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Role of omega-3 fatty acids in brain development and function: Potential implications for the pathogenesis and prevention of psychopathology

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Abstract

The principle omega-3 fatty acid in brain, docosahexaenoic acid (DHA), accumulates in the brain during perinatal cortical expansion and maturation. Animal studies have demonstrated that reductions in perinatal brain DHA accrual are associated with deficits in neuronal arborization, multiple indices of synaptic pathology including deficits in serotonin and mesocorticolimbic dopamine neurotransmission, neurocognitive deficits, and elevated behavioral indices of anxiety, aggression, and depression. In primates and humans, preterm delivery is associated with deficits in fetal cortical DHA accrual, and children/adolescents born preterm exhibit deficits in cortical gray matter maturation, neurocognitive deficits particularly in the realm of attention, and increased risk for attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. Individuals diagnosed with ADHD or schizophrenia exhibit deficits in cortical gray matter maturation, and medications found to be efficacious in the treatment of these disorders increase cortical and striatal dopamine neurotransmission. These associations in conjunct with intervention trials showing enhanced cortical visual acuity and cognitive outcomes in preterm and term infants fed DHA, suggest that perinatal deficits in brain DHA accrual may represent a preventable neurodevelopmental risk factor for the subsequent emergence of psychopathology.

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1. Introduction

Because mammals lack the capacity to introduce double bonds at the omega or n-6 and omega or n-3 positions from the carbonyl end of oleic acid, they are dependent on dietary sources of linoleic acid (LA, 18:2n-6) and α -linolenic acid (ALA, 18:3n-3), respectively, to meet their physiological needs for these families of fatty acids. Good dietary sources of ALA include flaxseed, linseed, canola, soy, and perilla oils. The principle omega-3 fatty acid metabolites of ALA are eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). DHA synthesis from dietary ALA is limited in humans [1-4]. However, preformed DHA and EPA can be obtained directly from the diet, particularly

fatty fish, e.g., salmon, trout, and tuna. Dietary DHA is significantly more effective than is dietary ALA as a source for DHA accrual in the developing human [5-7], primate [8], and rat brain [9], as well as in the adult rat brain [10].

Mammalian brain tissue is predominantly composed of lipids which are comprised of different saturated, monounsaturated, and polyunsaturated fatty acids (Fig. 1). The principle omega-3 fatty acid found in brain is DHA, comprising 10-20% of total fatty acids composition, whereas the omega-3 fatty acids ALA, EPA, and docosapentaenoic acid (22:5n-3) comprise <1% of total brain fatty acid composition. The ratio of saturated, monounsaturated, and polyunsaturated fatty acids observed in postmortem human frontal cortex is generally conserved among other mammals, including monkeys [11], rats [12], and mice [13]. For example, adult rodents/primates maintained on a diet containing

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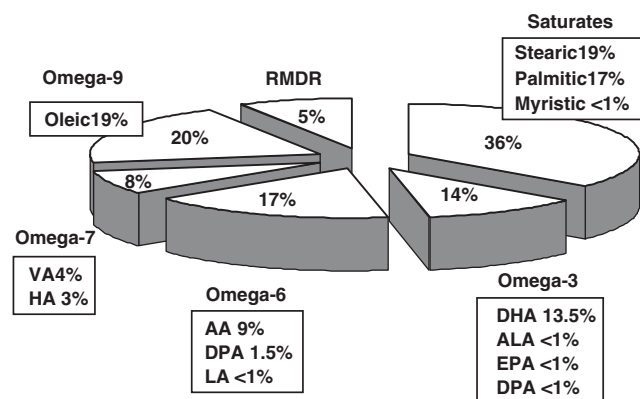


Fig. 1. Fatty acid composition of human postmortem prefrontal cortex (Brodmann Area 10) from normal male ($n = 15$) and female ($n = 15$) subjects aged 29–45 years old that resided in the US at time of death. Cortical fatty acid composition was determined by gas chromatography. Human frontal cortex is composed of a ratio of saturated fatty acids (~36% of total brain fatty acids), monounsaturated fatty acids, predominantly the omega-9 fatty acids oleic acid (~20% of total brain fatty acids), and polyunsaturated fatty acids, predominantly the omega-6 fatty acid, arachidonic acid (AA) (~10% of total brain fatty acids), and the omega-3 fatty acid, DHA (~15% of total brain fatty acids). The omega-3 fatty acids α -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA, 22:5n-3) comprise <1% of total brain fatty acid composition. The omega-6 fatty acids linoleic acid (LA) and docosapentaenoic acid (DPA, 22:5n-6) comprise ~2% of total brain fatty acid composition. Heptadecenoic acid (HA, 17:1n-7) and vaccenic acid (VA, 18:1n-7) are derived from palmitic acid. Remainder (RMDR) is composed of intermediate fatty acid metabolites and represents approximately 5% of total brain fatty acids.

ALA exhibit frontal cortex DHA concentrations of ~20% of total fatty acids. Studies in adult rodents and primates also demonstrate that DHA concentrations differ between brain regions. In rodents, DHA is most concentrated in the frontal cortex and hippocampus (16–22% of total fatty acids) and less concentrated in the striatum (~14% of total fatty acids), midbrain (~13% of total fatty acids), and pons/medulla (~10% of total fatty acids) [13–17]. In the neonatal baboon brain, the highest DHA concentrations are in the globus pallidus, superior colliculus, putamen and precentral regions (14% of total fatty acids), followed by cortical regions, including the frontal cortex (12.9% of total fatty acids) [18].

Within brain tissues, DHA preferentially accumulates in growth cones, synaptosomes, astrocytes, myelin, microsomal, and mitochondrial membranes [19–24]. DHA is predominantly acetylated into the *sn*-2 position of the phospholipids phosphatidylethanolamine and phosphatidylserine, and saturated fatty acids, predominantly stearic acid or palmitic acid, occupy the *sn*-1 position [25]. Fatty acids are mobilized from membrane phospholipids by PLA₂-mediated hydrolyses of the acyl ester bond. The calcium-independent iPLA₂ and PlsEtn-PLA₂ isoforms mobilize DHA, and the calcium-depend-

ent cPLA₂ isoform preferentially mobilizes the omega-6 fatty acid arachidonic acid [26]. Once mobilized, DHA may act as a second messenger in the modulation of synaptic signal transduction pathways [27], is metabolized into anti-inflammatory docosanoids [28], is degraded by β -oxidation or peroxidation [29], or is reacylated into membrane phospholipids by acyltransferases. It has been estimated that approximately 2–8% of brain DHA is replaced daily due to metabolism, and DHA has a loss half-life in total brain phospholipids of 33 days under steady-state ALA intake [30,31].

The dynamics associated with brain DHA accrual during perinatal development, and the consequences of deficits in perinatal brain DHA accrual on brain maturation and function, have been most extensively characterized in rodents, and preliminarily characterized in nonhuman primates and humans.

2. Rodents

2.1. Brain DHA accrual during perinatal brain development

Under conditions of maternal dietary ALA and/or DHA exposure during perinatal rat brain development, DHA concentrations increase sharply between embryonic day 14 and birth (embryonic day 21) to constitute 10–12% of total fatty acids. Postnatally, DHA concentrations continue to increase to plateau on postnatal day 21 at approximately 10–20% of total fatty acids [32–34]. This perinatal increase in cortical DHA concentrations coincides with active periods of neurogenesis, neuroblast migration and differentiation, synaptogenesis, and axonal myelination [32,33,35,36]. A role for DHA in cortical maturation is supported by findings that DHA promotes nerve growth factor (NGF) expression in brain [37], augments NGF-induced neurite outgrowth [38], and promotes neuronal differentiation and arborization [39]. Moreover, DHA accumulates in neuronal growth cones during gestation [40,41] where it plays an important role in growth cone membrane signaling dynamics and synaptogenesis [42,43]. Collectively, these findings are consistent with DHA having neurotrophic properties in the promotion of neuronal arborization and synaptogenesis during perinatal brain maturation.

2.2. Consequences of brain DHA deficiency

2.2.1. Brain fatty acid composition

Under our experimental conditions, maternal and offspring dietary ALA-deficiency led to a ~70% reduction in frontal cortex DHA concentrations in first generation adult (P90) offspring, and second generation offspring exhibited greater reductions (~80%) (Fig. 2). Postweaning (P21-P90) dietary ALA-deficiency led to a

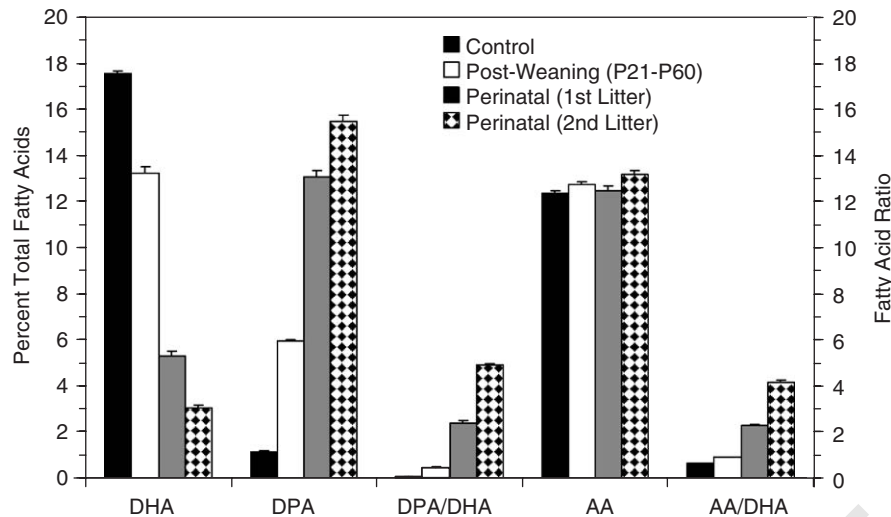


Fig. 2. Rat frontal cortex DHA concentrations (mean \pm S.E.M. percent of total fatty acids) and ratios of the omega-6 fatty acids docosapentaenoic acid (DPA, 22:5n-6) and arachidonic acid (AA) to DHA from adult (P90) rats (1) maintained on α -linolenic acid (ALA)-fortified diets (Control, $n = 20$), (2) rats subjected to post-weaning (P21–P90, $n = 13$) dietary ALA deficiency, and (3) rats subjected to perinatal (E0–P90) dietary ALA deficiency. For rats subjected to perinatal (E0–P90) dietary ALA deficiency, mothers were placed on ALA-deficient chow for 1 month prior to conception (1st litter, $n = 9$) or 2 months prior to conception (2nd litter, $n = 5$). Note: (1) Deficits in frontal cortex DHA concentrations are accompanied by reciprocal elevations in the omega-6 fatty acid DPA and the DPA:DHA ratio. (2) Deficits in cortical DHA concentrations are not associated with alterations in AA concentrations, but are associated with elevations in the AA:DHA ratio. (3) Greater maternal DHA deficiency is associated with greater cortical DHA deficiency (1st litter vs. 2nd litter). Cortical fatty acid compositions were determined by gas liquid chromatography after preparation of fatty acid methyl esters from extracts of brain lipids.

25% reduction in cortical DHA concentrations (Fig. 2). Cortical deficits in DHA are associated with reciprocal elevations in the omega-6 fatty acid docosapentaenoic acid (DPA, 22:5n-6) and DPA:DHA and AA:DHA ratios (Fig. 2). Deficits in brain DHA concentrations resulting from perinatal dietary omega-3 fatty acid deficiency can be normalized following dietary omega-3 fatty acid fortification. However, unlike peripheral tissues including serum, red blood cells, and liver, which recuperate control-level DHA concentrations after approximately 1–2 weeks, recuperation of brain DHA is considerably slower, requiring approximately 8–12 weeks to restore control levels from a \sim 70% deficiency [12,17]. In conjunction with brain DHA recuperation, DPA concentrations decrease reciprocally and DPA:DHA and AA:DHA ratios normalize.

Following rat brain maturation, whole brain DHA concentrations appear to be relatively resistance to DHA depletion following chronic (7 months) dietary omega-3 fatty acid deficiency [44]. The latter phenomenon may be attributable a significant $>$ 2-fold reduction in the loss half-life of DHA in rat brain in response to chronic ALA-deficiency [30]. However, dietary ALA deficiency initiated in adult mice (P60) does result in a progressive reduction in DHA concentrations in frontal cortex and striatum (Fig. 3). Although the discrepancy between these findings and those of Bourre et al. [44] may represent differences in rat and mouse brain DHA metabolism or brain-regional specific susceptibilities to DHA loss, these data would indicate that dietary

omega-3 fatty acid intake is necessary for the maintenance of regional brain DHA concentrations even following brain maturation. This receives further support from recent studies finding that adult female rats maintained on an omega-3 fatty acid-deficient diet exhibit significant reductions in brain DHA concentrations after one reproductive cycle that cannot be attributed to the effects of diet [45,46].

Different brain regions exhibit a differential loss of DHA accrual following perinatal omega-3 fatty acid deficiency. The greatest reductions are observed in the frontal cortex $>$ hippocampus $>$ cerebellum $>$ striatum $>$ hypothalamus $>$ midbrain [13,15,17]. Moreover, brain DHA concentrations recuperate at different rates in different brain regions. The frontal cortex and hippocampus are among the last brain regions to fully recuperate normal DHA concentrations following dietary fortification [12,13,17]. Therefore, perinatal deficits in DHA accrual within the frontal cortex and hippocampus may be the most difficult to restore in the absence of specific postnatal dietary intervention.

2.2.2. Neuroanatomy

Perinatal omega-3 fatty acid deficiency is not associated with gross neuronal lamination abnormalities or neuronal loss in the rat hippocampus [47–49]. A neuroimaging study did not find gross alterations in brain gray or white volumes in omega-3 fatty acid-deficient aged ($>$ 15 months) rats relative to aged control rats [50], though aged rats maintained on

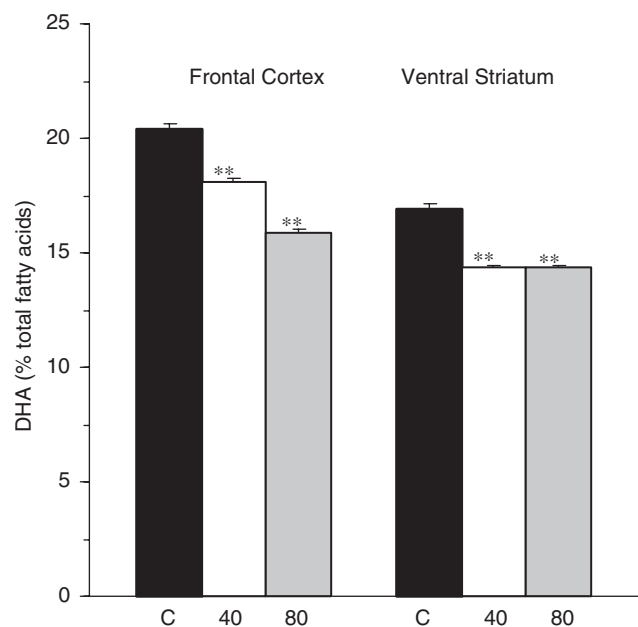


Fig. 3. Effect of dietary α -linolenic acid (ALA)-deficiency on adult mouse (DBA/2J) frontal cortex and ventral striatum DHA concentrations (mean \pm SEM percent of total fatty acids). Control mice ($n = 17$) were maintained on ALA-fortified diets for the duration of the experiment. Experimental mice were switched from ALA-fortified diet to ALA-deficient diets on postnatal day 60, and maintained on ALA-deficient diets for either 40 or 80 d, at which point they were sacrificed and tissue fatty acid composition determined by gas chromatography. Note: (1) 40 and 80 d feeding of ALA-deficient diets results in a progressively greater loss of DHA in the adult mouse frontal cortex, whereas DHA loss in the ventral striatum does not decrease further between 40 and 80 d. (2) DHA concentrations are initially greater in mouse frontal cortex relative to ventral striatum under steady state ALA intake.

normal feed may also exhibit age-related deficits in gray and white matter volume [51,52]. Nevertheless, reductions in NGF expression [37], neuronal size [47,48], and neuronal arborization [39] have been observed in DHA-deficient rat brain. Moreover, ultrastructural alterations in synaptic morphology, including greater synaptic vesicle densities in active release zones, have also been observed [53,54]. These findings are consistent with the role of DHA in promoting neuronal arborization and synaptogenesis during development, and the maintenance of normal synaptic functioning following maturation.

2.2.3. Plasma membrane properties

In synaptic membranes, DHA preferentially accumulates in phosphatidylethanolamine and phosphatidylserine phospholipids, and perinatal reductions in brain DHA (-75%) are associated with a significant reduction ($\sim 30\%$) in neuronal membrane phosphatidylserine concentrations [55,56]. Conversely, perinatal fish oil (EPA + DHA) supplementation resulting in significant elevations ($+15\%$) in brain DHA concentrations, is associated with a significant increase ($+30\%$) in

phosphatidylserine concentrations [57]. Because phosphatidylserine plays an important role in mediating the binding of several structural and signal transduction proteins with the plasma membrane (see below), reductions in synaptic membrane phosphatidylserine concentrations would be anticipated to lead to a dysregulation in synaptic second messenger cascades, deficits in growth cone motility, synaptogenesis, and synaptic function.

2.2.4. Synaptic signal transduction

Binding of the myristoylated alanine-rich C kinase substrate (MARCKS) protein to synaptic plasma membranes is mediated in part by electrostatic interactions between the highly basic phosphorylation site domain of the MARCKS protein and acidic phosphatidylserine [58]. Perinatal dietary omega-3 fatty acid deficiency (-70% DHA) was associated with a significant reduction (-30%) in mature neuronal membrane phosphatidylserine concentrations [55,56], and a significant reduction (-35%) in membrane-bound MARCKS expression [27]. Biochemical studies have demonstrated that binding of MARCKS to the plasma membrane plays an important role in regulating the phosphoinositide signal transduction pathway and intracellular calcium homeostasis [59–62]. These findings would suggest that even small reductions in MARCKS membrane binding would lead to elevations in receptor-generated phosphoinositide (IP_3) synthesis and intracellular free calcium concentrations. Perturbations in intracellular calcium homeostasis during neuronal development would be anticipated to induce premature growth cone collapse and deficits in synaptogenesis [63].

MARCKS membrane binding also plays an important role in modulating filamentous actin cytoskeletal plasticity to regulate neurotransmitter vesicle trafficking and neurotransmitter release efficacy (reviewed in [64]). Reductions in MARCKS binding to the plasma/vesicle membrane as a consequence of perinatal dietary omega-3 fatty acid deficiency could account for the observation that omega-3 fatty acid-deficient rats exhibit use-dependent reductions in neurotransmitter vesicle densities within presynaptic terminals [53] and reduced stimulated extracellular levels of several neurotransmitters, including serotonin [65], acetylcholine [66], and dopamine [67]. Deficits in filamentous actin cytoskeletal plasticity would also be anticipated to lead to a disruption of growth cone migration and motility, dendritic spine motility, and ultimately synaptogenesis [68–70].

Reductions in synaptic membrane phosphatidylserine concentrations also has implications for the protein kinase C (PKC) signal transduction pathway. Binding of PKC with phosphatidylserine is necessary for membrane binding and maximal kinase activity [71], and perinatal

1 omega-3 fatty acid deficiency (−70% DHA) has been
 2 associated with significant reductions in membrane-
 3 associated PKC isozyme (γ , ζ) expression [27]. Deficits in
 4 the PKC signal transduction pathway within neuronal
 5 growth cones during development would be anticipated
 6 to impair neurite outgrowth and synaptogenesis [72,73].
 7 Furthermore, PKC activation is associated with long-
 8 term elevations in neurotransmitter release efficacy via
 9 the phosphorylation of MARCKS (reviewed in [74]),
 10 and omega-3 fatty acid deficiency is associated with
 11 decrements in serotonergic and dopaminergic neuro-
 12 transmitters [75] and release of dopamine [67,76–79],
 13 serotonin [65], and acetylcholine [66].

14 Alterations in PKC signaling activity would also have
 15 implications for the activity, trafficking and membrane
 16 localization of serotonin 5-HT_{2A} receptors [80], dopa-
 17 mine D₂ receptors [81], noradrenalin transporters [82],
 18 dopamine transporters [83] and the serotonin transpor-
 19 ters [84]. Omega-3 fatty acid deficiency is associated with
 20 significant elevations in cortical serotonin 5-HT_{2A} re-
 21 ceptor binding density [76,85] and reductions in dopa-
 22 mine D₂ receptor binding density [67,76,85]. Although
 23 alterations in dopamine transporter binding have not
 24 been observed in the DHA-deficient rat brain [86],
 25 amphetamine-induced dopamine release is impaired in
 26 DHA-deficient rats [79], suggesting deficits in dopamine
 27 transporter function. Similarly, fenfluramine-induced
 28 serotonin release is impaired in DHA-deficient rats [65],
 29 suggesting deficits in serotonin transporter function.

30 Deficits in rat brain serotonin and dopamine neuro-
 31 transmission resulting from prenatal omega-3 fatty acid
 32 deficiency can be normalized if dietary omega-3 fatty acid
 33 fortification is initiated early in postnatal development.
 34 Specifically, Kodas et al. [65] found that deficits in
 35 fenfluramine-induced serotonin release in the adult (P60)
 36 rat hippocampus could be normalized when dietary
 37 omega-3 fatty acid fortification was initiated on postnatal
 38 day 0, 7 or 14, but not when initiated on postnatal day 21
 39 despite the normalization of hippocampal DHA concen-
 40 trations. Similarly, deficits in tyramine-induced dopamine
 41 release in the adult (P60) rat medial prefrontal cortex and
 42 nucleus accumbens could be normalized when dietary
 43 omega-3 fatty acid fortification was initiated on postnatal
 44 day 0, 7 or 14, but not when initialized on postnatal day
 45 21 despite the normalization of brain DHA concentra-
 46 tions in the prefrontal cortex [77]. These studies suggest
 47 that there is a critical developmental window of
 48 opportunity to normalize deficits in dopamine and
 49 serotonin neurotransmission following prenatal omega-3
 50 fatty acid deficiency in rat brain.

2.2.5. Behavior

51 The net effect of perinatal deficits in brain DHA
 52 accrual on behavioral and neurocognitive processes in
 53 omega-3 fatty acid deficient rats has been reviewed
 54 elsewhere [87]. Briefly, rodent perinatal omega-3 fatty

55 acid deficiency is associated with deficits in hippocam-
 56 pus-dependent spatial learning [88,89], deficits in frontal
 57 cortex-dependent working memory [90], deficits in
 58 olfactory discrimination learning [91], and elevated
 59 behavioral indices of anxiety [92], aggression and
 60 depression [93]. Deficits in hippocampus-dependent
 61 spatial learning [89], but not elevated indices in anxiety
 62 [92], are corrected following dietary omega-3 fatty acid
 63 fortification.

2.2.6. Behavioral pharmacology

64 Pharmacological challenge studies have found that
 65 deficits in perinatal brain DHA accrual is associated
 66 with significant elevations in amphetamine-induced
 67 locomotor activity [94], significant decrements in loco-
 68 motor activity in response to the cholinergic muscarinic
 69 receptor antagonist scopolamine [95], and significant
 70 decrements in catalepsy induced by the predominantly
 71 dopamine D₂ antagonist haloperidol [94]. Decrements in
 72 haloperidol-induced catalepsy, but not augmented
 73 amphetamine-induced locomotor activity, were normal-
 74 ized following early dietary fortification [94]. In the
 75 adult sensitization-resistant DBA/2J mice, chronic diet-
 76 ary ALA deficiency significantly augmented ampheta-
 77 mine-induced sensitization of locomotor activity [96].

3. Nonhuman primates

3.1. Brain DHA accrual during perinatal brain development

81 In the developing primate (monkey) brain, frontal
 82 cortex DHA concentrations at birth represent ~15% of
 83 total fatty acids, and between birth and 22 months of
 84 age, increase to comprise ~22% of total fatty acids
 85 [11,97]. Primates (baboon) born preterm (gestation week
 86 22 vs. term—gestation week 26) exhibit significantly
 87 lower (22–35%) postmortem brain DHA concentrations
 88 relative to term-born primates [98,99]. These findings
 89 indicate that in primates, the majority of brain DHA
 90 accrual occurs during the later phase of gestation.

3.2. Consequences of brain DHA deficiency

3.2.1. Brain fatty acid composition

91 A maternal diet low in ALA from 2 months prior to
 92 conception reduced neonatal monkey prefrontal cortex
 93 DHA concentrations by ~75% at birth relative to
 94 neonates whose mothers were maintained on a diet
 95 containing ALA [11,97]. Dietary omega-3 fatty acid
 96 fortification leads to a progressive increase in DHA
 97 concentrations in the DHA-deficient primate (monkey)
 98 cortex, reaching control levels after approximately 10–
 99 12 weeks [97,100]. By comparison, retinal DHA
 100 deficiency, and associated electroretinogram abnormal-

ities, were not restored to control levels following 3 years of dietary omega-3 fatty acid fortification [97]. Moreover, deficits in cortical DHA concentrations in preterm baboons were not restored to control (term, breastfed) levels following feeding with either human infant formula not fortified with DHA/EPA (-35%) or DHA/EPA-fortified formula (-10%) at 4 weeks [98]. These findings indicate that deficits in primate prenatal brain DHA accrual requires long-term (>4 weeks) daily dietary DHA intervention.

3.3. Behavior

Relative to rodents, little is known about the effects of perinatal omega-3 fatty acid deficiency on primate brain neurochemistry or behavior. Perinatal omega-3 fatty acid deficiency in primates is associated with deficits in visual acuity and electroretinogram abnormalities [11,97,101], visual attention processes [102], polydipsia (excessive thirst) [103], and increased home cage stereotypy and locomotion bouts [104]. Electroretinogram abnormalities have also been documented in neonatal baboons born preterm [105].

4. Humans

4.1. Brain DHA accrual during perinatal brain development

DHA accumulates in human brain tissue at a rapid rate (~14.5 mg/week) during the third trimester (gesta-

tional weeks 26–40) [106,107]. At term birth, DHA represents approximately 9% of total cortical fatty acid composition, and increases by an additional ~6% between birth and age 20 to compose ~15% total cortical fatty acid composition in postmortem brain tissue from subjects residing in the US at time of death [108]. Infants born preterm (<33 weeks of gestation) exhibit lower (-40%) postmortem cortical DHA concentrations relative to term infants when fed the same ALA-fortified formula postnatally [6,7,36,106,107]. These findings indicate that the majority of DHA accumulation occurs in the human brain during the last trimester of normal gestation, and that DHA continues to accumulate throughout postnatal brain maturation. As in rodents and primates, the linear increase in DHA accumulation in human frontal cortex between birth and 20 years of age corresponds with linear increases in frontal cortex white matter during this period, and additionally corresponds with the initial frontal gray matter expansion which continues until ~12 years of age and then declines thereafter [109,110] (Fig. 4).

4.2. Consequences of brain DHA deficiency

4.2.1. Prenatal deficiency

4.2.1.1. Brain fatty acid composition. Preterm infants fed formulas without DHA have lower red blood cell phospholipid DHA concentrations relative to those fed human milk [111] and DHA accumulates rapidly in the human fetal brain during the third trimester [36,106]. A number of randomized studies have measured and observed effects of DHA supplementation of infant

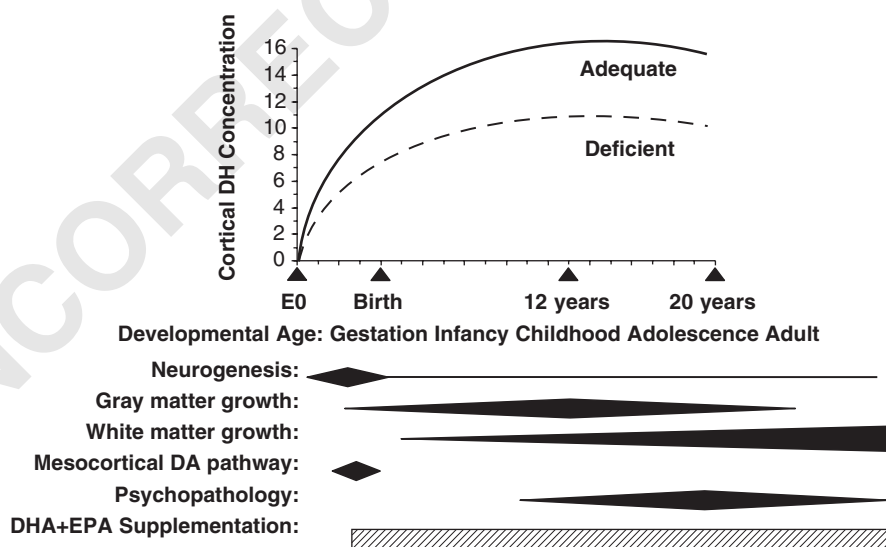


Fig. 4. Diagram illustrating hypothetical adequate and deficient human cortical DHA concentrations over the lifespan (embryonic day 0 (E0)–adulthood) in relation to the timing of perinatal neurogenesis, cortical gray and white matter expansion, maturation of the mesocortical dopamine pathway, and psychopathology onset (based on epidemiological data). It is proposed that increasing brain DHA beginning in midgestation with DHA + EPA supplementation of the mother would effectively prevent functional deficits in fetal brain DHA accrual during critical periods of cortical maturation, synaptogenesis, and myelination. It is further proposed that higher fetal/infant brain DHA concentrations during brain development may mitigate risk for neurocognitive deficits in childhood and psychopathology in young adulthood.

1 formula on visual acuity and other aspects of infant
2 development following premature birth (for reviews see
3 [112–114]). Infants born preterm (<36 weeks of gesta-
4 tion) and fed formulas without DHA after birth exhibit
5 lower (~40%) postmortem cerebral cortex DHA con-
6 centrations relative to term, human milk-fed, infants
7 [6,7,107]. These findings are consistent with those
8 obtained from primates born preterm [98,99].

9 Cerebellar DHA concentrations were also signifi-
10 cantly lower when the diet did not contain DHA,
11 however, there was no difference in cerebellar DHA
12 concentrations between infants born preterm and term
13 who had been fed the same infant formula [115],
14 suggesting that cerebellar cortex DHA accrual may
15 precede that of cerebral cortex during gestation. It is not
16 known for how long low brain DHA concentrations
17 persist following preterm delivery or whether dietary
18 DHA intake would reverse low DHA concentrations in
19 brain. Based on a primate recuperation study [97],
20 complete brain DHA recuperation would require
21 intensive (daily) and chronic (months) dietary DHA-
22 fortification.

23 *4.2.1.2. Neuroanatomy.* Although the effects of speci-
24 fic deficits in prenatal brain DHA accrual on human
25 neuroanatomical development are not known, neuro-
26 imaging studies have found that children or adolescents
27 that were born preterm (<33 weeks of gestation) exhibit
28 neuroanatomical abnormalities that are consistent with
29 deficits in perinatal corticogenesis. Specifically, preterm
30 children/adolescents exhibit significant reductions in
31 regional cortical and striatal gray matter volumes
32 [116,117], reduced amygdala and hippocampal volumes
33 [117], reduced corpus callosum [117,118] and white
34 matter volumes [118,119], and larger cerebral ventricles
35 [118] relative to age- and sex-matched term controls.
36 Although other factors associated with preterm delivery
37 may also contribute to these deficits, Peterson et al. [117]
38 found that regional volumetric deficits in preterm
39 children remained significant when preterm children
40 who had not had an intraventricular hemorrhage were
41 excluded from the analysis. It is not currently known
42 whether these deficits in gray and white matter volumes
43 are preventable with adequate postnatal DHA fortifica-
44 tion.

45 *4.2.1.3. Neurocognition.* Children and adolescents
46 born preterm exhibit a significantly higher incidence of
47 attention deficits, impulsivity, learning disability, lan-
48 guage impairments, hyperactivity, anxiety, motor im-
49 pairments, and poor social functioning relative to age-
50 and sex-matched term children/adolescents [120–128].
51 Preterm children are at increased risk for ADHD
52 [120,124], and postnatal dietary DHA supplementation
53 was found to improve visual attention processes in
54 infants born preterm [129,130], suggesting that third-

55 trimester DHA accrual plays an important role in the
56 maturation of brain regions implicated in attention,
57 including the dorsolateral prefrontal cortex (see below).
58 One study of maternal DHA supplementation during
59 pregnancy and at least seven observational studies link
60 higher maternal DHA status, or higher seafood intake
61 during pregnancy, with advantages for infant develop-
62 ment, including more mature sleep patterns in new-
63 borns, higher visual acuity, faster processing speed,
64 lower distractibility, higher stereo acuity and cognitive
65 function [131–138].

66 *4.2.2. Postnatal deficiency*

67 *4.2.2.1. Brain fatty acid composition.* After birth in-
68 fants are reliant on maternal breast milk (or formula) as
69 the sole source of DHA. Human breast milk DHA
70 concentrations are highly correlated with maternal
71 dietary DHA intake [139], and diets fortified with only
72 ALA do not increase breast milk DHA concentrations
73 [140]. Breast milk DHA concentrations vary widely
74 across different countries in accordance with dietary
75 seafood consumption rates, e.g., ~0.17% of total milk
76 fatty acids in the US and 1.1% of total milk fatty acids
77 in Japan [141]. The recognition that human breastmilk
78 DHA represents an important source for postnatal
79 infant brain DHA accrual has led to the recent (2002)
80 commercial availability of DHA-fortified infant formula
81 in the US. Prior to this time, infants in the US that were
82 not breastfed were maintained on formulas that did not
83 contain DHA. Term infants fed formulas without DHA
84 consistently exhibit significantly lower RBC and/or
85 postmortem brain cortex DHA concentrations relative
86 to breastfed infants or infants fed formula containing
87 DHA [5,7,14,114,115,142–144]. Consistent with primate
88 studies [98,99], infant frontal cortex accumulates DHA
89 faster over the course of postnatal development in
90 breast-fed infants relative to formula-fed infants [114].

91 *4.2.2.2. Neurocognition.* The effect of postnatal ome-
92 ga-3 fatty acid deficiency on neurocognitive develop-
93 ment of term infants has been reviewed in detail
94 previously [112–145]. Published studies have not always
95 yielded consistent results, and interpretation of these
96 findings must be made with caution in view of variability
97 in fetal brain DHA accrual during gestation, variability
98 in maternal breast milk DHA concentrations, and
99 variability in dietary DHA intake following weaning
100 from formula/breast milk. Nevertheless, studies have
101 found that infants fed formulas without DHA exhibit
102 several neurological and neurocognitive ‘soft signs’ in
103 infancy and childhood relative to infants fed formulas
104 with DHA or maternal breast milk, including lower
105 visual acuity, slower processing speed on tests of visual
106 recognition memory, more mature motor movement,
107 problem-solving, psychomotor function, and lower IQs
108 [129–131,146–155].

1 4.2.2.3. *Childhood deficiency.* The first documented
 2 case of human omega-3 fatty acid deficiency was
 3 reported in 1982 [156]. This case report describes a 6-
 4 year-old female patient maintained for 5 months on an
 5 ALA-deficient parenteral nutritional preparation fol-
 6 lowing intestinal surgery. The patient exhibited a 17%
 7 reduction in plasma DHA concentrations relative to
 8 age-matched controls, presented with dermatitis and
 9 neurological symptoms, including neuropathy, blurred
 10 vision, and 'psychological disturbances'. When the
 11 parenteral nutritional preparation was replaced with
 12 an ALA-fortified preparation, plasma omega-3 fatty
 13 acid levels normalized and neurological symptoms
 14 abated [156,157]. No standardized neurocognitive or
 15 psychiatric scales were administered to this subject.

17 4.2.3. *Psychopathogenesis*

18 A growing body of evidence suggests that deficits in
 19 attention and memory processes during childhood may
 20 precede and predict the subsequent emergence of
 21 psychopathology in high-risk populations [125,158-
 22 161]. The neurocognitive differences observed in chil-
 23 dren exposed to lower DHA in utero, born preterm or
 24 fed a diet without DHA postnatally suggest a link
 25 between perinatal brain DHA accrual and deficits that
 26 have been associated with risk of psychopathology in
 27 young adulthood. Furthermore, rodent studies have
 28 demonstrated that perinatal deficits in brain DHA
 29 accrual are associated with impaired mesocorticolimbic
 30 dopamine neurotransmission, which has been implicated
 31 in the pathophysiology and treatment of ADHD and
 32 schizophrenia.

33 In the following section, we will explore the potential
 34 role of perinatal deficits in brain DHA accrual in the
 35 pathogenesis of ADHD and schizophrenia, two psy-
 36 chiatric disorders that have been associated with familial
 37 transmission, a neurodevelopmental aetiology, abnor-
 38 malities in mesocorticolimbic dopamine neurotransmis-
 39 sion, and omega-3 fatty acid deficiency. It should be
 40 noted that bipolar disorder and major depressive
 41 disorder have also been associated with familial
 42 transmission, a neurodevelopmental etiology, abnor-
 43 malities in mesocorticolimbic dopamine neurotransmis-
 44 sion, and omega-3 fatty acid deficiency. However,
 45 discussion of these disorders is beyond the scope of
 46 the present review.

47 4.2.4. *Attention-deficit/hyperactivity disorder (ADHD)*

48 Children as well as adults with ADHD exhibit
 49 significantly lower RBC or plasma DHA concentrations
 50 relative to age- and sex-matched controls [162-166].
 51 Several trials have used DHA and EPA supplements as
 52 primary treatment for ADHD [167-170] and several
 53 others have used DHA and EPA supplements as
 54 adjunctive treatment [169,171,172]. Some intervention
 55 trials [167,172,173], but not others [168,171], have

56 observed significant symptomatic improvement in
 57 ADHD patients following dietary DHA and EPA
 58 supplementation. A report for the US Department of
 59 Health and Human Services [145] concluded there was
 60 little evidence for benefits of DHA or EPA for ADHD.
 61 Although there have been no prospective intervention
 62 treatment trials conducted to evaluate whether low
 63 prenatal or perinatal accrual of brain DHA accrual
 64 could contribute to the pathogenesis of ADHD, larger
 65 studies of pre- and postnatal DHA supplementation
 66 appear to be warranted.

67 Patients with ADHD exhibit significant deficits in
 68 frontal cortical dopamine synthesis and metabolism
 69 [174,175], and first-line medications (methylphenidate &
 70 atomoxetine) which reduce symptom severity in the
 71 majority of ADHD patients, increase extracellular
 72 dopamine levels in rat frontal cortex [176,177]. These
 73 data suggest that deficits in frontal cortex dopamine
 74 neurotransmission may be central to the underlying
 75 disease pathophysiology in ADHD. Rat studies have
 76 demonstrated that perinatal deficits in brain DHA
 77 accrual during the development and maturation of
 78 dopaminergic projections to the frontal cortex (E16-
 79 P60; [178]) lead to significant deficits in basal and
 80 stimulated extracellular dopamine concentrations in this
 81 region in young adulthood [54,77,79]. These deficits are
 82 reversible with early (P0-P14), but not late (P21),
 83 postnatal omega-3 fatty acid supplementation [77], and
 84 rodent maternal dietary fish oil supplementation
 85 throughout gestation and lactation significantly in-
 86 creases dopamine (+40%) concentrations in the frontal
 87 cortex of adult offspring [57]. Behaviors associated with
 88 altered dopaminergic function (reduced haloperidol-
 89 induced catalepsy, increased basal and amphetamine-
 90 stimulated locomotor activity, increased stereotyped
 91 behavior) have been observed in rodents and nonhuman
 92 primates with lower brain DHA [94,104]. In adult
 93 rodents, the effects of early DHA deficiency on
 94 haloperidol-induced catalepsy, but not the effects on
 95 amphetamine-induced locomotor activity, were normal-
 96 ized by restoring brain DHA concentration initiated at
 97 21 days of age [94]. These findings suggest that perinatal
 98 brain DHA accrual plays an important role in the
 99 functional development of the mesocortical dopamine
 100 pathway.

101 Patients with ADHD also exhibit deficits in meso-
 102 striatal dopamine neurotransmission which is augmented
 103 by methylphenidate treatment [179,180]. Rats subjected
 104 to perinatal deficits in brain DHA accrual also exhibit
 105 deficits in mesostriatal dopamine neurotransmission
 106 [67,79] which is reversible with early (P0-P14), but not
 107 late (P21), postnatal omega-3 fatty acid supplementa-
 108 tion [77]. Perinatal brain DHA accrual therefore also
 109 plays an important role in the functional development of
 110 the mesostriatal dopamine pathway.

The development and maturation of dopaminergic projections in the human frontal cortex occurs predominantly between midgestation and birth [181,182], suggesting that deficits in brain DHA accrual during the third trimester may contribute to deficits in attention in preterm children. Preterm delivery, which results in lower third trimester cortical DHA accrual [6], is associated with elevated rates of ADHD [120,124], and preterm infants provided with dietary DHA supplementation postnatally exhibited significant improvements in visual attention processes consistent with increased processing speed [129,130].

In addition to early delivery, brain DHA accrual may be modified both in utero and postnatally by the DHA intake and other factors that influence DHA status of the mother and infant, including individual variability in DHA synthesis [1–4]. Term infants, the majority of whom received formula without DHA postnatally, exhibited differences in focused attention in infancy and distractibility in toddlerhood relative to the amount of DHA in their mother's blood (a putative surrogate for prenatal DHA accrual). Specifically, infants/toddlers whose mothers had red blood cell DHA concentrations below the median at delivery demonstrated less mature attention, slower processing, and higher distractibility relative to those whose contents were above the median [134]. As well, a retrospective study found that children with ADHD had significantly shorter breastfeeding durations (a putative surrogate for postnatal DHA accrual) relative to children without ADHD [183]. These findings suggest that perinatal deficits in brain DHA accrual may contribute to deficits in attentional processing and ADHD, and that postnatal DHA supplementation may represent a safe and efficacious strategy to mitigate these deficits.

Neuroimaging studies suggest that ADHD is associated with perinatal deficits of cortical maturation. As with children born preterm, ADHD children exhibit cortical gray and white matter volume reductions, though the magnitude of these volume reductions are greater in preterm children (cf. [117,184]). Specifically, ADHD children exhibit significantly smaller (3–5%) frontal and temporal cortex gray and white matter volumes [184,185], reduced corpus callosum (splenium) volumes [186,187], and enlarged cerebral ventricles [187]. Nine independent studies have observed significant reductions in prefrontal cortical volumes in ADHD patients (reviewed in [188]).

Collectively, these findings provide support for the proposition that reduced perinatal DHA accrual in brain may represent a risk factor for ADHD. In view of the high prevalence rate of ADHD in preterm children, and rat data demonstrating the limited reversibility of deficits in mesocorticolimbic dopamine with later omega-3 fatty acid intervention, gestational or early postnatal DHA supplementation would be anticipated

to have greatest therapeutic efficacy in human subjects. This perinatal time window may also account for the limited efficacy of chronic DHA + EPA treatment in children (6–12 years) with ADHD [168,171–173].

4.3. Schizophrenia

Several lines of evidence suggest that low brain DHA accumulation may be associated with the pathophysiology of schizophrenia. For example, cross-national and -sectional epidemiological surveys link low seafood consumption with increased symptom severity in schizophrenia [189,190]. RBC or plasma DHA concentrations are significantly lower in male and female patients with first-episode psychosis [191–193] or schizophrenia [194–196]. DHA concentrations are significantly lower in the postmortem prefrontal cortex of adult schizophrenic patients [197] but not in the postmortem temporal cortex [198], cingulate gyrus [199], caudate nucleus [200] or cerebellum [201] of adult schizophrenic patients.

Intervention trials have observed significant symptomatic improvement in medicated-schizophrenic patients following chronic treatment with DHA + EPA or EPA alone [202–206]. Although it is not currently known whether DHA deficiency during perinatal brain development contributes to the pathogenesis of schizophrenia, preterm delivery which is associated in part with deficits in cortical DHA accrual (above), increases risk for schizophrenia [207–211].

Abnormalities in the development and maturation of mesocorticolimbic dopamine pathways implicated in the pathophysiology of ADHD have also been implicated in the pathophysiology of schizophrenia [212–214], and attentional impairments are a core negative feature of schizophrenia. Atypical antipsychotic medications that are efficacious in the treatment of psychosis in the majority of patients have in common the ability to increase extracellular dopamine concentrations in rat frontal cortex and ventral striatum [215,216]. Furthermore, chronic treatment with atypical antipsychotic medications at therapeutically relevant concentrations decrease (–50%) serotonin 5-HT_{2A} receptor density [217] and increase (+30%) dopamine D₂ receptor density [218] in adult rat frontal cortex. Conversely, rat studies have demonstrated that perinatal deficits in brain DHA accrual is associated with significant deficits in tyramine-stimulated extracellular dopamine concentrations in prefrontal cortex and ventral striatum [67,77–79], elevations in (+50%) in serotonin 5-HT_{2A} receptor density, and significant reductions (–25%) in dopamine D₂ receptor density, in the adult rat frontal cortex [76,85]. These findings demonstrate that perinatal deficits in brain DHA accrual lead to changes in dopamine and serotonin neurotransmission and receptor binding in the adult rat brain that are opposite to

1 those produced by clinically efficacious atypical anti-
2 psychotic medications.

3 Epidemiological surveys have found that the duration
4 of postnatal breastfeeding (a putative surrogate for
5 postnatal DHA intake) is inversely correlated with age
6 at onset of schizophrenia [219,220], and infants with no
7 or short-term (≤ 2 weeks) breast feeding have a 1.7-fold
8 higher risk of developing schizophrenia relative to
9 infants breast fed for ≥ 2 weeks [221]. Notwithstanding
10 the methodological limitations associated with this type
11 of retrospective epidemiological analysis, including
12 variability in maternal breast milk DHA concentrations,
13 and the failure of other studies to demonstrate excess
14 risk in infants breastfed < 1 month [222,223], these
15 findings remain intriguing because they suggest that very
16 early postnatal DHA deficiency may be associated with
17 increased risk for schizophrenia.

18 As observed in children and adolescents born
19 preterm, children, adolescents, and adults with schizo-
20 phrenia exhibit neuroanatomical abnormalities indica-
21 tive of deficits in cortical maturation. Specifically,
22 children with schizophrenia (early-onset) [224–228],
23 first-episode psychotic patients [229–238], and adult
24 patients with schizophrenia (reviewed in [239]) exhibit
25 significant reductions in cortical gray and white matter
26 volumes, reductions in amygdala and hippocampal
27 volumes, reductions in corpus callosum volumes, and
28 enlargements in ventricular volumes. Postmortem his-
29 tological studies indicate that the cortical and hippo-
30 campal gray matter volume reductions observed in
31 schizophrenic patients are attributable to deficits in
32 synaptic and dendritic spine density and reductions in
33 cell body size rather than neuronal loss [240–246]. This
34 histological pattern is therefore consistent with perinatal
35 deficits in brain DHA accrual, which is associated with
36 deficits in neuronal arborization [39] and neuronal
37 shrinkage [47,48] but not neuronal loss [50].

38 Regarding genetic liability, monozygotic twin studies
39 suggest that schizophrenic twins in monozygotic twin
40 pairs exhibit significant volume reductions in dorsolat-
41 eral prefrontal cortex, hippocampus, whole brain gray
42 matter, as well as ventricular enlargement, relative to
43 unaffected twins [247–250]. These findings indicate that
44 gray matter deficits are not related to genotype and are
45 therefore attributable to environmental factors. A case
46 study found that a schizophrenic twin in a discordant
47 monozygotic twin pair exhibited significantly lower
48 birth weight relative to the unaffected monozygotic
49 twin as well as deficits in gray matter volume [251]. It is
50 of interest, therefore, that lower umbilical plasma
51 polyunsaturated fatty acid concentrations are associated
52 with smaller birth weights among twins [252], and
53 schizophrenic twins exhibit significantly lower plasma
54 DHA concentrations relative to their unaffected mono-
55 zygotc twins [253]. Differential brain DHA accrual
among monozygotic twins may therefore represent an in

56 utero environmental risk factor for impaired gray matter
57 maturation and schizophrenia.

58 It is of additional interest that individuals at high-risk
59 for developing schizophrenia (e.g., having a first-degree
60 relative with schizophrenia) have a significantly higher
61 frequency of birth complications [254], and exhibit
62 significant reductions in whole brain volumes, reduc-
63 tions in amygdala-hippocampal volumes, and increased
64 third ventricle volumes, relative to healthy controls
65 during the prodromal phase of the illness (pre-psychosis)
66 [255–257]. Moreover, children at high-risk for develop-
67 ing schizophrenia exhibit deficits in attention and verbal
68 memory during the prodromal phase which were found
69 to be strong predictors for the subsequent emergence of
70 psychosis in young adulthood [159,258]. Furthermore,
71 ADHD is more prevalent in high-risk children (31%)
72 relative to the general population 4–12% and is
73 associated with a poorer psychiatric prognosis
74 [160,161,259]. These findings suggest that high-risk
75 children exhibit neurocognitive and neuroanatomical
76 deficits that are also observed in children and adoles-
77 cence born preterm and may indicate a common
78 pathoetiology.

79 Maternal dietary DHA intake has important implica-
80 tions for the developing fetal/infant brain. Maternal
81 DHA stores in plasma and breast milk are largely
82 determined by maternal dietary DHA intake [260–263],
83 and DHA is preferentially transferred from maternal
84 plasma to the fetus in utero in a concentration-
85 dependent manner [264–267]. DHA transfer from
86 mother to the neonate continues if infants are fed
87 human milk postnatally and this transfer is also
88 dependent upon maternal milk DHA concentrations
89 [268]. Female and male schizophrenic patients exhibit
90 significantly lower RBC or plasma DHA concentrations
91 (-25%) relative to normal controls [194,195]. Tobacco
92 smoking has been associated with reduced RBC DHA
93 levels in schizophrenic women, but not in schizophrenic
94 men [269], and schizophrenic women have been reported
95 to smoke tobacco at a significantly higher rate prior to
96 and during pregnancy than non-schizophrenic women
97 [270,271]. As well, lower maternal RBC/plasma DHA
98 content is associated with shorter gestation length [272–
99 277], and women with schizophrenia exhibit higher rates
100 of preterm delivery than non-schizophrenic women
101 [271,278,279]. Based on primate studies, maternal
102 deficits in RBC/plasma DHA concentrations of 25%
103 would be anticipated to be associated with significant
104 ($\sim 70\%$) deficits in fetal frontal cortex DHA accrual
105 [97,101]. Based on these various lines of evidence, the
106 risk of perinatal deficits in brain DHA accrual would be
107 anticipated to be greater in the offspring of schizo-
108 phrenic women, and may represent a nongenetic mode
109 of risk transmission.

110 Collectively, these findings support the idea that
111 perinatal deficits in brain DHA accrual may represent

a potential neurodevelopmental insult that increases susceptibility to deficits in cortical DHA accrual, cortical maturation, prodromal neurocognitive deficits in attention and memory, and increased risk for schizophrenia. Definitive support for this hypothesis will require prospective follow-up with neuroimaging studies to determine whether treatment of schizophrenic mothers with DHA during and following pregnancy can prevent or mitigate gray matter and neurocognitive deficits during childhood/adolescence.

4.3.1. Preventative strategies

The evidence reviewed in the previous sections outline neurobiological evidence which supports the hypothesis that deficits in perinatal brain DHA accrual contribute to the pathogenesis of ADHD and schizophrenia. These deficits could be due to low exposure or intake as well as to an impaired ability to synthesize DHA. Regardless, the hypothesis predicts that risk for neurochemical, neuroanatomical, and neurocognitive features associated with DHA deficiency in ADHD and schizophrenia would be reduced if maternal DHA intake were initiated during gestation. Direct evaluation of this hypothesis will require randomized, double blind, placebo-controlled, prospective, longitudinal trials in which high-risk women (e.g., women with schizophrenia) would be randomly assigned to receive either DHA + EPA supplements or placebo beginning in the second trimester. The DHA + EPA dose would be based on doses previously found to be safe for the mother and fetus and to significantly reduce recurrence risk of preterm delivery (~2–3 g/day of DHA + EPA from fish oil) [274,276,280]. Neuroimaging, neurocognitive, electroretinogram, and maternal and offspring RBC omega-3 fatty acid composition analyses could be conducted at intervals over the course of postnatal maturation.

Previous studies have demonstrated that women supplemented with DHA + EPA during pregnancy exhibit significantly greater DHA concentrations in RBC/plasma [281–284] and breast milk relative to controls [285,286]. Accordingly, fetal/infant RBC/plasma DHA concentrations are also increased at birth when women receive DHA + EPA supplementation during gestation [274,282,286,287]. Although there are currently no published data available regarding fetal/infant brain DHA accrual following maternal DHA + EPA supplementation during pregnancy, rat studies have demonstrated that maternal dietary fortification with fish oil significantly increases regional brain DHA concentrations (+15%) in offspring [57], and infant brain DHA concentrations are higher when human milk is consumed postnatally compared to formula without DHA [5–7,14,114,115]. Collectively, these studies, and the variability found in intrauterine brain DHA accumulation over the course of gestation [106], support the idea that higher maternal DHA intakes during

pregnancy could result in higher fetal brain DHA accrual.

Maternal DHA + EPA supplementation during pregnancy may also offer additional advantages for schizophrenic mothers and their offspring. For example, maternal DHA + EPA supplementation has been found to be protective against obstetric complications more common in women with schizophrenia, including preterm delivery [272–277,280] and preeclampsia [207,288]. Moreover, because DHA + EPA supplementation has previously been demonstrated to significantly reduce positive and negative symptom severity in medicated male and female schizophrenic patients [202–206], DHA + EPA treatment during pregnancy may have prophylactic efficacy in pregnant schizophrenic patients when antipsychotic/mood stabilizer/antidepressant medications are discontinued to avoid potential teratogenesis [289]. Indeed, DHA (2 g/d) + EPA (4 g/d) monotherapy was previously found to reduce positive and negative symptom severity in a pregnant schizophrenic women following medication discontinuation [290].

5. Summary and conclusions

There is now good evidence suggesting that DHA is accrued in rodent, primate, and human brain during active periods of perinatal cortical maturation, and that DHA plays an important role in neuronal differentiation, synaptogenesis, and synaptic function. In animal studies, prenatal deficits in brain DHA accrual that are not corrected via postnatal dietary fortification are associated with enduring deficits in neuronal arborization, multiple indices of synaptic pathology, deficits in mesocorticolimbic dopamine neurotransmission, deficits in hippocampal serotonin and acetylcholine neurotransmission, neurocognitive deficits on hippocampus- and frontal cortex-dependent learning tasks, and elevated behavioral indices of anxiety, aggression, and depression. Human and primate infants born preterm or fed diets without DHA postnatally exhibit lower cortical DHA accrual compared to infants born at term or fed human milk postnatally. Children/adolescents born preterm exhibit deficits in cortical gray matter expansion, neurocognitive deficits, and are at increased risk for attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. Individuals diagnosed with ADHD or schizophrenia exhibit peripheral indices of lower DHA status and exhibit deficits in cortical gray matter expansion and deficits in cortical dopamine neurotransmission. Based on this body of evidence, it is hypothesized that perinatal deficits in brain DHA accrual represents a modifiable neurodevelopmental risk factor for the emergence of neurocognitive deficits and

subsequent psychopathology. Evaluation of this hypothesis is currently feasible.

In view of the potential contribution of perinatal deficits in brain DHA accrual to the pathogenesis of ADHD and schizophrenia, increasing awareness of the importance of maternal DHA status during pregnancy, particularly in high-risk groups, represents an important future challenge for mental health researchers and practitioners. This is particularly relevant in the US where dietary consumption of DHA has declined [291–295], resulting in breast milk DHA concentrations that are among the lowest in the world [141]. Furthermore, the recent (2004) US advisory issued jointly by the Food and Drug Administration and Environmental Protection Agency recommends that pregnant women, women who might become pregnant, young children, and nursing mothers modify their fish intake due to the threat of mercury contamination. These recommendations may have inadvertently led to further reductions in maternal and fetal/infant DHA accrual during critical stages of brain development [296]. The IOM Committee on Nutrient Relationships in Seafood: Selections to Balance Benefits and Risks, has undertaken the task to provide guidance that may be used for consumers to safely choose seafood sources of DHA [297], and DHA + EPA supplements are widely available which do not pose a risk for mercury contamination (Consumer Reports, Vol. 68, p. 30).

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