HHS Public Access

Author manuscript

Prostaglandins Leukot Essent Fatty Acids. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Prostaglandins Leukot Essent Fatty Acids. 2018 September ; 136: 23–34. doi:10.1016/j.plefa.2017.05.001.

Role of Polyunsaturated Fatty Acids in Human Brain Structure and Function Across the Lifespan: An Update on Neuroimaging Findings

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Abstract

There is a substantial body of evidence from animal studies implicating polyunsaturated fatty acids (PUFA) in neuroinflammatory, neurotrophic, and neuroprotective processes in brain. However, direct evidence for a role of PUFA in human brain structure and function has been lacking. Over the last decade there has been a notable increase in neuroimaging studies that have investigated the impact of PUFA intake and/or blood levels (i.e., biostatus) on brain structure, function, and pathology in human subjects. The majority of these studies specifically evaluated associations between omega-3 PUFA intake and/or biostatus and neuroimaging outcomes using a variety of experimental designs and imaging techniques. This review provides an updated overview of these studies in an effort to identify patterns to guide and inform future research. While the weight of evidence provides general support for a beneficial effect of a habitual diet consisting of higher omega-3 PUFA intake on cortical structure and function in healthy human subjects, additional research is needed to replicate and extend these findings as well as identify response mediators and clarify mechanistic pathways. Controlled intervention trials are also needed to determine whether increasing *n*-3 PUFA biostatus can prevent or attenuate neuropathological brain changes observed in patients with or at risk for psychiatric disorders and dementia.

Graphical abstract

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DISCLOSURES

The other authors do not have any financial disclosures.

Keywords

Omega-3 fatty acids; Docosahexaenoic acid; Arachidonic acid; Brain development; Aging; Neurodegeneration; White matter

1. Introduction

Over the past 30 years a considerable body of translational evidence has emerged implicating polyunsaturated fatty acids (PUFA) in normal brain development and function [1]. Omega-3 (n -3) and omega-6 (n -6) fatty acids are members of the PUFA family. α -linolenic acid (ALA, 18:3 n -3) and linoleic acid (18:2 n -6), the precursors of n -3 and n -6 PUFA respectively, are considered 'essential' because mammals cannot biosynthesize them *de novo* and are therefore reliant on dietary sources for procurement. The most abundant PUFAs in mammalian brain gray matter are the n -3 PUFA docosahexaenoic acid (DHA, 22:6 n -3) and the n -6 PUFA arachidonic acid (AA, 20:4 n -6)[2,3]. Although the n -3 PUFA precursors of DHA, including ALA, eicosapentaenoic acid (EPA, 20:5 n -3), and docosapentaenoic acid (DPA, 22:5 n -3), cross the blood-brain barrier, they comprise <1% of total brain fatty acid composition due in part to rapid oxidation [4]. Unesterified DHA readily diffuses from plasma to brain [5,6], and preferentially accumulates in gray matter synaptosomal and mitochondrial membranes [7]. In rodents, dietary n -3 PUFA insufficiency, particularly during early development, is associated with robust cortical DHA deficits and associated elevations in the AA/DHA ratio [8], whereas dietary n -6 PUFA insufficiency leads to cortical AA deficits and associated decreases in the AA/DHA ratio [9]. In general, DHA and AA have opposing effects on synaptic signal transduction [10] and inflammatory [11,12] signaling pathways.

Rodent developmental studies have provided important insight into the role of dietary PUFA on brain development and function. In brief, dietary n -3 PUFA insufficiency, and associated increases in the brain AA/DHA ratio, during peri- or postnatal development is associated

with reductions in neurogenesis [13,14], delays in neuronal migration, embryonic cortical plate expansion, synaptic pruning [15–17], impaired glutamate and monoamine synaptic function [18,19], and reductions in brain glucose uptake and metabolism [20,21]. Dietary *n*-3 PUFA insufficiency during development is also associated with behavioral abnormalities including impaired learning [22,23] and elevated behavioral indices of depression and aggression [24,25]. Elevations in the AA/DHA ratio in the rodent brain are also associated with increases in pro-inflammatory signaling [11,26], decreased neuronal resilience to a range of insults including ischemia [27,28], and age-related neurodegenerative processes [29].

As observed in rodents, DHA concentrations increase sharply in the non-human primate brain during perinatal development [3,30,31], and preterm birth is associated with cortical DHA deficits compared with term births [32,33]. Dietary-induced deficits in cortical DHA accrual, and associated increases in the brain AA/DHA ratio, during perinatal development are associated with deficits in retinal signal transduction, deficits in visual attention, and behavioral abnormalities [3,31,34,35]. Of direct relevance to the current review, emerging evidence from non-human primate neuroimaging studies indicates a positive association between *n*-3 PUFA intake/biostatus and resting state cerebral glucose uptake and metabolism [36], regional functional connectivity [37], and neurovascular coupling [38].

In human brain, postmortem studies suggest that DHA levels increase and the AA/DHA ratio decreases at a rapid rate during early perinatal development and throughout childhood and adolescence [2,39,40] in parallel with active periods of synaptogenesis and the establishment of structural connectivity [41,42]. However, limitations associated with the postmortem approach have hindered progress in our understanding of the role of PUFA in human brain structure, function, and pathology. Conventional magnetic resonance imaging (MRI) techniques are well-suited to elucidate the role of PUFA in human brain structure, function, and pathology, and permit longitudinal investigation of dynamic changes in cortical structure, chemistry, and functional activity. Over the last decade there has been a substantial increase in the number of neuroimaging studies that have investigated associations between PUFA intake/biostatus and human brain structure and function. The majority of these studies specifically evaluated associations between *n*-3 PUFA intake and/or biostatus and neuroimaging outcomes using a variety of different experimental designs and imaging techniques. In these studies PUFA intake is extrapolated from questionnaires and PUFA biostatus is calculated from blood (plasma, erythrocyte, or whole blood) levels. Blood *n*-3 PUFA levels are highly correlated with the frequency of dietary intake of preformed *n*-3 PUFA (e.g., fish/seafood)[43] and to a lesser extent ALA intake [44]. This review will provide an updated overview of neuroimaging findings in an effort to identify patterns to guide and inform future studies.

2. Methods

A computerized search was performed to identify eligible peer-reviewed studies published up to March 2017 using PubMed at the National Library of Medicine. Search terms included: “omega-3”, “DHA”, “PUFA”, “MRI”, “fMRI”, “DTI”, “PET”, “MRS”, “NIRS”, “structural”, “elderly”, “infant”, and/or “psychiatry.” Additional articles were identified

from the reference lists of identified manuscripts. Articles were included if they were written in English, specifically investigated relationships between PUFA measures (i.e., intake or biostatus) and neuroimaging outcomes, and were peer-reviewed. The literature search identified 54 original research articles published between 2002 and 2017, and no studies were excluded based on inclusion criteria. Articles were sub-classified according to neuroimaging modality (i.e., fMRI, DTI, etc), and within each modality further sub-classified by study design (i.e., cross-sectional, prospective longitudinal, retrospective, supplementation) and reviewed in separate sections.

3. Structural MRI

Structural magnetic resonance imaging (MRI) uses T1-weighted images and voxel-based morphometry methods to measure regional gray and white matter volumes. T2-weighted images are used to identify white matter hyperintensities (WMH) which are common in elderly subjects and psychiatric patients, and are caused by a variety of factors including ischemia, micro-hemorrhages, or loss and deformation of the myelin sheath [45]. The majority of studies adjusted for variables known to contribute to imaging outcome measures including age and gender, and MRI field strength ranged from 1.5 to 4.0 Tesla.

3.1. Cross-sectional studies

A seminal cross-sectional structural MRI study of healthy middle-aged adults (mean age: 44.7 years, $n=55$) found that greater dietary $n-3$ PUFA intake was associated with larger gray matter volumes in the anterior cingulate cortex (ACC), the right hippocampus, and the right amygdala [46]. A study of dementia-free elderly subjects (mean age: 87 years; $n=104$) found that a nutrient pattern associated with higher fasting plasma EPA+DHA levels was associated with smaller WMH volumes and better executive function [47]. Covarying for depression attenuated the relationship between this nutrient pattern and WMH volume. A larger study of dementia-free elderly subjects (mean age: 67 years, $n=1,575$) found that the lowest quartile of erythrocyte DHA levels was associated with lower total brain volume, but not temporal horn volume, greater WMH volumes, and lower memory and executive function scores compared with the combined higher erythrocyte DHA quartiles [49]. Two additional cross-sectional studies similarly observed an inverse association between fasting serum EPA, EPA+DHA, or the EPA/AA ratio and WMH burden in of elderly subjects [50,51]. A study of cognitively healthy elderly subjects (mean age: 69 years, $n=40$) with the apolipoprotein E (APOE) $\epsilon 4$ polymorphism, which may be associated with impaired DHA transport [52], investigated the relationships among fasting plasma EPA and DHA levels, regional gray matter volumes, and executive function [53]. In the adjusted model, plasma EPA+DHA levels were positively correlated with left rostral ACC gray matter volume which partially mediated the positive relationship between plasma EPA+DHA levels and executive function. A recent study of elderly subjects with no or mild cognitive impairment (mean age: 77 years, $n=61$) investigated the relationship between fasting serum DHA levels and regional gray and white matter volumes [54]. In the adjusted model, serum DHA levels were positively associated with hippocampus, entorhinal cortex, bilateral precuneus, and total gray matter volumes, but not white matter volumes or WMH burden.

3.2. Prospective longitudinal studies

A 5-year prospective study of healthy elderly subjects (mean age: 75 years; $n=3,660$) investigated the relationship between baseline fish intake frequency and white and gray matter volumes and subclinical infarcts [55]. In the adjusted model, a higher baseline intake frequency (>3 times/week) of tuna or baked or broiled fish, but not fried fish, was associated with fewer white matter abnormalities, but not markers of gray matter atrophy, and reduced risk for developing subclinical infarcts compared with lower fish intake frequency (<1 times/month). A follow-up study conducted in the same cohort evaluated the relationship between baseline fasting plasma phospholipid EPA+DPA+DHA levels and white and gray matter abnormalities 5 years later [56]. Consistent with their previous observations, the risk for having a subclinical infarct and white matter abnormalities, but not markers of gray matter atrophy, were significantly lower in subjects in the highest versus lowest plasma EPA+DPA+DHA quartile.

A 4-year prospective study of cognitively healthy elderly subjects (age >65 years; $n=281$) found that higher baseline plasma EPA, but not DHA, levels were associated with slower right hippocampus and amygdala gray matter atrophy over 4 years [57]. A 5-year prospective study of cognitively healthy elderly subjects (mean age: 70 years; $n=252$) found that greater self-reported EPA and DHA intake at baseline was positively associated with global gray matter volume, but not global white matter or total or regional brain volume, and increased global cognitive performance 5 years later [58]. A 9-year prospective study of cognitively healthy elderly subjects (mean age: 78 years; $n=260$) found that greater weekly consumption of baked or broiled fish was associated with larger hippocampus, precuneus, posterior cingulate, and orbital frontal cortex gray matter volumes 9 years later [59]. In the latter study baseline baked or broiled fish consumption was positively correlated with plasma EPA+DHA levels but EPA+DHA levels were not significantly associated with regional gray matter volumes. A 3.6-year prospective study of cognitively healthy elderly subjects (mean age: 63 years; $n=92$) found that higher whole blood DHA levels, but not EPA levels, at study endpoint were associated with less baseline-endpoint cortical thinning in the left middle and superior temporal gyrus and similar trends were also observed in the right hemisphere [60]. An 8-year prospective study of postmenopausal dementia-free women (mean age: 78 years, $n=1,111$) found that higher erythrocyte EPA and DHA levels at baseline were associated with larger total brain and hippocampal volumes 8 years later [61].

3.3. Retrospective studies

A 2-year retrospective cohort study of elderly subjects (mean age: 77 years) with mild cognitive impairment randomized to placebo ($n=83$) or high-dose B vitamin supplementation (folic acid, 0.8 mg; vitamin B-6, 20 mg; vitamin B-12, 0.5 mg)($n=85$), found that subjects with high non-fasting baseline plasma EPA+DHA levels exhibited a slower rate of whole brain atrophy rate in the B vitamin group but not in the placebo group [62]. A second retrospective cohort study investigated the relationship between fish oil supplement use and cerebral cortex gray matter, hippocampus, and ventricular volumes in a cohort of older adults consisting of cognitively healthy individuals (mean age: 76 years, $n=229$), patients with mild cognitive impairment (mean age: 75 years, $n=397$), and 193 patients with Alzheimer's disease (mean age: 75 years, $n=193$), during follow-up at 6–48

months [63]. Across the entire cohort, fish oil use during study participation was associated with reduced atrophy in cerebral cortex gray matter and hippocampus, less ventricular enlargement, and less cognitive decline during follow-up compared with subjects not using fish oil.

3.4. Supplementation trials

A randomized, double-blind, placebo-controlled trial investigated the effects of 72-week supplementation with algal DHA (2 g/d) or placebo (corn/soy oil) on the rate of total brain atrophy in a subsample of participants with mild to moderate Alzheimer disease (mean age: 76 years; $n=102$)[64]. DHA supplementation significantly increased plasma and cerebrospinal fluid DHA levels, but did not alter cognitive measures or rate of atrophy in total brain volume or hippocampal volume, or ventricular enlargement compared with placebo. A second controlled trial investigated the effects of 26-week supplementation with fish oil (1.5:1 EPA/DHA – 2,200 mg/d) or placebo (sunflower oil) on regional gray matter volumes in a cohort of healthy older adults (mean age: 64 years; $n=65$)[65]. Compared with placebo, supplementation with fish oil significantly increased erythrocyte EPA and DHA levels and attenuated decreases in gray matter volume in the left hippocampus, precuneus, superior temporal, inferior parietal and postcentral gyri, and right middle temporal gyrus. Fish oil supplementation was also associated with better performance on tests of executive function but not memory. A third trial investigated the effects of 24-week combined treatment with fish oil supplementation (1.5:1 EPA/DHA – 2,200 mg/d), aerobic exercise, and cognitive stimulation on regional gray matter volume in patients with mild cognitive impairment (mean age: 70 years; $n=20$)[66]. Although the combined intervention did not alter cognitive performance, it attenuated frontal, parietal, and cingulate cortex gray matter volume reductions observed in patients receiving the control intervention consisting of fish oil supplementation plus stretching and toning.

4. Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a technique that permits a detailed analysis of white matter microstructural integrity by measuring water diffusion in different directions along white matter fibers [67,68]. Commonly used parameters are fractional anisotropy (the degree of directionality of water diffusivity), axial diffusivity (parallel diffusion along white matter fibers), radial diffusivity (perpendicular diffusion to white matter fibers), and mean diffusivity (a global measure of water diffusion). Animal studies suggest that an increase in radial diffusivity is a specific measurement of demyelination or dysmyelination, whereas a decrease in axial diffusivity is more closely associated with axonal damage [69–71]. Although fractional anisotropy will decrease following either a decrease in axial diffusivity or an increase in radial diffusivity, anisotropy is not always correlated with histological markers of axonal damage or demyelination [69]. A pattern of decreasing fractional anisotropy, and increasing radial diffusivity, is observed in older adults [72–74] and in disorders associated with white matter pathology including multiple sclerosis [75]. Recent evidence further suggests that the decrease in fractional anisotropy in older subjects is mediated in part by variants in the enzymes that regulate PUFA biosynthesis [76]. Studies combining MRI and DTI suggest that age-related reductions in fractional anisotropy and

increases in radial diffusivity may precede and contribute to the formation of WMH in elderly subjects [77,78].

The second and third trimesters of human gestation are a critical neurodevelopmental period associated with the establishment of major axonal white matter tracts that mediate frontal lobe connectivity, including the uncinate fasciculus [41,79]. The early organization and maturation of these cortical circuits is highly vulnerable, and children and adolescents born prior to the completion of the third trimester (i.e., preterm birth) exhibit long-standing decreases in frontal white matter integrity [80]. A cross-sectional study investigated the relationship between early preterm or near-term erythrocyte PUFA levels and white matter microstructural integrity in a cohort of 60 infants born preterm (<32 weeks gestation) at 33 months of age [81]. In adjusted models, early preterm erythrocyte DHA levels were inversely associated with mean diffusivity in the internal capsule and the optic radiations, and axial diffusivity in the internal capsule. After excluding infants with more severe intraventricular hemorrhage, DHA levels were inversely associated with radial diffusivity in the optic radiations. Linoleic acid (18:2 n -6) levels were associated with higher mean diffusivity in the optic radiations, and no statistically significant associations were found with EPA or AA. An early prospective randomized, double-blinded, placebo-controlled study investigated the effects of standard preterm formula without DHA or AA, or formula supplemented with algal DHA (15 mg/100 ml) and fungi AA (31 mg/100 ml), in infants (n =42) born premature (<34 weeks gestation) on white matter maturation over 3 and 12 months [82]. Preterm infants fed formula supplemented with DHA and AA did not exhibit differences in white matter maturation at 3 or 12 months compared with infants fed formula without DHA or AA. An 8-year prospective randomized, double-blinded, placebo-controlled study investigated the effects of postnatal supplementation with DHA (32 mg/100 ml human milk) and AA (31 mg/100 ml human milk) on white matter microstructural integrity at 8 years of age in infants with very low birth weight (n =98)[83]. Although no significant differences between the intervention and control groups were found, a non-significant increase in fractional anisotropy was observed in the left corpus callosum of the intervention group.

A cross-sectional study of dementia-free elderly subjects (mean age: 84 years, n =239) investigated the relationship between a nutritional pattern characterized by high intakes of n -3 and n -6 PUFA and vitamin E, global fractional anisotropy, and executive function [84]. In the adjusted model, subjects in the highest tertile of this nutritional pattern had significantly higher global white matter fractional anisotropy compared with those in the lowest tertile, and higher global fractional anisotropy mediated the positive relationship between the nutrient pattern and several cognitive measures including executive function. A randomized, double-blind, placebo-controlled trial investigated the effects of 26-week supplementation with fish oil (1.5:1 EPA/DHA – 2,200 mg/d) or placebo (sunflower oil) on white matter integrity in a cohort of healthy older adults (mean age: 64 years, n =65)[65]. Compared with placebo, fish oil supplementation significantly increased fractional anisotropy, and decreased mean diffusivity and radial diffusivity, in left hemisphere anterior corpus callosum, uncinate fasciculus, and inferior-occipital fasciculus, and in right hemisphere superior longitudinal fasciculus and superior and inferior fronto-occipital fasciculus.

A preliminary cross-sectional study of young adult male patients with recent onset schizophrenia (mean age: 23 years, $n=12$) found that total erythrocyte PUFA (omega-3 and omega-6) concentrations were positively correlated with fractional anisotropy in the uncinate fasciculus but not other white matter tracts [85]. A second independent cross-sectional study of young adult male patients with recent onset schizophrenia (mean age: 23 years, $n=30$) similarly found that total erythrocyte PUFA concentration (omega-3 and omega-6) was positively correlated with fractional anisotropy, and inversely correlated with radial diffusivity but not axial diffusivity, in the corpus callosum and bilateral parietal, occipital, temporal and frontal white matter tracts [86]. Nervonic acid, AA, and DPA concentrations were positively correlated with regional fractional anisotropy, and a trend was observed for DHA. Greater severity of negative symptoms was associated with lower nervonic acid concentrations and lower fractional anisotropy values.

An open-label trial investigated the effects of 6-week supplementation with fish oil (2:1 EPA/DHA – 2,400 mg/d) on regional white matter microstructural integrity in acutely depressed patients with major depressive disorder (MDD)(mean age: 34 years, $n=16$) and healthy participants (mean age: 31 years, $n=12$)[87]. At baseline, fractional anisotropy in the genu and splenium of corpus callosum, anterior corona radiata bilaterally, and right superior longitudinal fasciculus was significantly lower in MDD patients compared with healthy controls. Baseline fasting plasma phospholipid DHA was positively correlated with fractional anisotropy in the corpus callosum of MDD patients. Following fish oil supplementation, increases in plasma phospholipid DHA, but not increases in EPA or decreases in AA, were associated with increased fractional anisotropy in the genu and body of corpus callosum, bilateral anterior corona radiata, and cingulum of patients with MDD, but not in healthy controls. The reduction in depression symptom severity observed in MDD patients following fish oil supplementation was associated with increases in fractional anisotropy in left corticospinal tract and superior longitudinal fasciculus.

5. fMRI

Functional magnetic resonance imaging (fMRI) measures signal intensity changes attributed to blood oxygen level-dependent (BOLD) effects. Elevations in BOLD signal are related to increases in synaptic activity and associated increases in local blood volume [88], and reductions in BOLD signal are thought to reflect a suppression of neural activity and shunting of blood from less active to more active regions [89]. fMRI studies can be performed in a resting state, during performance of cognitive tasks, or during exposure to emotional images to activate specific regional brain networks of interest. For example, working memory and sustained attention tasks have been widely used to interrogate functional activity in the prefrontal cortex, whereas functional activity in limbic emotional structures including the amygdala can be interrogated using emotional images. Using a voxelwise approach, fMRI can additionally investigate functional connectivity among different brain regions, either in a resting state or during performance of cognitive tasks.

A cross-sectional study investigated event-related functional connectivity by fMRI during performance of a sustained attention task (CPT-IP) in male children (mean age: 9 years) divided into ‘low-DHA’ ($n=18$) and ‘high-DHA’ ($n=18$) biostatus groups by a median split

of erythrocyte DHA levels [90]. Groups were demographically similar and mean erythrocyte DHA levels in the low-DHA group were significantly lower than the high-DHA group. The anterior cingulate cortex (ACC) served as the seed region. The low-DHA group exhibited reduced functional connectivity between the ACC and the ventrolateral prefrontal cortex, insula, precuneus, superior parietal lobule, middle occipital gyrus, inferior temporal gyrus, and lingual gyrus compared with the high-DHA group. These findings are similar to results obtained in non-human primates [37], and suggest that low DHA biostatus is associated with reduced event-related functional connectivity in cortical networks of typically developing children.

A randomized double-blind placebo-controlled dose-ranging trial investigated the effects of 8-week supplementation with one of two doses of algal DHA (400 or 1,200 mg/d) or placebo (corn oil) in healthy male children (mean age: 9 years, $n=33$)[91]. fMRI scans were acquired during performance of a sustained attention task (identical pairs continuous performance task, CPT-IP). At 8 weeks erythrocyte membrane DHA composition increased significantly from baseline in subjects receiving low-dose and high-dose DHA (high > low), but not placebo, and there were no group differences in CPT-IP performance at baseline or study endpoint. Compared with placebo, both DHA dose groups exhibited significantly greater increases from baseline in the activation of dorsolateral prefrontal cortex (DLPFC), and low-dose and high-dose DHA groups exhibited greater decreases in the occipital cortex and cerebellar cortex, respectively. Relative to low-dose DHA, high-dose DHA resulted in greater decreases in activation of bilateral cerebellum. In an exploratory analysis using progressively less stringent statistical thresholds, more extensive baseline-endpoint increases in prefrontal cortex activation, and baseline-endpoint decreases in parietal cortex, temporal cortex, and cerebellar cortex activation, are observed in boys receiving DHA (1,200 mg/d) versus placebo during sustained attention (Figure 1). Among all subjects, erythrocyte DHA composition was positively correlated with DLPFC activation, and inversely correlated with reaction time, at baseline and endpoint.

A randomized double-blind study investigated the effects of 4-week supplementation with either an EPA-rich formulation (3:1 EPA/DHA - 727 mg/d) or a DHA-rich formulation (4:1 DHA/EPA - 576 mg/d) using a crossover design and a 30-day washout period in healthy young adults (aged 20–34 years, $n=13$)[92]. fMRI scans were acquired during performance of color-word Stroop task and a Spatial Working Memory task. Although both supplements decreased the AA/EPA ratio in plasma, neither significantly increased plasma EPA or DHA. Subjects receiving the EPA-rich supplement exhibited decreased activation in the left ACC and increased activation in the right precentral gyrus during performance of the Stroop task. EPA-rich supplementation was also associated with a decrease in reaction times. Subjects receiving the DHA-rich supplement exhibited decreased activation in the right precentral gyrus during the Stroop and Spatial Working Memory tasks without significant changes in task performance measures. It was concluded that the observed reductions in the left ACC and increased activation in the right precentral gyrus, and associated reductions in reaction time, following EPA-rich supplementation may be attributable to improvements in cortical processing efficiency and that DHA-rich supplementation is less effective.

A third randomized double-blind placebo-controlled trial investigated the effects of 16-week supplementation (via margarine) with an EPA+DHA formulation (1:1 EPA/DHA – 1,300 mg/d) or placebo in male ADHD children and demographically similar healthy male children (mean age: 10.5 years, $n=72$) [93]. The majority (95%) of ADHD subjects were taking psychostimulant medication (methylphenidate) during the trial and were instructed not to take their medication for 24 h prior to scanning. fMRI scans were acquired during performance of a Go/NoGo task. Supplementation with EPA+DHA, but not placebo, increased cheek cell phospholipid DHA levels and improved parent-rated attention in both ADHD and healthy children. During performance of the Go/NoGo task, ADHD children had longer reaction times compared with healthy children during the Go trials, and exhibited decreased activation in bilateral inferior parietal lobule and the right middle frontal gyrus compared with healthy controls. However, no significant effects of treatment were observed in either ADHD subjects or healthy children.

A fourth randomized double-blind placebo-controlled trial investigated the effects of 24-week supplementation with fish oil (2:1 EPA/DHA – 2,400 mg/d) or placebo (corn oil) in older adults (mean age: 68 years, $n=21$) with subjective memory impairment but not meeting criteria for mild cognitive impairment or dementia [94]. fMRI scans were acquired during performance of a sequential letter n -back working memory task. Subjects receiving fish oil, but not placebo, exhibited increases in erythrocyte membrane EPA+DHA composition and greater accuracy on the more difficult 2-back memory loading condition of the n -back working memory task. Subjects receiving fish oil, but not placebo, exhibited a significant baseline-endpoint increase posterior cingulate cortex activation during the 1- and 2-back conditions. Among all subjects, the baseline-endpoint change in erythrocyte EPA+DHA was associated with better performance in the 2-back working memory task and posterior cingulate activation during performance of the 2-back condition.

6. Near infrared spectroscopy

Similar to fMRI, near infrared spectroscopy (NIRS) is a non-invasive technique that measures hemodynamic responses to neuronal activation indexed by changes in concentrations of oxygenated hemoglobin (oxy-Hb), deoxy-Hb, and total hemoglobin which are correlated with cerebral blood flow and fMRI BOLD signal [95]. Unlike fMRI, NIRS is based on the intrinsic optical absorption of blood involving the transmission of wavelengths of light introduced through the skull via a laser emitter and measured from the upper surface of the cortex by a detector. To date two cross-sectional studies and four prospective intervention studies have investigated the relationship between fish/fish oil intake and/or blood EPA and DHA biostatus and NIRS measures during performance of cognitive tasks.

The first cross-sectional study of healthy adults residing in Japan (aged 20–49 years, $n=64$) investigated the relationship between blood EPA and DHA levels and NIRS measures in the prefrontal cortex during performance of an arithmetic task and investigated associations with mood state and arousal level [96]. In the adjusted model, blood EPA levels were positively correlated with the ratio of oxy-Hb to oxy-Hb + deoxy-Hb in the prefrontal cortex while completing the arousal level questionnaire, and inversely correlated while completing the mood state questionnaire. Both EPA and DHA were inversely correlated with depression-

dejection and positively associated with arousal level. A second cross-sectional study of healthy adult males residing in Japan (mean age: 35 years, $n=208$) investigated the relationship between fish intake frequency during the prior 3 months, and NIRS measures in the DLPFC during performance of a 2-back working memory task [97]. When the cohort was divided into high ($n=92$) and low ($n=116$) fish consumption groups, greater increases in oxy-Hb were observed in the high consumption group in the left DLPFC during performance of the working memory task despite exhibiting similar performance. Among all subjects, a positive correlation was observed between fish consumption and oxy-Hb in the left DLPFC during performance of the working memory task, and this remained significant after controlling for confounding variables (age, education levels, BDI total scores). No significant correlations were observed between plasma EPA and DHA levels and oxy-Hb in the left DLPFC.

A randomized double-blind placebo-controlled study investigated the effects of 12-week supplementation with an EPA-rich formulation (1.5:1 EPA/DHA - 500 mg/d), a DHA-rich formulation (5:1 DHA/EPA - 540 mg/d), or placebo (olive oil) in healthy young adult males (mean age: 22 years, $n=22$)[98]. NIRS was acquired from the prefrontal cortex during the performance of the Stroop task, peg-and-ball task, 3-back task, and Wisconsin card sort task. Supplementation with the DHA-rich formulation increased serum DHA levels, and the EPA-rich formulation also increased serum DHA levels but not EPA levels. Compared with placebo, at study endpoint subjects receiving the DHA-rich formulation, but not the EPA-rich formulation, exhibited elevated concentrations of oxy-Hb and total Hb (the sum of oxy- and deoxy-Hb) during performance of the Stroop task, and there were similar trends observed for the other tasks. A second randomized double-blind placebo-controlled dose-ranging trial investigated the effects of 12-week supplementation with one of two doses of DHA-rich fish oil (1:5 EPA/DHA - 540 mg/d or 1,080 mg/d) or placebo (olive oil) in healthy adults (aged 18–29 years, $n=65$)[99]. At study endpoint, NIRS was acquired from the prefrontal cortex during performance of several different computerized cognitive tasks. Blood EPA+DHA levels were not determined/reported. There were no group differences while in a resting state. Subjects receiving both doses of fish oil, but not placebo, exhibited greater increases in oxy-Hb and total Hb levels during performance of cognitive tasks. Compared with placebo, faster reaction times were observed in the fish oil groups on a subset of tasks. It was concluded that 12-week supplementation with both doses of DHA-rich fish oil increased cerebral blood flow in the prefrontal cortex during performance of cognitive tasks.

A randomized double-blind placebo-controlled trial investigated the effects of 6-month supplementation with DHA-rich fish oil (1:7 EPA/DHA - 1,024 mg/d) or placebo (sunflower oil) in older adults (mean age: 60 years, $n=248$) with subjective memory impairment [100]. At study endpoint, NIRS was acquired from the prefrontal cortex during performance of several different computerized cognitive tasks. Supplementation with DHA-rich fish oil increased whole blood EPA and DHA levels, and decreased the AA/EPA ratio. However, no effect of treatment was observed for NIRS measures (total Hb) or cognitive task performance. A second randomized double-blind placebo-controlled investigated the effects of 12-week supplementation with either krill oil (2:1 EPA/DHA - 285 mg/d), sardine oil (2:1 EPA/DHA - 742 mg/d), or placebo (medium chain triglycerides) in cognitively

healthy older adults (mean age: 67 years, $n=45$) residing in Japan [101]. Plasma EPA, but not DHA, increased in subjects receiving krill oil or sardine oil. At study endpoint, NIRS measures were acquired in the DLPFC during performance of a 2-back working memory task or a calculation task. Subjects receiving krill oil or sardine oil exhibited greater increases in oxy-Hb in the DLPFC during performance of the working memory task compared with placebo. Subjects receiving krill oil also exhibited greater increases in oxy-Hb during performance of the calculation task compared with placebo.

7. ^1H MRS

Proton magnetic resonance spectroscopy (^1H MRS) is a voxel-based technique that determines regional concentrations of glutamate, glutamine, glutathione, γ -aminobutyric acid (GABA), *myo*-inositol, *N*-acetyl aspartate, choline, and creatine. *N*-acetyl aspartate is primarily localized to neurons [102,103] and is positively correlated with mitochondrial metabolism [104], and ^1H MRS studies have observed reductions in regional *N*-acetyl aspartate concentrations in association with neuronal and axonal atrophy [105–109]. Similarly, choline and creatine are reduced in human cerebral infarcts during the acute or subacute phase of ischemic stroke [106,110,111]. *Myo*-inositol is metabolized from glucose via 1L-*myo*-inositol 1-phosphate synthase and is predominantly concentrated in astrocytes [102,103]. The *myo*-inositol peak detectable by ^1H MRS likely reflects the astrocyte pool. Glutathione is primarily present in astrocytes and is thought to have anti-oxidant properties [112]. In general, lower concentrations of *N*-acetyl aspartate, choline, creatine, and glutathione are associated with reductions in cortical structural and functional integrity.

A cross-sectional study segregated healthy typically developing male children (mean age: 9 years) into low-DHA ($n=19$) and high-DHA ($n=19$) biostatus groups by a median split of erythrocyte DHA levels [113]. ^1H MRS voxels were placed in the right and left DLPFC and bilateral ACC. Mean erythrocyte DHA levels in the low-DHA group were significantly lower than the high-DHA group. Subjects in the low-DHA group exhibited lower *myo*-inositol, *N*-acetyl aspartate, choline, and creatine concentrations in the ACC compared with the high-DHA group. There were no group differences for any metabolite in the left or right DLPFC. Among all subjects, erythrocyte DHA was positively correlated with *myo*-inositol concentrations in the ACC.

A dose-ranging trial investigated the effects of 10-week open-label supplementation with low (2.4 g/d, $n=7$) or high (16.2 g/d, $n=7$) dose fish oil (EPA/DHA: 2:1) on prefrontal metabolite concentrations in adolescents with MDD (mean age: 15 years)[114]. ^1H MRS voxels were placed in the right and left DLPFC and bilateral ACC. Baseline erythrocyte EPA composition was positively correlated, and the AA/EPA ratio inversely correlated, with choline concentrations in the right DLPFC, and erythrocyte DHA composition was inversely correlated with *myo*-inositol in the left DLPFC. Erythrocyte EPA and DHA composition increased significantly in both dose groups. While there were no significant baseline-endpoint changes in metabolite levels in each voxel, the low-dose group exhibited trends with large effect sizes including a decrease in *myo*-inositol in the left DLPFC and increases in glutamate/glutamine and choline in the right DLPFC. The high-dose group exhibited trends with large effect sizes including increases in choline in the right DLPFC.

Three randomized double-blind placebo-controlled trials have investigated the effects *n*-3 PUFA supplementation on cortical and subcortical metabolite concentrations using ^1H MRS. The first trial investigated the effects of 12-week supplementation with ethyl-EPA (2,000 mg/d) or placebo (liquid paraffin) in lithium-treated female patients with bipolar disorder (mean age: 41 years, $n=14$)[115]. A single voxel was placed in the cingulate gyrus region. Blood EPA levels were not determined/reported. EPA supplementation selectively increased *N*-acetyl aspartate concentrations, and there were no corresponding changes in depression symptom severity. The second trial investigated the effects of 12-week supplementation with ethyl-EPA (2,000 mg/d) or placebo (not specified) in first-episode psychotic patients (mean age: 20 years, $n=24$)[116]. The voxels were placed in bilateral anterior hippocampus. The majority of patients were drug-naïve at baseline and started treatment with a second generation antipsychotic during the 12-week trial. Blood EPA levels were not determined/reported. Supplementation with ethyl-EPA increased glutathione concentrations bilaterally, and increased glutamate/glutamine in the left hemisphere. Change in negative symptom severity was inversely correlated with changes in glutathione concentrations, and changes in glutamate/glutamine and glutathione were positively correlated. A third trial investigated the effects of 12-week supplementation with fish oil (EPA/DHA: 1.5:1 – 2,000 mg/d) or placebo (paraffin oil) in healthy older adults (mean age: 71 years, $n=51$), a subset of which had a history of depression [117]. The single voxel was placed in the thalamus, and the glutathione/creatine ratio was the primary measure of interest. Blood EPA and DHA levels were not determined. Over the 12 week trial subjects in the placebo group exhibited a significant increase in the glutathione/creatine ratio, which was moderately associated with a worsening of depression, whereas subjects in the fish oil did not exhibit a significant change in the glutathione/creatine ratio.

8. ^{31}P MRS

Phosphorous magnetic resonance spectroscopy (^{31}P MRS) permits measurement of concentrations of phosphorus-containing compounds, including phospholipid anabolites (i.e., phosphomonoesters, PME) and catabolites (i.e., phosphodiesteres, PDE), high-energy phosphate compounds, as well as indices of cortical energy utilization (i.e., ATP). Reductions in the PME:PDE ratio, secondary to either elevations in PDE or reductions in PME, are thought to reflect a decrease in the synthesis and/or an increase in the breakdown of membrane phospholipids. An early case study reported that 6 month treatment with ethyl-EPA resulted in the normalization of brain membrane phospholipid metabolism in a drug-naïve patient with schizophrenia [118]. A preliminary ^{31}P MRS study found that cortical PDE levels in the basal ganglia were inversely correlated with erythrocyte DHA and EPA levels in a small cohort of healthy young adults (mean age: 29 years, $n=9$)[119]. A cross-sectional study of neuroleptic-naïve first-episode psychosis patients (mean age: 26 years, $n=11$) found that erythrocyte total PUFA levels and AA were positively correlated with bilateral prefrontal cortex PME levels, and linoleic acid (18:2 n -6) was positively correlated with PDE levels [120]. No associations with fatty acid levels were observed in other brain regions, including the basal ganglia, occipital, inferior parietal, and superior temporal cortex, and no significant associations were observed for erythrocyte DHA and EPA levels.

9. Positron emission tomography

Positron emission tomography (PET) is an imaging technique that uses radiotracers to investigate several different metabolic processes. For example, radiotracers have been developed to interrogate regional neurotransmitter receptor or transporter binding levels (e.g., [^{11}C]-DTBZ), glucose metabolic rates (e.g., [^{18}F]-FDG), cerebral blood flow (e.g., [^{15}O]H₂O), neuroinflammation (e.g., [^{11}C]PBR28), as well as fatty acid incorporation and turnover rates (e.g., [$1\text{-}^{11}\text{C}$]DHA). A pioneering cross-sectional PET study using radiolabeled DHA ([$1\text{-}^{11}\text{C}$]DHA) investigated DHA incorporation and turnover rates in small group of healthy adult subjects (mean age: 36 years, $n=14$)[121]. The brain DHA incorporation rate from plasma was equivalent to net rate of DHA consumption and suggested that the half-life of DHA in the human brain is approximately 2.5 years. Using [^{15}O]H₂O this study also demonstrated that DHA incorporation was positively correlated with regional cerebral blood flow (rCBF). A follow-up case-control study of chronic alcoholics and healthy controls found that the DHA incorporation rate and rCBF were significantly elevated in chronic alcoholics consistent with a hypermetabolic state and increased consumption of DHA [122].

A cross-sectional study of adult medication-free MDD patients (mean age: 41 years, $n=29$) found that plasma DHA levels, but not plasma EPA levels, were positively correlated with resting glucose metabolism ([^{18}F]-FDG) in the temporoparietal cortex, and inversely correlated with resting glucose metabolism in prefrontal cortex and anterior cingulate cortex [123]. Plasma AA levels were positively correlated with resting glucose metabolism in the temporoparietal cortex. A second cross-sectional study of healthy middle-aged adults (mean age: 54 years, $n=52$) found that a nutrient pattern associated with higher $n\text{-}3$ PUFA intake from fish, as well as monounsaturated and $n\text{-}6$ PUFA intake, was associated with greater glucose metabolism ([F]-FDG) in the bilateral prefrontal cortex [124]. A recent cross-sectional study of elderly subjects with no or mild cognitive impairment (mean age: 77 years, $n=61$) investigated the relationship between fasting serum DHA levels and cerebral amyloid deposition using PET imaging and the radiotracer C-labeled Pittsburgh Compound B ([^{11}C]PiB)[125]. In adjusted models, serum DHA levels were inversely correlated with cerebral amyloid load and were significantly lower in participants with cerebral amyloidosis than those without.

A prospective intervention study used PET to investigate the effects of 24-week fish oil (1:1.2 EPA/DHA – 1,680 mg/d) supplementation on vesicular monoamine transporter binding ([^{11}C]-DTBZ) in healthy young adults (mean age: 22 years, $n=11$)[126]. Although fish oil supplementation significantly increased erythrocyte EPA and DHA levels, no significant change in [^{11}C]-DTBZ binding was observed in striatal subdivisions. A preliminary prospective study found that 3-week fish oil (1:2 EPA/DHA – 1,000 mg/d) supplementation did not significantly alter glucose metabolism ([^{18}F]-FDG) in several different regions, including the hippocampus, ACC, or prefrontal cortex, in healthy young (mean age: 23, $n=5$) or elderly (mean age: 76, $n=6$) adults [127].

10. Summary and Discussion

Over the last decade there has been a substantial increase in the number of studies using different neuroimaging techniques to specifically investigate associations between PUFA and human brain structural and functional integrity. Although there have been inconsistencies within different neuroimaging modalities, to date no study has reported a detrimental effect of increasing *n*-3 PUFA intake/biostatus on any measure of human brain structure or function. Indeed, the weight of evidence from cross-sectional and prospective longitudinal MRI studies conducted in healthy subjects suggests that greater dietary fish intake frequency and/or higher blood DHA and/or EPA levels are associated with increased global gray matter volumes as well as increased regional volumes, including the ACC and temporal lobe structures including the hippocampus and amygdala. A subset of studies additionally found that the positive association between blood DHA and/or EPA levels and performance on cognitive measures, particularly executive function, may be mediated in part by gray matter volumes. The majority of studies did not observe an association between *n*-3 PUFA intake/biostatus and white matter volumes in either infants or older adults. However, several studies observed an inverse association between *n*-3 PUFA intake/biostatus and WMH burden in older adults, and emerging DTI evidence suggests a positive association between PUFA and white matter microstructural integrity. Evidence from fMRI and NIRS studies further suggest a positive association between *n*-3 PUFA intake/biostatus and activity dependent cerebral blood flow in children and young adults, and MRS studies suggest a positive association between *n*-3 PUFA intake/biostatus and chemical indices of cortical integrity in children and adults.

A subset of studies investigated associations between *n*-3 PUFA intake/biostatus and neuroimaging measures in elderly patients with dementia or Alzheimer's disease. The one controlled trial in patients with moderate Alzheimer's disease did not observe a protective effect of algal DHA supplementation on global or hippocampal gray matter atrophy [64]. However, additional research is needed to determine whether this negative finding is attributable to the intervention (algal DHA) or the advanced stage of cognitive decline of the study population. For example, a controlled supplementation trial conducted in a younger cohort of cognitively healthy older adults did observe a beneficial effect of fish oil on gray matter volume in the left hippocampus [65], and other studies have observed apparent protective effects of *n*-3 PUFA intake/biostatus against brain pathology, including subclinical infarcts, WMH burden, and cerebral amyloid load in older adults. Therefore, increasing *n*-3 PUFA intake/biostatus early in the aging process may be required to prevent or attenuate neurodegenerative processes leading to dementia or Alzheimer's disease which may be less amenable to modification once established. Furthermore, additional research is warranted to evaluate whether supplementation with DHA or EPA alone or in combination is more effective for altering different neuroimaging outcomes.

A small number of neuroimaging studies have investigated associations between PUFA intake/biostatus in infants and children. To date, there have been no studies in typically developing term-born infants and the results from studies assessing associations between *n*-3 PUFA intake/biostatus on white matter of infants born preterm have been equivocal. It is notable, however, that neuroimaging studies in infants are complicated by the PUFA intake/

biostatus of the mother and associated PUFA levels in breastmilk. Nevertheless, in view of evidence that preterm birth is associated with early deficits in cortical DHA accrual [32,33] and enduring decreases in frontal white matter integrity [80], additional research is warranted to replicate and extend preliminary evidence for a positive association between DHA biostatus and white matter microstructural integrity [81]. While the effects of increasing *n*-3 PUFA intake/biostatus on functional cortical activity in typically developing children have also been inconsistent, preliminary cross-sectional evidence supports a positive association between *n*-3 PUFA intake/biostatus and frontal cortical integrity and regional connectivity. Because pediatric and adolescent development is associated with increases in cortical DHA accrual and rapid changes in cortical structure and function, additional neuroimaging research is warranted to further define whether *n*-3 PUFA intake/biostatus is associated with cortical structural and functional maturation in typically developing youth.

Several studies also investigated associations between *n*-3 PUFA intake/biostatus and neuroimaging measures in patients with neuropsychiatric disorders. Schizophrenia is associated with blood DHA and AA deficits [128] and progressive neuropathological brain changes characterized in part by reduced cortical white matter microstructural integrity [129]. It is of interest, therefore, that emerging evidence suggests that PUFA biostatus is positively associated with white matter microstructural integrity in schizophrenic patients [86]. Moreover, mood disorders including MDD and bipolar disorder are associated with blood EPA+DHA deficits, and associated increases in the AA/EPA+DHA ratio [130,131], reduced gray matter volumes in corticolimbic structures [132], increased WMH burden [133], and reduced cortical white matter microstructural integrity [134,135]. It is notable, therefore that fish oil supplementation was found to increase white matter microstructural integrity in patients with MDD in association with reductions in depression symptom severity [87]. In a preliminary cross-sectional study of adolescent MDD patients we have additionally found that erythrocyte DHA levels are positively correlated with prefrontal cortex activation during performance of a sustained attention task (Figure 2). These and other neuroimaging findings suggest that blood measures of *n*-3 PUFA biostatus may represent a peripheral biomarker that is relevant to cortical pathology observed in patients with psychiatric disorders. However, additional research is needed to directly investigate whether increasing *n*-3 PUFA biostatus early in the course of illness can prevent or attenuate neuropathological brain changes in youth with or at risk for psychiatric disorders.

While the mechanisms mediating the observed protective effects of *n*-3 PUFA against gray matter atrophy, WMH, and cerebral infarct burden remain to be elucidated, observations from fMRI, NIRS, and PET studies suggest that higher *n*-3 PUFA levels are associated with increased cerebral blood flow. It is relevant, therefore, that increasing *n*-3 PUFA biostatus decreases blood triglyceride levels [137] and reduces blood platelet aggregation [136], potentially by attenuating platelet thromboxane A₂ production which has vasoconstriction effects [138–140]. Moreover, neuroimaging studies have observed inverse associations between triglyceride levels and cerebral blood flow [141,142]. Therefore, greater *n*-3 PUFA biostatus may promote cerebral blood flow in part by reducing blood viscosity and arterial occlusion (Figure 3). Additionally, *n*-3 PUFA biostatus is inversely correlated with circulating blood pro-inflammatory cytokine and C-reactive protein (CRP) levels [143]

which adversely impact vascular endothelial cells [144]. Neuroimaging studies have observed inverse associations between circulating blood pro-inflammatory cytokine and CRP levels and corticolimbic gray matter volumes and white matter pathology [145–149]. While the causal relationships between these factors remains to be determined, it is relevant that patients with MDD exhibit elevated blood *n*-6/*n*-3 PUFA levels [130], increased blood viscosity [150], elevated blood cytokine levels [151], neuroinflammation [152], regional cerebral hypoperfusion [150,153], increased WMH burden [133], reduced cortical white matter microstructural integrity [135], and regional gray matter volume reductions [132]. Nevertheless, additional research using neuroimaging techniques that are more sensitive to cerebral perfusion dynamics, including Computed Tomography, will be required to directly evaluate whether any or all of these factors mediate the observed beneficial effects of *n*-3 PUFA on human cortical structure and function.

In summary, the recent increase in neuroimaging studies investigating the impact of PUFA intake and/or biostatus on human brain structure and function provide important new insight into the role of dietary PUFA on human brain maturation and resilience. To date, findings from human and non-human primate imaging studies provide general support for a beneficial role of higher *n*-3 PUFA intake on cortical structure and function during both development and aging. Nevertheless, additional research is needed to replicate and extend these early findings as well as identify response mediators and clarify mechanisms of action.

Acknowledgments

This work was supported in part by National Institute of Health grants DK097599, MH097818, and MH107378 to R.K.M.

R.K.M. has received research support from NARSAD, Martek Biosciences/DSM Inc, Ortho-McNeil Janssen, AstraZeneca, Eli Lilly, Kyowa Hakko Bio Co., LTD, and the Inflammation Research Foundation (IRF), was a member of the IRF scientific advisory board, and served as a paid consultant for VAYA Pharma Inc., and Vifor Pharma Inc. The NIH did not have any role in the design, implementation, analysis or interpretation of the research.

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Highlights

- There has been a substantial increase in neuroimaging studies investigating associations between PUFA and human brain structure and function.
- The weight of evidence suggests that greater *n*-3 PUFA intake/biostatus is associated with increased gray matter volumes.
- Studies have observed an inverse association between *n*-3 PUFA intake/biostatus and white matter microstructural integrity.
- Functional imaging studies suggest a positive association between *n*-3 PUFA intake/biostatus and activity dependent cerebral blood flow.

Figure 1.

Functional magnetic resonance images illustrating greater baseline-endpoint increases in blood oxygen level-dependent (BOLD) activity in the prefrontal cortex (top row, DHA>Placebo), and greater baseline-endpoint decreases in BOLD activity in parietal, temporal, and cerebellar cortices (bottom row, DHA<Placebo), in healthy boys receiving DHA (1,200 mg/d) or placebo for 8 weeks. Scans were acquired during performance of a sustained attention task (CPT-IP). Results are presented over progressively less stringent statistical thresholds, and the voxel-extent threshold was held constant at T25.

Figure 2.

Erythrocyte DHA levels are positively correlated with blood oxygen level-dependent (BOLD) activity in prefrontal and anterior cingulate subregions of adolescent MDD patients (mean age: 16 years, $n=20$) during performance of a sustained attention task (CPT-IP). The color gradient reflects increasing (red → yellow) statistical significances from p 0.05 (corrected).

Figure 3.

Diagram illustrating candidate mechanisms mediating the relationship between n -3 PUFA deficiency, and associated elevations in the n -6/ n -3 PUFA ratio, and gray matter atrophy, white matter pathology (e.g., WMH), and cerebral infarct burden. An elevated n -6/ n -3 PUFA ratio reduces cerebral blood flow (i.e., cerebrovascular hypoperfusion) in part by increasing blood viscosity by increasing triglyceride levels and platelet aggregation, and increasing vasoconstriction via elevated platelet thromboxane A₂ production. Elevated n -6/ n -3 PUFA ratio also increases circulating pro-inflammatory cytokine levels which adversely impact vascular endothelial cells and have been found to be associated with white matter pathology and reduced corticolimbic gray matter volumes.