychotic disorders as well as neurocognitive impairment. Increased glutamatergic synaptic efficacy is required for the induction of long-term potentiation (LTP) and the formation of new axodendritic synaptic connections subserve the maintenance of LTP[78-80]. Importantly, deficits in DHA accrual during perinatal development are associated with impaired LTP and a significant reduction in glutamate synapses in the rat hippocampus[24]. LTP is also thought to mediate the consolidation and storage of new memories[81,82], and perinatal deficits in DHA accrual are associated with impaired learning on hippocampus-dependent spatial learning tasks[83-85] and olfactory discrimination tasks[86-88]. Together, these

findings provide additional support for a role of cortical DHA in activity-dependent synaptic plasticity and synaptogenesis.

Critical to the "fine tuning" of cortical circuits during postnatal development is the pruning of extraneous and aberrant synapses. For example, during the peri-adolescent period there is a substantial (approximately 50%) pruning of glutamatergic connections between the rat frontal cortex and the amygdala[89]. While there is currently little known about the role of DHA in cortical synaptic pruning, in the developing rat visual system DHA deficits were associated with aberrant axonal innervation outside the main terminal zones of the superior colliculus which was transient and consistent with a delay in synaptic pruning[90]. It is also relevant that synaptic pruning is mediated in part by microglial phagocytosis[91,92], and a recent study found that DHA application to cultured microglia stimulated phagocytosis (M2 phenotype) and decreased the production and secretion of pro-inflammatory cytokines including TNF-α (M1 phenotype)[93]. The latter study also demonstrated that DHA application increased microglia BDNF biosynthesis, which was positively correlated with microglia phagocytosis, and BDNF expression is reduced in the frontal cortex of DHA-deficient rats[21]. A second study found that deficits in brain DHA accrual during perinatal development increased microglial pro-inflammatory cytokine production in the neonatal rat hippocampus, consistent with a non-phagocytotic pro-inflammatory phenotype[94]. These preliminary findings suggest that deficits in brain DHA accrual during perinatal development may disrupt synaptic pruning by altering the phenotype of microglia.

An important aspect of cortical circuit maturation is the myelination of axons, and DHA accumulates in myelin during perinatal rat development[17,95]. While there is currently little known about the role of DHA in the maturation of myelin sheaths and axonal conduction, intracerebroventricular administrations of either EPA or DHA in 2-day-old rats increased the expression myelin-related genes in different brain regions[96]. However, maternal FO supplementation, as well as maternal *n*-3 fatty acid deficiency, during pregnancy and lactation was found to impair auditory brainstem responses in neonates which was interpreted as a slowing of neural signal conduction[97,98]. A subsequent study found that initially lower auditory brainstem responses dissipated by young adulthood[98]. Another study found that maternal DHA supplementation during pregnancy and lactation impaired auditory startle response in neonates[95]. In adult rodents increasing dietary LC*n*-3 fatty acid status is protective against inflammation-[99] and trauma-induced[100,101] axonal white matter injury, as well as histopathological features in the experimental autoimmune encephalomyelitis model of multiple sclerosis[102]. While these preliminary findings suggest that there are optimal DHA levels required for normal axonal white matter integrity and resilience, additional research is needed to evaluate the role of perinatal brain DHA accrual on myelin integrity and circuit connectivity.

PRIMATE NEURODEVELOPMENT

Consistent with rodent studies, DHA concentrations increase sharply in the developing monkey brain during perinatal development[103,104], and baboons born preterm exhibit cortical DHA deficits compared with term births[105,106]. Primate perinatal *n*-3 fatty acid deficiency is associated with deficits in visual attention[107], polydipsia (excessive thirst)[108], and deficits in visual acuity and electroretinogram abnormalities[103,104]. Electroretinogram abnormalities have also been observed in neonatal baboons born preterm[109]. Consistent with dysregulated dopamine activity, perinatal *n*-3 fatty acid deficiency is associated increased home cage stereotypy and locomotion bouts[110]. A recent neuroimaging study found that resting-state functional connectivity among prefrontal cortical networks was impaired in young adult monkeys raised on an *n*-3 fatty acid deficient diet compared with monkeys raised on FO-fortified diet[111]. Specifically, *n*-3 fatty acid deficient monkeys exhibited reduced connectivity between the dorsal anterior insula (seed region) and ventromedial prefrontal, orbitofrontal, dorsolateral prefrontal cortices as well as with superior temporal sulcus and medial parietal areas. Although not specifically investigated, tracer studies demonstrate monosynaptic connections between monkey orbito-frontal cortex and amygdala[112]. Together these findings suggest that uncorrected deficits in cortical DHA accrual during perinatal brain development leads to reduced connectivity within prefrontal cortical networks in young adult non-human primates.

HUMAN NEURODEVELOPMENT

During human neonatal development, DHA accumulates in brain tissue at a rapid rate during the third trimester in association with active periods of neurogenesis, neuroblast migration, differentiation, synaptogenesis, and gray matter expansion[113,114]. Importantly, the third trimester of gestation is also a period associated with the initial formation of connections between brain regions including the uncinate fasciculus and superior longitudinal fasciculus[115]. Postpartum the neonatal brain continues to grow from approximately 350 g at birth to approximately 925 g at 1 year of age[116], during which DHA represents approximately 9% of total cortical fatty acid composition[1,117]. Neonates are wholly reliant on maternal breast milk (or formula) as the sole source of DHA. Term infants fed formulas without DHA consistently exhibit significantly lower erythrocyte and postmortem brain cortex DHA concentrations relative to breastfed infants or infants fed formula containing DHA[118-125]. The recognition that human breast milk DHA represents an important source for postnatal infant

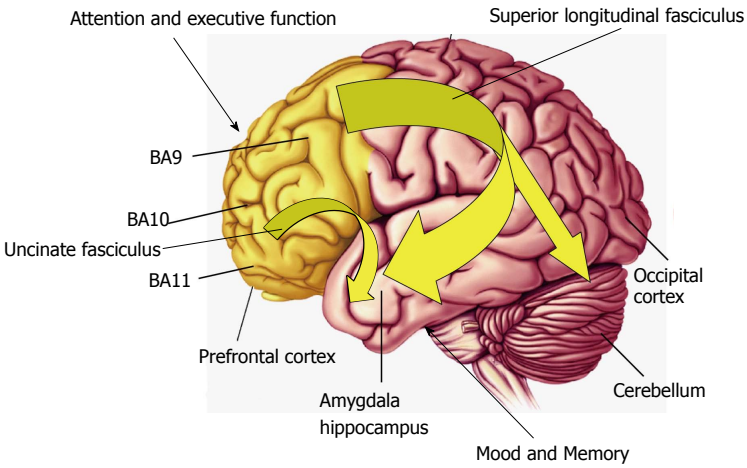

Figure 2 Diagram illustrating connectivity between frontal lobe regions, including the dorsolateral prefrontal cortex (Brodmann area 9, BA9,) and orbitofrontal cortex (BA11) which regulate attention and executive function, and temporal lobe structures including the amygdala and hippocampus which regulate mood and memory. Frontal lobe connectivity with limbic structures is mediated in part by the uncinate fasciculus and superior longitudinal fasciculus which develop during gestation and undergo significant maturation during childhood and adolescence. Reduced frontal circuit connectivity is exhibited by DHA-deficient non-human primates, children and adolescents born preterm, and patients with psychiatric disorders including ADHD and bipolar disorder which are associated with DHA deficits. DHA: Docosahexaenoic acid; ADHD: Attention deficit/hyperactivity disorder.

brain DHA accrual led to the widespread commercial availability of DHA-fortified infant formula in the United States in 2002.

During early childhood development DHA levels continue to increase in the frontal cortex[1] in association with linear increases in frontal cortex gray matter expansion and myelination[9-11,115], and the maturation of frontal lobe-mediated neurocognitive processes including attention and executive function[10,126]. During adolescent development cortical DHA levels continue to increase to approximately 15% total cortical fatty acids in young adulthood[1], and this increase coincides with frontal cortex synaptic pruning[127-129], white matter expansion and maturation[9-11,130,131]. Human neuroimaging studies indicate that the childhood and adolescent period is associated with the maturation of frontal cortical regions that mediate attention and executive function and the maturation of uncinate fasciculus and superior longitudinal fasciculus functional connectivity between frontal regions and limbic structures that mediate mood including the amygdala[9-11](Figure 2).

As observed in non-human primates[106], human infants born preterm exhibit lower erythrocyte and postmortem cortical DHA concentrations compared with term infants fed the same ALA-fortified formula postpartum[113,114,122,132,133]. Structural imaging studies have found that children and adolescents born preterm exhibit significant reductions in frontal and temporal cortical gray matter volumes, reduced amygdala and hippocampal volumes, reduced corpus callosum and white matter volumes, and enlarged cerebral ventricles[134-142]. Reductions in preterm cortical brain gray matter volume are correlated with functional connectivity deficits[143], and children, adolescents, and adults born preterm exhibit reduced connectivity within prefrontal cortical networks and decreased white matter integrity in different tracts including the uncinate fasciculus and superior fasciculus[144-155]. Importantly, deficits in white matter integrity have been observed in preterm born children with no neonatal ultrasound evidence for intraventricular hemorrhage, periventricular leukomalacia, low-pressure ventriculomegaly, or cytic white matter injury[145]. While these imaging findings suggest that deficits in third trimester DHA accrual may be associated with long-standing deficits in cortical circuit maturation, additional research is needed to determine whether early DHA supplementation can prevent or reverse these deficits.

Studies have also found that decreased white matter integrity in children and adolescents born preterm are associated with cognitive impairment and psychiatric symptoms[145,156-160]. Children and adolescents born preterm exhibit a significantly higher incidence of attention deficits, impulsivity, learning disability, language impairments, hyperactivity, anxiety, motor impairments, and poor social functioning relative to age- and sex-matched term children/adolescents[161,162]. Importantly, preterm birth and/or low birth weight is associated with increased risk for developing attention deficit/hyperactivity disorder (ADHD) in childhood[161,163-165] and mood, anxiety, and psychotic disorders during adolescence and young adulthood independent of multiple confounding variables including maternal history of psychiatric illness[163,166-170]. These findings suggest that deficits in cortical circuit maturation resulting from preterm birth are relevant to the etiology of ADHD in childhood and mood and psychotic disorders during adolescence and young adulthood.

While the contribution of DHA deficits to neurological and cognitive impairments commonly observed in preterm infants and children is poorly understood,

fortifying human milk or formula with higher levels of DHA is associated with improvements in visual acuity, sustained attention, and recognition memory compared with infants receiving DHA-free formula[171-174]. However, a systematic review of randomized controlled trials studying the effects of DHA-fortified formula for preterm infants concluded that there was no consistent effect on infant cognition or visual function[175]. It is notable, however, the DHA doses used in the majority of studies (0.2%-0.3% DHA) may have been too low to compensate for intestinal malabsorption, DHA oxidation, and early central DHA deficits in preterm infants. Indeed, a dose-response study found that milk DHA concentrations of 1% were required to increase DHA status in preterm infants to levels similar to term infants[176]. Moreover, deficits in cortical DHA concentrations in preterm baboons were not fully restored to control levels following 4 wk feeding formula fortified with a moderate dose of DHA (0.61%)[106]. It is also relevant that a placebo-controlled structural MRI study found that feeding formula containing lower levels of DHA (0.34%) did not significantly alter white matter volume in premature infants[177], whereas a preliminary intervention study observed improvements in brain white matter volumes in neonates with peroxisomal disorders following supplementation with higher DHA doses (100-600 mg/d)[178]. These and other findings have led to new recommendations for higher dose DHA supplementation for preterm infants to improve neurological and cognitive outcomes[179].

Prospective longitudinal studies have investigated the relationship between fetal cord blood DHA levels and neurodevelopmental outcomes in older children. These studies have found that higher LC*n*-3 fatty acid intake or cord blood DHA levels are associated with higher movement scores at 7 years of age[180,181], better neurological scores at 5.5 years[182], better visual function at 5 years of age[183], and better recognition memory and associated event-related potentials at approximately 11 years of age[184]. Another study found that higher cord blood DHA or LC*n*-3 fatty acid levels were associated with lower parent-reported hyperactivity/inattention and emotional symptoms among 416 children at 10 years of age[185]. A longitudinal study also found that higher cord blood DHA status was associated with lower levels of internalizing emotional problems including depression and externalizing conduct problems among 393 children at 7 years of age in subjects fed DHA-free formula but not those fed human milk[186]. The latter finding suggests that increasing postnatal dietary DHA intake can mitigate the emergence of psychiatric problems in youth exposed to low DHA levels *in utero*. Together, these data suggest that lower cord blood DHA levels are associated with an enduring negative impact on neurocognitive development.

Neonates become wholly reliant on maternal breast milk (or formula) as the sole source of DHA. Human breast milk DHA concentrations are highly correlated with maternal dietary DHA intake[6,187,188] and vary widely across different countries in accordance with habitual dietary fish consumption, *e.g.*, approximately 0.17% of total milk fatty acids in the United States *vs* approximately 1.1% of total milk fatty acids in Japan[189]. Several studies suggest that longer breastfeeding duration, a putative surrogate for early postnatal DHA intake, is associated with improved white matter microstructure and volume[190,191] and better neurocognitive outcomes in childhood, adolescence, and adulthood[192-194]. Prospective and retrospective studies have also found that shorter breastfeeding duration is associated with increased risk for developing ADHD in childhood[195-198]. However, the latter studies did not determine breast milk DHA concentrations to evaluate contribution to functional outcomes and additional/alternative benefits of longer breastfeeding (*i.e.,* better mother-child attachment) may also play an important role.

To investigate the relationship between breast-feeding duration and indices of neuronal integrity and function, we conducted a pilot study using proton magnetic resonance spectroscopy (^{1}H MRS) in healthy boys (age 8-10 years, mean 9.1 ± 0.9 years, n = 38). Regions of interest included right and left dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Subjects were breastfed for an average of 9.83 ± 1.7 mo (range: 0-42 mo). Following a median split of breastfeeding duration, we compared children who had received ⩾ 12 mo (n = 16, mean duration: 20 ± 8.9 mo) of breastfeeding with those who had received < 12 mo (n = 22, mean duration: 2.9 ± 3.2 mo). There were no significant differences in demographic variables between groups. Children receiving ⩾ 12 mo of breastfeeding exhibited higher concentrations of *N*-acetyl aspartate (NAA), a putative marker of neuronal integrity, in the right DLPFC and ACC compared with subjects receiving < 12 mo breastfeeding (Figure 3). Children receiving ≥ 12 mo breastfeeding also exhibited higher levels of glutamate+glutamine (Glx) in the right DLPFC and ACC. These preliminary data suggest that longer durations of breastfeeding may be an important determinant of cortical functional integrity in brain regions mediating attention and executive function in healthy developing children.

In summary, evidence from animal studies suggests that normal brain development requires optimal levels of DHA which has neurotrophic and neuroprotective properties. A potential ultrastructural mechanism mediating the beneficial effects of DHA on synaptic maturation and axo-dendritic connectivity is increased F-actin cytoskeletal stability in pre- and post-synaptic terminals mediated through reductions in PKC activity. Additional evidence from non-human primate and clinical imaging studies suggest that low DHA levels during perinatal development may lead to long-standing impairments in functional connectivity in cortical networks as well as the emergence of cognitive impairment, hyperactivity/inattention and emotional symptoms in children. Taken collectively, these

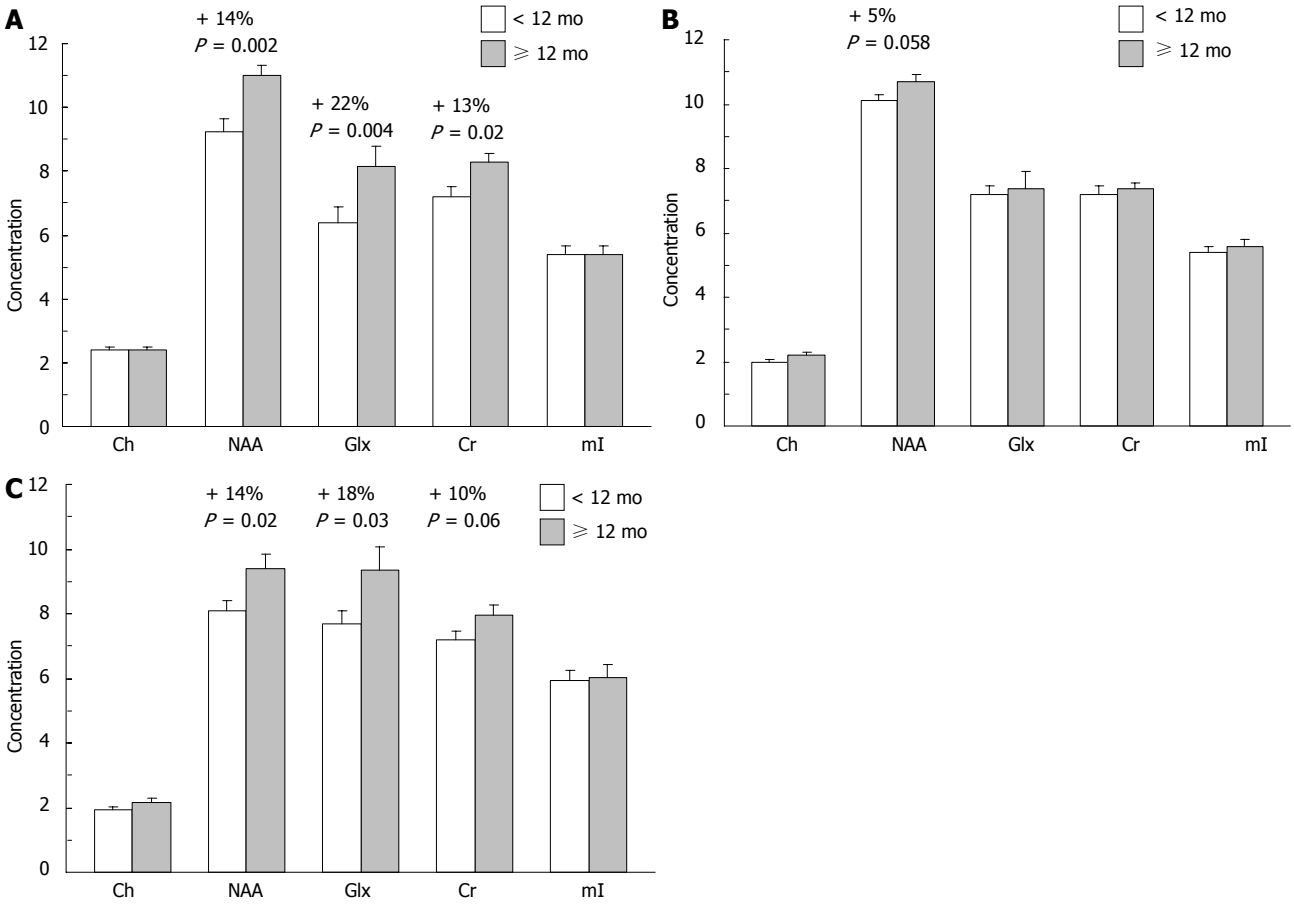

Figure 3 Mean concentrations of choline (Ch), N-acetyl aspartate (NAA), glutamate+ glutamine (Glx), creatine (Cr), and myo-inositol (ml) in the right dorsolateral PFC (A), left dorsolateral PFC (B), and anterior cingulate cortex (C) of children breastfed for < 12 mo (*n* = 22) or ⩾ 12 mo (*n* = 16). Note that NAA concentrations are significantly greater in the right dorsolateral PFC and anterior cingulate cortex of children breastfed for ⩾ 12 mo vs < 12 mo. Values are group means ± SEM. PFC: Prefrontal cortex.

associations support the assertion that cortical DHA accrual during perinatal brain development may play a role in the maturation of human cortical networks mediating cognitive and emotional processes.

IMPLICATIONS FOR PSYCHOPATHOLOGY

Major depressive disorder (MDD), bipolar disorder, schizophrenia, and ADHD are chronic and recurrent neuropsychiatric disorders that are a prominent cause of premature disability. The initial onset of ADHD typically occurs prior to seven years of age, and the initial onset of major mood and psychotic disorders frequently occur during adolescence or early adulthood[199-201]. Functional neuroimaging studies suggest that deficits in the functional maturation of frontal connectivity with limbic structures including the amygdala and/or the striatum are associated with psychopathology[202-206]. For example, event-related fMRI studies have repeatedly observed greater amygdala activation, and associated deficits in orbitofrontal activation, in response to emotional stimuli in youth and adults with bipolar disorder[207-209]. Although the initial onset of major psychiatric disorders commonly coincides with active and dynamic changes in frontal circuit connectivity, and psychopathology is associated with deficits in frontal circuit connectivity, a causal relationship has not been established. Moreover, the etiological mechanisms contributing to frontal circuit connectivity deficits in psychiatric disorders remain poorly understood.

Evidence from cross-national and cross-sectional studies suggests that LC*n*-3 fatty acid deficiency is relevant to pathophysiology and potentially etiology of different psychiatric disorders. Cross-national epidemiological studies have found that higher per capita intake of fish/seafood, a surrogate for LC*n*-3 fatty acid intake and status[210-212], is associated with lower lifetime prevalence rates of unipolar and bipolar depression[213-215]. Several population studies have similarly found that lower LC*n*-3 fatty acid intake is associated with increased risk for developing depressive symptoms[216-221]. It is also relevant that a large percentage of adolescents residing in western countries consume low quantities of LC*n*-3 fatty acids in their habitual diet[222-225], and lower LC*n*-3 fatty acid intake by adolescents is associated with a higher prevalence

of depressive symptoms[226-228]. Together, these data suggest that higher habitual dietary LC*n*-3 fatty acid intake may be protective against the development of mood dysregulation.

Habitual dietary LC*n*-3 fatty acid intake is highly correlated with erythrocyte membrane LC*n*-3 fatty acid levels[212], and multiple case-control studies have observed significant erythrocyte membrane LC*n*-3 fatty acid deficits in patients with psychopathology. A meta-analysis of 14 case-control studies found significantly lower erythrocyte EPA and DHA levels in MDD patients[229]. In bipolar patients, three independent studies have observed significant erythrocyte DHA deficits compared with healthy controls[230-232]. Importantly, erythrocyte DHA deficits have also been observed in pediatric and adolescent patients with MDD or bipolar disorder proximal to illness onset[233-235]. Medication-naïve first-episode psychotic patients exhibit erythrocyte DHA deficits compared with healthy controls[236,237], and a recent meta-analysis of 18 case-control studies observed significant DHA deficits in schizophrenic patients[238]. A recent meta-analysis of nine cross-sectional studies observed significantly lower blood DHA levels in ADHD children compared with healthy controls[239]. Together, these case-control studies provide evidence that different psychiatric disorders are characterized by low DHA status which coincide with, and may precede, the initial onset of psychopathology.

Dietary LC*n*-3 fatty acid supplementation has been found to significantly increase patient erythrocyte LC*n*-3 fatty acid levels[240-242]. This observation indicates that LC*n*-3 fatty acid deficits in psychiatric patients are modifiable by increasing dietary LC*n*-3 fatty acid intake. Importantly, meta-analyses of controlled trials have observed a significant advantage of LC*n*-3 fatty acid supplementation over placebo for reducing depressive symptoms in patients with MDD[243] or bipolar disorder[244]. Preliminary trials have found that LC*n*-3 fatty acid supplementation significantly reduces depression and manic symptom severity in pediatric and adolescent patients[235,241,242,245]. Accumulating evidence also suggests that LC*n*-3 fatty acid supplementation may be efficacious for the treatment of positive and negative symptoms in patients with or at ultra-high risk for developing schizophrenia[240,246,247], and for reducing attention deficits in pediatric and adolescent ADHD patients[239,248]. These data suggest that LC*n*-3 fatty acid deficits observed in patients with psychiatric disorders are correctable and associated with psychiatric symptom severity.

In general human erythrocyte and frontal cortex DHA levels are positively correlated[1], though non-human primate studies indicate that DHA recuperation occurs more rapidly in erythrocytes than cortical gray matter[2]. A growing number of case-control studies have investigated the fatty acid composition of postmortem frontal gray matter from patients with mood and psychotic disorders. Some studies have observed lower LC*n*-3 fatty acid levels[249-253] while others have not[254-256]. Our group reported that young adult patients with MDD[249], bipolar disorder[250], and schizophrenia[251] exhibit significant frontal cortex DHA deficits compared with controls. In a preliminary postmortem study, we also found that DHA composition increases sharply in the frontal cortex during normal human adolescent development, and that this increase is significantly blunted in young adult suicide victims[257]. It is also relevant that postmortem brain studies have observed reduced dendritic spine density and synaptic markers in the frontal cortex of patients with mood or psychotic disorders[258-260]. While these findings suggest that psychopathology may be associated with deficits in cortical DHA accrual and reduced synaptic density, limitations associated with the postmortem approach constrain interpretation[261].

Emerging evidence from structural neuroimaging studies provide additional support a beneficial effect of LC*n*-3 fatty acids on cortical integrity over the lifespan[262-266]. For example, one study found that greater habitual dietary LC*n*-3 fatty acid intake, which is positively correlated with erythrocyte DHA composition, was associated with larger cortical gray matter volumes in several corticolimbic regions including the anterior cingulate cortex, hippocampus, and amygdala[262]. It is relevant, therefore, that patients with psychiatric disorders commonly exhibit gray matter volume deficits in the anterior cingulate cortex, hippocampus, and amygdala[267-269]. Similar to children and adolescents born preterm, patients with ADHD[270-275], mood disorders[276-283], and psychotic disorders[284-287] also exhibit decreased frontal white matter tract integrity and reduced functional connectivity within cortical networks. Together these findings support the hypothesis that perinatal deficits in DHA accrual may contribute to diminished cortical circuit development observed in major psychiatric disorders.

The pathogenic mechanisms underlying major psychiatric disorders are viewed as polygenic and multifactorial, and there is strong evidence for familial transmission and subtotal heritability estimates indicating the important contribution of shared to-be-defined environmental factors[288-293]. Reviewed evidence supports a hypothetical link between dietary LC*n*-3 fatty acid deficiency and the familial transmission of psychopathology (Figure 4). Specifically, observational and controlled studies suggest that maternal DHA status during pregnancy is an important determinant of gestational length and risk of preterm birth[294-299]. For example, in Japan where maternal DHA status based on breast milk DHA levels (1.1%) is approximately 6-fold higher than breast milk DHA levels in the United Sates (0.17%)[189], the prevalence rate of preterm birth is approximately one-third that observed in United Sates (Japan: 4.3%-5.0% *vs* United Sates: 11.7%)[300,301]. Importantly, adolescent and young adult females of childbearing potential with mood disorders residing in the United Sates exhibit significant blood

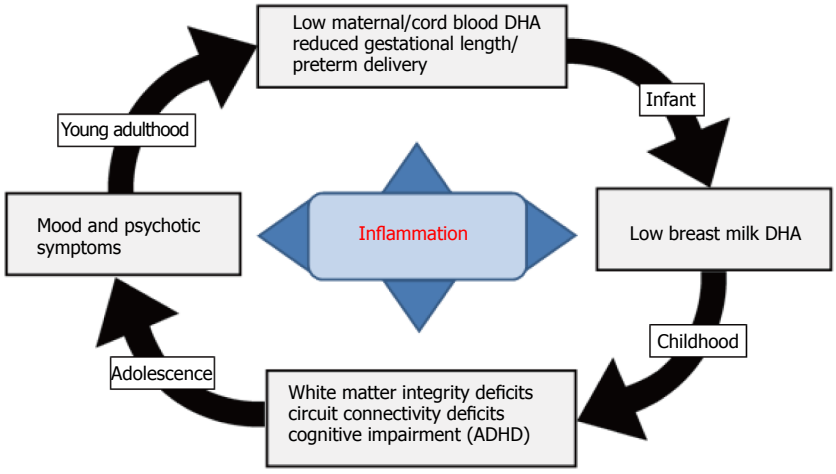

Figure 4 Diagram illustrating a hypothetical role of LCn-3 fatty acid deficiency in the familial transmission of psychopathology. Adolescent and young adult females with mood disorders exhibit significant blood DHA deficits leading to reduced fetal (cord blood) DHA accrual during pregnancy. Low maternal DHA status during pregnancy also increases risk for preterm delivery due in part to elevated pro-inflammatory cytokine levels, as well as low breast milk DHA levels postpartum. Uncorrected deficits in fetal brain DHA accrual lead to long-standing deficits in white matter resilience and integrity and reduced functional connectivity in fronto-striatal circuits and increase risk of developing ADHD symptoms in childhood. Deficits in white matter integrity and reduced functional connectivity in fronto-limbic circuits during adolescent development is associated with the emergence of emotional and/or thought dysregulation and the onset of mood and/or psychotic symptoms. DHA: Docosahexaenoic acid; ADHD: Attention deficit/hyperactivity disorder.

DHA deficits compared with healthy women[231,235], and are at increased risk for preterm delivery[302-304]. Risk of preterm delivery is associated with maternal or intrauterine elevations in pro-inflammatory cytokines including interleukin-6 (IL-6)[305-307], and lower LC*n*-3 fatty acid intake and status is associated with higher serum IL-6 levels[308]. The very low DHA status exhibited by mothers with mood disorders would be anticipated to reduce fetal cortical DHA accrual *in utero*, increase maternal risk for preterm birth and associated deficits in third trimester fetal cortical DHA accrual, and reduce postnatal fetal DHA accrual secondary to low breast milk DHA levels. Based the reviewed evidence, such perinatal deficits in cortical DHA accrual would be predicted to impair cortical circuit maturation and increase the risk of developing psychopathology during childhood and adolescent development.

CONCLUSION

Over the past 30 years a body of evidence from animal and clinical studies supports the general assertion that normal brain development requires optimal DHA levels. Rodent studies suggest that cortical DHA has neurotrophic as well as neuroprotective properties in the developing and adult brain, and that dietary-induced reductions in perinatal rat brain DHA accrual are associated with deficits in synaptic maturation and functional plasticity. Deficits in perinatal rat brain DHA accrual also lead to impairments on neurocognitive tasks requiring activity-dependent synaptic plasticity. Decreases in F-actin cytoskeletal stability in pre- and post-synaptic terminals, as well as reduced resilience against neurotoxic, synaptotoxic, and myelinotoxic insults, represent plausible mediating mechanisms. Non-human primate studies further suggest a link between *n*-3 fatty acid deficiency during perinatal development and long-standing deficits in functional connectivity in cortical networks, hyperactivity, and impairments in visual attention. Evidence from animal studies therefore provide strong evidence for a role of perinatal DHA accrual for the normal maturation of cortical circuits and provide important clues into candidate molecular and ultrastructural mechanisms.

Additional evidence for a role of DHA in normal brain development comes from human studies finding that preterm birth, which results in deficits in third trimester fetal cortical DHA accrual, is associated with enduring prefrontal cortical network connectivity deficits, and a spectrum of neurocognitive impairments which may be mitigated by postnatal high-dose DHA supplementation. Preterm birth is also associated with increased risk for psychiatric disorders including ADHD, psychosis, and mood disorders which are associated with deficits in functional connectivity within cortical networks. More direct evidence is provided by prospective longitudinal studies finding that lower cord blood DHA levels are associated with the emergence of cognitive impairment, hyperactivity/inattention and emotional symptoms in children. Moreover, longer breastfeeding duration (a putative surrogate for early postnatal DHA intake) is associated with improvements in white matter microstructure and volume and better neurocognitive outcomes in childhood, adolescence, and adulthood. Taken in conjunction with non-human primate imaging data, these associations suggest that cortical DHA accrual during perinatal brain development may play a role in the maturation of human cortical networks mediating cognitive and emotional processes that are dysregulated in psychiatric disorders.

It is not currently known whether LC*n*-3 fatty acid supplementation alone is sufficient to reverse deficits

in functional connectivity within cortical networks once established. Indeed, it is possible that cortical circuit maturation deficits secondary to LC*n*-3 fatty acid deficits may represent a permanent neurodevelopmental "scar" that is potentially irreversible once established. However, LC*n*-3 fatty acid supplementation has been found to reduce symptom severity in patients with psychiatric disorders and neurological and cognitive symptoms in preterm infants. Moreover, a controlled functional neuroimaging trial found that DHA supplementation increased cortical activity in prefrontal regions, and decreased activity in the temporal cortex and cerebellum, during performance of sustained attention task in healthy developing children[309]. While these findings suggest that increasing DHA status may augment functional connectivity within fronto-limbic networks, additional neuroimaging studies will be required to evaluate this potential therapeutic mechanism.

Although the role of perinatal brain DHA accrual on the maturation and long-term stability of cortical circuitry is only beginning to be fully understood, extant translational evidence suggests that DHA plays a role in the initial development and early maturation of cortical circuits. Emerging evidence from human neuroimaging studies further suggests that psychiatric disorders that initially emerge in childhood and adolescence and associated with low blood DHA levels are characterized by frontal circuit deficits compared with healthy developing youth. Moreover, maternal LC*n*-3 fatty acid deficiency is associated with increased risk of preterm birth, deficits in functional connectivity with cortical circuits, and ensuing cognitive impairments and mood dysregulation. These associations provide a neurobiological foundation and impetus for additional research to develop a more comprehensive understanding of the requirement for LC*n*-3 fatty acids during critical periods of neurodevelopment. Based on existing evidence, this research could have significant implications for informing novel early intervention strategies aimed at reducing the transmission of psychopathology.

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