Published in final edited form as:

Harv Rev Psychiatry. 2019 ; 27(2): 94–107. doi:10.1097/HRP.0000000000000199.

Omega-3 Polyunsaturated Fatty Acid Deficiency and Progressive Neuropathology in Psychiatric Disorders: A Review of Translational Evidence and Candidate Mechanisms

Robert K. McNamara¹ and Daniel M. Almeida²

¹Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, OH 45219

²Division of Child and Adolescent Psychiatry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45224 United States

Abstract

Meta-analytic evidence indicates that mood and psychotic disorders are associated with both omega-3 polyunsaturated fatty acid (omega-3 PUFA) deficits and progressive regional gray and white matter pathology. Although the association between omega-3 PUFA insufficiency and progressive neuropathological processes remains speculative, evidence from translational research suggests that omega-3 PUFA insufficiency may represent a plausible and modifiable risk factor for not only enduring neurodevelopmental abnormalities in brain structure and function, but also for increased vulnerability to neurodegenerative processes. Recent evidence from human neuroimaging studies suggests that lower omega-3 PUFA intake/status is associated with accelerated gray matter atrophy in healthy middle-aged and elderly adults, particularly in brain regions consistently implicated in mood and psychotic disorders including the prefrontal cortex, hippocampus, amygdala, anterior cingulate, and temporal cortex. Human neuroimaging evidence also suggests that both low omega-3 PUFA intake/status and psychiatric disorders are associated with reductions in white matter microstructural integrity and increased rates of white matter hyperintensities. Preliminary evidence suggests that increasing omega-3 PUFA status is protective against gray matter atrophy and deficits in white matter microstructural integrity in patients with mood and psychotic disorders. Plausible mechanisms mediating this relationship include elevated pro-inflammatory signaling, increased synaptic regression, and reductions in cerebral perfusion. Together these associations encourage additional neuroimaging research to directly investigate whether increasing omega-3 PUFA status can mitigate neuropathological processes in patients with or at high-risk for psychiatric disorders.

Keywords

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

*Corresponding author: Robert K. McNamara, Ph.D., Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 260 Stetson Street, Cincinnati, OH 45219-0516, PH: 513-558-5601, FAX: 513-558-4805, robert.mcnamara@uc.edu.

INTRODUCTION

Neuropsychiatric disorders, including major depressive disorder (MDD), bipolar disorder, and schizophrenia, are associated with significant psychosocial and cognitive impairment, and excess premature mortality attributable to increased rates of suicide and cardiovascular disease.^{1–5} The onset of mood and psychotic disorders frequently initially occurs during adolescence and young adulthood,^{6–9} a period associated with cortical circuit maturation involving increases in synaptic pruning and myelination.^{10–15} However, the initial onset can also occur in late-adulthood and the prevalence of psychiatric symptoms including psychosis increase in elderly patients with dementia and Alzheimer's disease.^{16,17} Over the past three decades, magnetic resonance imaging (MRI) has been used extensively to investigate central pathological processes associated with mood and psychotic disorders, and recent meta-analyses provide strong evidence that these disorders are associated with progressive gray and white matter pathology.

Meta-analyses of cross-sectional structural MRI studies indicate that MDD is associated with reduced total gray and white matter volumes, and reduced gray matter volumes in the hippocampus, amygdala, and anterior cingulate.^{18–20} Meta-analyses indicate that bipolar I disorder is associated with reduced anterior cingulate and inferior frontal gyrus gray matter volumes,²¹ and that children and adolescents, but not adults, with bipolar I disorder exhibit smaller amygdala volumes.²² Prospective and longitudinal and cross-sectional structural imaging studies further suggest that bipolar I disorder is associated with an accelerated loss in frontal gray matter volume compared with healthy subjects.^{23,24} Moreover, meta-analyses indicate that schizophrenia is characterized by progressive gray matter atrophy particularly in the superior temporal gyrus,^{25–28} and reductions in hippocampus and whole brain volumes are observed in first-episode patients.^{29,30} Additionally, white matter volume reductions are observed in first-episode patients with schizophrenia and bipolar disorder,³¹ as are increased rates of deep white matter hyperintensities (WMH).^{32,33} Meta-analyses of cross-sectional diffusion tensor imaging studies indicate widespread reductions in cortical white matter microstructural integrity in patients with first-episode schizophrenia,³⁴ bipolar disorder,³⁵ and MDD.³⁶ Extant meta-analytic evidence therefore suggests that psychiatric disorders are associated with overlapping as well as unique structural and microstructural neuropathological features which are apparent early in the illness course and prior to long-term exposure to psychotropic medications.

Despite this body of evidence, however, etiopathogenic mechanisms contributing to progressive structural pathology remain poorly understood. A growing and converging body of translational evidence suggests that omega-3 polyunsaturated fatty acids (PUFA) play a central role in normal brain development and resilience to insult, and that mood and psychotic disorders are associated with omega-3 PUFA deficits. Until recently, the majority of evidence for a role of omega-3 PUFA in brain development, resilience, and degeneration has come from animal studies. However, several neuroimaging studies have emerged recently which offer new insight into the role of omega-3 PUFA intake or biostatus in human brain structure and function. This review will provide a brief overview of omega-3 PUFAs and evidence for an association between omega-3 PUFA insufficiency and neuropsychiatric disorders, will then review evidence from human neuroimaging and animal studies

implicating omega-3 PUFA in neurodevelopmental and neurodegenerative processes, and will then discuss candidate mediating mechanisms and clinical implications.

METHODS

Relevant peer-reviewed articles published up to November 2017 were identified using PubMed and the following search terms: “omega-3”, “DHA”, “PUFA”, “MRI”, “DTI”, “PET”, “SPECT”, “NIRS”, “structural,” “rat”, “non-human primate”, “brain”, and/or “psychiatry.” Additional relevant articles were selected from the bibliographies of identified papers. Articles were excluded if they were not peer-reviewed, were written in a language other than English, and/or did not specifically investigate relationships between PUFA measures and relevant brain outcomes. A total of 260 relevant articles were identified that met inclusion criteria. When available meta-analyses were used in order to provide a systematic synthesis of different studies.

PUFA BACKGROUND

The PUFA family includes omega-3 and omega-6 fatty acids. Flaxseed, linseed, canola, soy, and perilla oils are primary dietary sources of the short-chain omega-3 PUFA α -linolenic acid, and safflower, soy, and corn oils are primary sources of the short-chain omega-6 fatty acid linoleic acid. Because mammals cannot endogenously synthesize these short-chain PUFAs, they are considered ‘essential’ and necessitate procurement through the diet. Long-chain omega-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and long-chain omega-6 PUFAs, including arachidonic acid (AA), are biosynthesized from short-chain precursors by common microsomal desaturation and elongation reactions,³⁷ and peroxisomal enzymes catalyze the biosynthesis of DHA.³⁸ While nucleotide sequence polymorphisms^{39,40} and epigenetic (i.e., DNA methylation) modifications⁴¹ have been observed in desaturase and peroxisomal genes, it is estimated that only one quarter of the variability in EPA and DHA levels can be attributed to heritable factors.⁴² Moreover, in healthy human subjects the biosynthesis of long-chain omega-3 and omega-6 PUFA from short-chain fatty acid precursors is limited.^{43–46} Accordingly, dietary intake of preformed omega-3 PUFA, e.g., from fatty cold water fish, and omega-6 PUFA, e.g., from animal-based foods including beef, chicken, and eggs, is significantly more effective for increasing peripheral and central tissue DHA and AA levels.^{44,47–51} Therefore, fish and seafood, as well as dietary fish oil supplements, are the primary dietary source of preformed EPA+DHA (hence forth: omega-3 PUFA) in humans. Because omega-3 and omega-6 PUFAs compete for incorporation onto tissue phospholipids, a reduction in dietary omega-3 PUFA intake is associated with systemic increases in the omega-6/omega-3 ratio (e.g., AA/EPA+DHA ratio).

OMEGA-3 PUFA AND PSYCHIATRIC DISORDERS

Cross-national epidemiological studies have observed a significant inverse relationship between lifetime prevalence rates of MDD^{52,53} and bipolar spectrum disorders⁵⁴ and per capita fish or seafood consumption. A recent meta-analysis of cross-sectional and prospective observational studies indicate that higher fish or omega-3 PUFA intake is

associated with reduced risk of depression in the general population.⁵⁵ The lifetime prevalence rates of schizophrenia are not associated with per capita fish or seafood consumption,⁵⁴ and there is conflicting evidence regarding whether higher fish or seafood consumption is associated better functional outcomes.^{53,56} Although these findings provide general support for an inverse association between fish or omega-3 PUFA intake and mood disorders, cultural, socioeconomic, and/or genetic variables may also contribute to this association. It is also relevant that the omega-3 PUFA content in different types of fish and seafood varies widely, and fish and seafood also contain other potentially therapeutically-relevant substances including vitamin D and selenium.

A more objective and targeted approach is to investigate omega-3 PUFA levels in blood and tissues as an index of 'biostatus'. For example, habitual dietary fish intake frequency^{57,58} and fish oil supplementation dose⁵⁹ are positively and linearly correlated with erythrocyte (red blood cell) phospholipid membrane omega-3 PUFA (EPA+DHA) levels. Meta-analytic evidence from fourteen cross-sectional studies indicates that patients with MDD exhibit significant blood (plasma, erythrocyte) deficits in EPA and DHA, but not AA or total omega-6 fatty acids.⁶⁰ Similarly, cross-sectional studies indicate that patients with bipolar I disorder exhibit significant erythrocyte deficits in DHA, and to a lesser extent EPA, and no differences in the omega-6 PUFAs linoleic acid or AA.⁶¹ Meta-analyses also indicate that schizophrenia is associated with lower blood DHA and/or EPA levels as well as deficits in the omega-6 PUFA AA.⁶² Robust erythrocyte DHA deficits have also been observed in first-episode schizophrenia⁶² and bipolar disorder⁶³ patients, as well as adolescents at ultra-high risk for developing bipolar I disorder⁶⁵ i.e., they have MDD and a biological parent with bipolar I disorder.^{64,66} These findings suggest that low omega-3 PUFA biostatus coincides with the initial onset of mood and psychotic symptoms and may be associated with symptom progression in high-risk youth.

A recent prospective longitudinal study further suggests that low omega-3 PUFA biostatus increases risk for the initial onset of mood symptoms. A 7-year prospective study found that lower erythrocyte omega-3 PUFA levels and a higher omega-6/omega-3 ratio at baseline were significant predictors for developing a mood disorder at follow-up in youth at high-risk for psychosis.⁶⁷ Prospective studies have similarly found that lower baseline DHA levels, or a higher AA/EPA+DHA ratio, predict the emergence of MDD in initially non-depressed hepatitis C patients during treatment with pro-inflammatory interferon- α (IFN- α).^{68,69} Additionally, the emergence of anger and irritability, core symptoms of bipolar I disorder, are also predicted by a higher baseline AA/EPA+DHA ratio in hepatitis C patients during IFN- α treatment.⁷⁰ These prospective findings therefore suggest that low omega-3 PUFA biostatus increases vulnerability to inflammation-induced as well as endogenous mood dysregulation.

While the omega-3 PUFA deficits observed in patients with mood and psychotic disorders may be due to different factors, extant evidence indicates that supplementing the diet with omega-3 PUFAs is sufficient to increase blood and presumably brain omega-3 PUFA levels.^{71–73} Additionally, some meta-analyses of controlled trials,^{74–76} but not all,⁷⁷ have found that omega-3 PUFA supplementation is superior to placebo for reducing depressive symptoms in patients with MDD, and may additionally have antidepressant efficacy in

patients with bipolar disorder.^{75,78} Preliminary trials have also reported significant reductions in depression and manic symptom severity in pediatric and adolescent patients following omega-3 PUFA supplementation.^{71–73} Omega-3 PUFA supplementation was also found to be protective against the initial onset of depressive symptoms in hepatitis C patients being treated with the pro-inflammatory cytokine IFN- α ,⁷⁹ and greater antidepressant efficacy is observed following omega-3 PUFA supplementation in MDD patients with higher pro-inflammatory biomarkers.⁸⁰ Additional evidence suggests that omega-3 PUFA supplementation reduces positive and negative symptom severity in early stage schizophrenic patients.⁸¹ In general, these findings suggest that increasing omega-3 PUFA intake reduces mood and psychotic symptoms and that early intervention may additionally reduce vulnerability to the initial onset of symptoms.

In mammalian brain gray matter, DHA is the most abundant omega-3 PUFA whereas other omega-3 PUFA comprise a small fraction of total brain fatty acid composition.⁸² Under steady-state dietary conditions, mammalian erythrocyte and cortical gray matter DHA levels are positively correlated,⁸³ and DHA levels increase gradually in both erythrocyte and cortical gray matter following dietary omega-3 PUFA supplementation.⁴⁸ However, cross-sectional postmortem studies investigating the fatty acid composition of regional gray matter from patients with mood and psychotic disorders have yielded inconsistent results, with some studies^{84–89} but not others^{90–96} finding lower omega-3 PUFA levels in patients. It is important to note, however, that the postmortem approach has several limitations including a lack of information regarding habitual dietary omega-3 PUFA intake, omega-3 PUFA deficits in non-psychiatric ‘controls’ dying from cardiovascular disease,⁸⁸ and translational evidence that psychotropic medications impact brain fatty acid turnover⁹⁷ and composition.^{86,87,98} These and other limitations have prompted the use of alternative methods including neuroimaging to delineate associations between omega-3 PUFA and neuropathological processes in human brain.

HUMAN NEUROIMAGING FINDINGS

Recently several neuroimaging studies have investigated the role of omega-3 PUFA dietary intake or biostatus in human brain structure and function. Because low omega-3 PUFA intake/status has also been implicated in the pathophysiology of age-related cognitive decline and dementia,^{99–101} the majority of these studies were conducted in healthy middle-aged or elderly adults without psychiatric illness. Findings from these studies provide important insight into progressive age-related brain changes that are not confounded by psychotropic medications which may contribute to or ameliorate brain structural abnormalities in psychiatric patients.^{102–107} The results of these studies have been reviewed in detail previously¹⁰⁸ and key findings are summarized below.

Different cross-sectional and prospective longitudinal MRI studies of healthy elderly subjects have found that greater dietary fish intake frequency and/or biostatus are associated with slower gray matter atrophy over time and greater global gray matter volumes and larger anterior cingulate, hippocampus, and amygdala gray matter volumes.^{109–117} However, a placebo-controlled trial found that 72-week supplementation with algal DHA did not significantly alter total brain or hippocampal volume atrophy rates in participants with mild

to moderate Alzheimer disease.¹¹⁸ While the majority of cross-sectional and prospective studies did not observe an association between omega-3 PUFA intake and/or biostatus and global white matter volume, some cross-sectional and prospective longitudinal MRI studies found that greater omega-3 PUFA intake and/or biostatus were associated with reduced rates of white matter hyperintensity (WMH) in healthy elderly subjects.^{109,119–123} Moreover, a 26-week controlled fish oil supplementation trial observed significant increases in white matter microstructural integrity in several white matter tracts of healthy older adults.¹²⁵ A subset of studies also observed a positive association among blood DHA and/or EPA levels, gray matter volumes, and performance on cognitive tests of executive function.^{109,117,125}

These neuroimaging findings highlight several notable parallels with neuroimaging findings in psychiatric patients. Specifically, reduced hippocampus, amygdala, and anterior cingulate gray matter volumes are among the most consistent structural abnormalities observed in patients with MDD,^{18–20} and lower omega-3 PUFA intake and/or biostatus are associated with smaller hippocampal, amygdala, and anterior cingulate volumes in healthy middle-aged and elderly adults.^{112–114} Moreover, a prospective study found that lower baseline plasma EPA levels were associated with faster right hippocampus and amygdala gray matter atrophy in healthy elderly adults,¹¹⁵ and a controlled trial found that 26-week fish oil supplementation attenuated decreases in gray matter volume in the left hippocampus of healthy older adults.¹²⁵ It is also notable that schizophrenia is associated with accelerated deficits in the superior temporal gyrus gray matter volume,^{27,28} and a 3.6-year prospective study found that lower whole blood DHA levels were associated with greater baseline-endpoint cortical thinning in the superior temporal gyrus of healthy elderly subjects.¹¹⁶ Additionally, a controlled trial found that 26-week supplementation with fish oil attenuated decreases in superior temporal gyrus gray matter volume in healthy older adults.¹²⁵ As discussed, reductions in cortical white matter microstructural integrity are observed in several white matter tracts of patients with schizophrenia,³⁴ bipolar disorder,³⁵ and MDD,³⁶ and a controlled trial found that 26-week fish oil supplementation significantly increased white matter microstructural integrity in the same white matter tracts of healthy older adults.¹²⁵

While these findings suggest that the omega-3 PUFA deficits and progressive neuropathological processes observed in patients with mood and psychotic disorders may be linked, there have been comparably fewer neuroimaging studies that have directly evaluated this relationship in patients with psychiatric disorders. A recent placebo-controlled trial found that 26-week adjunctive fish oil supplementation significantly attenuated reductions in cortical thickness in the parieto-occipital regions of first-episode antipsychotic-treated schizophrenia patients.¹²⁶ An open-label 6-week fish oil supplementation study using diffusion tensor imaging found that the resulting increase in plasma phospholipid DHA levels were associated with increased white matter integrity in the corpus callosum, cingulum, and bilateral anterior corona radiata of MDD patients.¹²⁷ Importantly, fish oil supplementation also reduced depression symptom severity which was associated with increases in white matter integrity in left corticospinal tract and superior longitudinal fasciculus. While limited, these preliminary findings corroborate prior findings indicating an association between omega-3 PUFA intake and/or biostatus and gray matter atrophy and

white matter microstructural integrity in elderly adults and may therefore be mediated by common mechanisms.

ANIMAL STUDIES

There now exists an extensive body of evidence from rodent and non-human primate studies regarding the effects of omega-3 PUFA insufficiency and enrichment on brain maturation, resilience, degeneration. In rodents, omega-3 PUFA insufficiency during development causes delays in neurogenesis and neuroblast migration,^{128–131} and reduces nerve growth factor and brain-derived neurotrophic factor (BDNF) expression,^{132,133} synaptogenesis and plasticity,¹³⁴ forebrain white matter microstructural integrity,¹³⁵ and astrocyte-mediated glucose uptake and metabolism.^{136–138} Although developmental omega-3 PUFA insufficiency is not associated with enduring gross neuronal lamination abnormalities or neuronal loss in the adult rat cortex,¹³⁹ enduring reductions in neuronal size have been observed in the rat hippocampus.¹⁴⁰ Moreover, omega-3 PUFA insufficiency is associated with an enduring dysregulation in serotonin,^{141,142} acetylcholine,¹⁴³ glutamate,^{134,144,145} and mesolimbic and mesocortical dopamine neurotransmission.^{146–148} Omega-3 PUFA insufficiency is associated with elevated behavioral indices of depression and aggression,¹⁴⁹ abnormalities in dopamine-mediated behavior,^{150,151} and impaired learning across a variety of different tasks.^{152–158} Evidence from rodent studies therefore suggests that omega-3 PUFA insufficiency during development leads to enduring abnormalities in brain chemistry and function.

In contrast, omega-3 PUFA enrichment increases dendritic spine density,^{159–161} increases frontal cortex dopamine levels,¹⁶² and is protective against age-related neurodegenerative processes¹⁶³ and associated reductions in hippocampus and prefrontal cortex volumes.¹⁶⁴ Omega-3 PUFA enrichment also increases neuronal and white matter resilience to degeneration resulting from inflammation,^{165–167} lipid peroxidation,^{168,169} glutamate excitotoxicity,^{170–172} and cerebral ischemia.^{173,174} Similar to antidepressant medications, dietary fish oil supplementation significantly reduces depression-like behavior in the forced swimming test,^{175–177} and combining fish oil with fluoxetine reduces depression-like behavior to a greater extent than fluoxetine alone.^{177,178} These findings suggest that omega-3 PUFA enrichment increases neuronal and white matter resilience, mitigates age-related neurodegenerative processes, and produces robust antidepressant-like effects in rodents.

In non-human primates maintained on standardized laboratory diets, developmental omega-3 PUFA insufficiency is associated with deficits in visual attention¹⁷⁹ and increased home cage activity and agitation.¹⁸⁰ A neuroimaging study found that developmental omega-3 PUFA insufficiency impaired resting-state functional connectivity among prefrontal cortical networks in adult monkeys compared with omega-3 PUFA enrichment.¹⁸¹ Omega-3 PUFA enrichment was also found to correct age-related deficits in cerebral blood flow in somatosensory cortex in response to tactile stimulation,¹⁸² and resting state cerebral glucose uptake and metabolism.¹⁸³ These findings provide additional evidence that omega-3 PUFA insufficiency is associated with a range of neurodevelopmental abnormalities as well as reduced resilience in the non-human primate brain.

CANDIDATE MEDIATING MECHANISMS

Although evidence from human neuroimaging and animal studies suggest that omega-3 PUFA insufficiency is associated with accelerated gray matter atrophy and reductions in white matter microstructural integrity, it is not currently known whether this is a direct effect or if there are mediating mechanisms. Below we briefly review translational evidence for plausible mechanisms that could mediate the association between omega-3 PUFA insufficiency and neuropathological processes in psychiatric disorders, including elevated inflammation, synaptic regression, and deficits in cerebral perfusion and glucose utilization (Figure 1).

Inflammation

Meta-analytic evidence indicates that patients with MDD,¹⁸⁴ bipolar disorder,¹⁸⁵ and schizophrenia¹⁸⁶ exhibit elevated pro-inflammatory cytokine levels. Neuroimaging evidence suggests that higher pro-inflammatory cytokine or C-reactive protein levels are associated with white matter microstructural integrity deficits,^{187,188} smaller hippocampus and temporal lobe gray matter volumes,^{189–194} elevated prefrontal and anterior cingulate activity,^{195,196} and decreased functional connectivity.^{195,197} It is relevant, therefore, that metabolites of omega-6 PUFAs including AA (i.e., prostaglandins and thromboxanes) and omega-3 PUFAs including EPA and DHA (i.e., D- and E-series resolvins) serve as precursors for immune-inflammatory modulators and in general have opposing effects on pro-inflammatory signaling processes.^{198–202} Accordingly, omega-3 PUFA insufficiency increases constitutive peripheral and central pro-inflammatory processes,^{203–206} and augment lipopolysaccharide-induced pro-inflammatory cytokine production.²⁰⁷ Conversely, omega-3 PUFA enrichment attenuates inflammation-induced elevations in brain pro-inflammatory cytokines, oxidative stress, and apoptosis,^{208–210} and is protective against inflammation-induced white matter,^{165,167} dendritic spine regression,²¹¹ and hippocampal neuronal degeneration.¹⁶⁶ Therefore, neuropathological processes associated with omega-3 PUFA insufficiency may be mediated in part by increases in, or impaired resolution of, pro-inflammatory signaling activity.

Synaptic regression

Postmortem studies have observed reduced dendritic spine density and synaptic markers in the prefrontal cortex of patients with mood or psychotic disorders.^{212–220} In the absence of evidence for gross neuronal cell loss, this reduction in neuropil likely contributes to reductions in prefrontal cortex gray matter volume observed in patients with psychiatric disorders.²²¹ It is relevant, therefore, that omega-3 and omega-6 PUFAs have opposing effects on second messenger signaling pathways that regulate synaptic plasticity and stability.²²² Specifically, DHA inhibits, and arachidonic activates, protein kinase C (PKC) activity.^{223–226} Importantly, PKC hyperactivity has been implicated in dendritic spine loss in the prefrontal cortex in response to chronic stress,²²⁷ and is associated with age-related prefrontal cortex dendritic atrophy and working memory impairment.²²⁸ PKC-mediated phosphorylation of substrate proteins, including myristoylated alanine-rich C kinase substrate (MARCKS) which cross-links actin filaments in a phosphorylation-reversible manner,²²⁹ markedly decreases dendritic spine formation and stability.²³⁰ Consistent with an

inhibitory effect of DHA on PKC-induced dendritic instability, higher brain DHA levels are associated with elevated dendritic spine density^{159–161} and is protective against inflammation-induced dendritic spine regression,²¹¹ whereas perinatal deficits in DHA accrual are associated with synaptic regression or agenesis.¹³⁴ Together, these findings suggest that the association between omega-3 PUFA insufficiency and gray matter volume deficits, and potentially functional connectivity deficits,¹⁸¹ may be mediated in part by elevations in PKC-mediated synaptic regression.

It is also noteworthy that PKC activity is elevated in postmortem frontal cortex of patients with bipolar disorder,²³¹ and that chronic lithium treatment decreases PKC activity²³² and increases in prefrontal cortex gray matter volume in patients with bipolar disorder.¹⁰⁷ Lithium is also protective against stress-induced dendritic remodeling²³³ and NMDA-induced dendritic spine collapse.²³⁴ Moreover, chronic antidepressant treatment mitigates stress-induced spine synapse loss,²³⁵ and ketamine, an NMDA receptor antagonist and rapid-acting antidepressant, increases spine synapse number in the prefrontal cortex of rodents and reverses the effects of chronic stress.²³⁶ These findings suggest that the antidepressant effects associated with omega-3 PUFA supplementation may also be mediated in part by preventing synaptic regression.

Cerebral perfusion and glucose utilization

Evidence from PET and SPECT studies indicate regional reductions in cerebral blood flow and glucose metabolism in the anterior cingulate and subregions of the prefrontal cortex of patients with MDD^{237–242} and schizophrenia,²⁴³ and emerging translational evidence suggests that omega-3 PUFA regulates both cerebral blood flow and cerebral glucose uptake and metabolism. A cross-sectional PET study found that regional cerebral blood flow was positively correlated with DHA incorporation in a small group of healthy adult subjects.²⁴⁴ Several near-infrared spectroscopy studies have observed a positive association between omega-3 PUFA intake/status and cerebral blood flow in human subjects.^{245–249} A SPECT study found that higher erythrocyte EPA+DHA levels were associated with greater cerebral perfusion in the right parahippocampal gyrus, right precuneus, and vermis in a cohort of middle-aged subjects with mixed diagnoses of depression, anxiety disorders, and ADHD.²⁵⁰ Plausible mechanisms by which omega-3 PUFA may promote cerebral blood flow include decreasing blood viscosity by reducing blood platelet aggregation²⁵¹ and blood triglyceride levels.²⁵² This is supported in part by findings that patients with MDD exhibit increased blood viscosity²⁴² and neuroimaging studies finding an inverse association between triglyceride levels and cerebral blood flow.^{253,254} Additionally or alternatively, omega-3 PUFA may promote cerebral blood flow by attenuating platelet thromboxane A2 production which has vasoconstriction effects.^{255–257}

Regarding glucose uptake and metabolism, developmental omega-3 PUFA insufficiency impairs astrocyte-mediated glucose uptake and metabolism in rat brain.^{136–138} A non-human primate study found that omega-3 PUFA enrichment increases resting state cerebral glucose uptake and metabolism.¹⁸³ In a cohort of healthy middle-aged adults, a nutrient pattern associated with higher omega-3 PUFA intake from fish was associated with greater glucose metabolism in the bilateral prefrontal cortex.²⁵⁸ However, a preliminary 3-week fish oil

supplementation study did not observe alterations in glucose metabolism in the anterior cingulate, prefrontal cortex, or hippocampus of healthy young or elderly adults.²⁵⁹ In adult medication-free MDD patients, plasma DHA levels were negatively correlated with resting glucose metabolism in the anterior cingulate and prefrontal cortex, and positively correlated in the temporoparietal cortex.²⁶⁰ Alterations in astrocyte-mediated neurovascular coupling represents one plausible mechanism by which omega-3 PUFA could modulate cortical glucose uptake and metabolism.^{136–138,182}

CLINICAL IMPLICATIONS

The reviewed evidence suggests that omega-3 PUFA deficiency may contribute to progressive pathological processes in brain regions repeatedly implicated in psychopathology. Therefore, correcting omega-3 PUFA deficiency in patients with or at high-risk for developing psychiatric disorders may represent a plausible strategy to increase neuronal and white matter resilience. While it is not currently clear whether correcting omega-3 PUFA deficiency can ‘reverse’ regional brain pathology, existing evidence suggests that it can optimize neurodevelopmental processes as well as mitigate progressive neurodegenerative processes. Therefore, intervention prior to the onset of symptoms in high-risk youth or early in the course of illness (e.g., first-episode) may offer the greatest benefit. Importantly, omega-3 PUFA supplementation is safe and well-tolerated making it ideally suited for early intervention. Moreover, the Food and Drug Administration has approved and regulates several prescription fish oil formulations for the treatment of hypertriglyceridemia, and considers omega-3 PUFA doses up to 3 g/d to be ‘generally regarded as safe’. The American Psychiatric Association has adopted the consensus recommendations of the American Heart Association for an EPA+DHA dose of 1 g/d in patients with MDD.²⁶¹ It is also notable that standardized blood screening protocols now exist for determining omega-3 PUFA biostatus, and pilot studies have demonstrated the feasibility of routine blood omega-3 PUFA screening in psychiatric patients in clinic settings.^{262,263} Therefore, early detection and treatment of omega-3 PUFA deficiency is currently feasible and may represent an urgently needed approach to mitigate progressive pathological brain changes in patients with or at high-risk for psychiatric disorders.

CONCLUSIONS

There is now strong evidence derived from meta-analyses that mood and psychotic disorders are associated with both omega-3 PUFA insufficiency and progressive regional gray and white matter pathology. Although the association between omega-3 PUFA insufficiency and progressive neuropathological processes in mood and psychotic disorders remains speculative, evidence from translational research suggests that omega-3 PUFA insufficiency may represent a plausible and modifiable risk factor for not only enduring neurodevelopmental abnormalities, but also for increased vulnerability to neurodegenerative processes in brain regions consistently implicated in mood and psychotic disorders. Moreover, low omega-3 PUFA intake/status is associated with reductions in white matter pathology, and early evidence suggests that increasing omega-3 PUFA status is protective against gray matter atrophy and white matter pathology in patients with mood and psychotic disorders. Animal studies additionally suggest that omega-3 PUFA insufficiency during

developmental leads to enduring abnormalities in brain chemistry and function, and that omega-3 PUFA enrichment increases neuronal and white matter resilience and is protective against age-related neurodegenerative processes. Plausible mechanisms that could mediate the association between omega-3 PUFA insufficiency and neurodegenerative processes include elevated pro-inflammatory signaling, synaptic regression or agenesis, and reductions in cerebral perfusion and glucose uptake. Together these associations encourage additional neuroimaging research to directly investigate whether increasing omega-3 PUFA status can prevent or reverse central pathological processes in patients with or at high-risk for psychiatric disorders.

Acknowledgments

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

DISCLOSURES

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.. D.M.A. has received research support from AACAP.

References

1. Brown S. Excess mortality of schizophrenia. A meta-analysis. *Br J Psychiatry*. 1997; 171:502–508. [PubMed: 9519087]
2. Brown S, Kim M, Mitchell C, Inskip H. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry*. 2010; 196:116–121. [PubMed: 20118455]
3. Osby U, Correia N, Brandt L, Ekblom A, Sparén P. Mortality and causes of death in schizophrenia in Stockholm County, Sweden. *Schizophr Res*. 2000; 45:21–28. [PubMed: 10978869]
4. Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. *J Affect Disord*. 2002; 68:167–181. [PubMed: 12063145]
5. Osby U, Brandt L, Correia N, Ekblom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001; 58:844–850. [PubMed: 11545667]
6. Perlis RH, Dennehy EB, Miklowitz DJ, Delbello MP, Ostacher M, Calabrese JR, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62:593–602. [PubMed: 15939837]
7. Häfner H, Maurer K, Löffler W, Riecher-Rössler A. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry*. 1993; 162:80–86. [PubMed: 8425144]
8. Drake RJ, Addington J, Viswanathan AC, Lewis SW, Cotter J, Yung AR, Abel KM. How age and gender predict illness course in a first-episode nonaffective psychosis cohort. *J Clin Psychiatry*. 2016; 77:e283–289. [PubMed: 26890690]
9. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62:593–602. [PubMed: 15939837]
10. Giedd JN, Lalonde FM, Celano MJ, White SL, Wallace GL, Lee NR, et al. Anatomical brain magnetic resonance imaging of typically developing children and adolescents. *J Am Acad Child Adolesc Psychiatry*. 2009; 48:465–470. [PubMed: 19395901]
11. Glantz LA, Gilmore JH, Hamer RM, Lieberman JA, Jarskog LF. Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. *Neuroscience*. 2007; 149:582–591. [PubMed: 17916412]
12. Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res*. 1979; 163:195–205. [PubMed: 427544]

13. Nagy Z, Westerberg H, Klingberg T. Maturation of white matter is associated with the development of cognitive functions during childhood. *J Cogn Neurosci*. 2004; 16:1227–1233. [PubMed: 15453975]
14. Hasan KM, Iftikhar A, Kamali A, Kramer LA, Ashtari M, Cirino PT, et al. Development and aging of the healthy human brain uncinate fasciculus across the lifespan using diffusion tensor tractography. *Brain Res*. 2009; 1276:67–76. [PubMed: 19393229]
15. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat Neurosci*. 1999; 2:859–861. [PubMed: 10491602]
16. Koppel J, Sunday S, Goldberg TE, Davies P, Christen E, Greenwald BS. Alzheimer's Disease Neuroimaging Initiative. Psychosis in Alzheimer's disease is associated with frontal metabolic impairment and accelerated decline in working memory: findings from the Alzheimer's Disease Neuroimaging Initiative. *Am J Geriatr Psychiatry*. 2014; 22:698–707. [PubMed: 23672944]
17. Murray PS, Kumar S, Demichele-Sweet MA, Sweet RA. Psychosis in Alzheimer's disease. *Biol Psychiatry*. 2014; 75:542–552. [PubMed: 24103379]
18. Bora E, Fornito A, Pantelis C, Yücel M. Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *J Affect Disord*. 2012; 138:9–18. [PubMed: 21511342]
19. Du MY, Wu QZ, Yue Q, Li J, Liao Y, Kuang WH, et al. Voxelwise meta-analysis of gray matter reduction in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012; 36:11–16. [PubMed: 22001316]
20. Kempton MJ, Salvador Z, Munafò MR, Geddes JR, Simmons A, Frangou S, et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. *Arch Gen Psychiatry*. 2011; 68:675–690. [PubMed: 21727252]
21. Bora E, Fornito A, Yücel M, Pantelis C. Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Biol Psychiatry*. 2010; 67:1097–1105. [PubMed: 20303066]
22. Pfeifer JC, Welge J, Strakowski SM, Adler CM, DelBello MP. Meta-analysis of amygdala volumes in children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry*. 2008; 47:1289–1298. [PubMed: 18827720]
23. Blumberg HP, Krystal JH, Bansal R, Martin A, Dziura J, Durkin K, et al. Age, rapid-cycling, and pharmacotherapy effects on ventral prefrontal cortex in bipolar disorder: a cross-sectional study. *Biol Psychiatry*. 2006; 59:611–618. [PubMed: 16414030]
24. Kalmar JH, Wang F, Spencer L, Edmiston E, Lacadie CM, Martin A, et al. Preliminary evidence for progressive prefrontal abnormalities in adolescents and young adults with bipolar disorder. *J Int Neuropsychol Soc*. 2009; 15:476–481. [PubMed: 19402934]
25. Chan RC, Di X, McAlonan GM, Gong QY. Brain anatomical abnormalities in high-risk individuals, first-episode, and chronic schizophrenia: an activation likelihood estimation meta-analysis of illness progression. *Schizophr Bull*. 2011; 37:177–188. [PubMed: 19633214]
26. Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biol Psychiatry*. 2011; 70:88–96. [PubMed: 21457946]
27. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry*. 2012; 2:e190. [PubMed: 23168990]
28. Honea R, Crow TJ, Passingham D, Mackay CE. Regional deficits in brain volume in schizophrenia: a meta-analysis of voxel-based morphometry studies. *Am J Psychiatry*. 2005; 162:2233–2235. [PubMed: 16330585]
29. Adriano F, Caltagirone C, Spalletta G. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. *Neuroscientist*. 2012; 18:180–200. [PubMed: 21531988]
30. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA. Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *Br J Psychiatry*. 2006; 188:510–518. [PubMed: 16738340]

31. De Peri L, Crescini A, Deste G, Fusar-Poli P, Sacchetti E, Vita A. Brain structural abnormalities at the onset of schizophrenia and bipolar disorder: a meta-analysis of controlled magnetic resonance imaging studies. *Curr Pharm Des.* 2012; 18:486–494. [PubMed: 22239579]
32. Beyer JL, Young R, Kuchibhatla M, Krishnan KR. Hyperintense MRI lesions in bipolar disorder: A meta-analysis and review. *Int Rev Psychiatry.* 2009; 21:394–409. [PubMed: 20374153]
33. Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM. Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Arch Gen Psychiatry.* 2008; 65:1017–1032. [PubMed: 18762588]
34. Yao L, Lui S, Liao Y, Du MY, Hu N, Thomas JA, et al. White matter deficits in first episode schizophrenia: an activation likelihood estimation meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013; 45:100–106. [PubMed: 23648972]
35. Nortje G, Stein DJ, Radua J, Mataix-Cols D, Horn N. Systematic review and voxel-based meta-analysis of diffusion tensor imaging studies in bipolar disorder. *J Affect Disord.* 2013; 150:192–200. [PubMed: 23810479]
36. Jiang J, Zhao YJ, Hu XY, Du MY, Chen ZQ, Wu M, et al. Microstructural brain abnormalities in medication-free patients with major depressive disorder: a systematic review and meta-analysis of diffusion tensor imaging. *J Psychiatry Neurosci.* 2017; 42:150–163. [PubMed: 27780031]
37. Reardon, HT, Brenna, JT. Microsomal biosynthesis of omega-3 fatty acids. In: McNamara, RK, editor. *The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention.* Nova Science Publishers, Inc.; U.S.A.: 2013. 3–17.
38. Ferdinandusse S, Denis S, Mooijer PA, Zhang Z, Reddy JK, Spector AA, et al. Identification of the peroxisomal beta-oxidation enzymes involved in the biosynthesis of docosahexaenoic acid. *J Lipid Res.* 2001; 42:1987–1995. [PubMed: 11734571]
39. Lattka E, Illig T, Koletzko B, Heinrich J. Genetic variants of the FADS1 FADS2 gene cluster as related to essential fatty acid metabolism. *Curr Opin Lipidol.* 2010; 21:64–69. [PubMed: 19809313]
40. Steinberg S, Chen L, Wei L, Moser A, Moser H, Cutting G, et al. The PEX Gene Screen: molecular diagnosis of peroxisome biogenesis disorders in the Zellweger syndrome spectrum. *Mol Genet Metab.* 2004; 83:252–263. [PubMed: 15542397]
41. Hoile SP, Clarke-Harris R, Huang RC, Calder PC, Mori TA, Beilin LJ, et al. Supplementation with N-3 long-chain polyunsaturated fatty acids or olive oil in men and women with renal disease induces differential changes in the DNA methylation of FADS2 and ELOVL5 in peripheral blood mononuclear cells. *PLoS One.* 2014; 9:e109896. [PubMed: 25329159]
42. Harris WS, Pottala JV, Lacey SM, Vasan RS, Larson MG, Robins SJ. Clinical correlates and heritability of erythrocyte eicosapentaenoic and docosahexaenoic acid content in the Framingham Heart Study. *Atherosclerosis.* 2012; 225:425–431. [PubMed: 22727409]
43. Brenna JT, Salem N Jr, Sinclair AJ, Cunnane SC. International Society for the Study of Fatty Acids and Lipids, ISSFAL. alpha-Linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukot Essent Fatty Acids.* 2009; 80:85–91. [PubMed: 19269799]
44. Adam O, Wolfram G, Zöllner N. Influence of dietary linoleic acid intake with different fat intakes on arachidonic acid concentrations in plasma and platelet lipids and eicosanoid biosynthesis in female volunteers. *Ann Nutr Metab.* 2003; 47:31–36. [PubMed: 12624485]
45. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. *Am J Clin Nutr.* 2006; 83:1467S–1476S. [PubMed: 16841856]
46. Rett BS, Whelan J. Increasing dietary linoleic acid does not increase tissue arachidonic acid content in adults consuming Western-type diets: a systematic review. *Nutr Metab (Lond).* 2011; 8:36. [PubMed: 21663641]
47. Anderson GJ, Neuringer M, Lin DS, Connor WE. Can prenatal N-3 fatty acid deficiency be completely reversed after birth? Effects on retinal and brain biochemistry and visual function in rhesus monkeys. *Pediatr Res.* 2005; 58:865–872. [PubMed: 16257925]
48. Connor WE, Neuringer M, Lin DS. Dietary effects on brain fatty acid composition: the reversibility of n-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocytes, and plasma of rhesus monkeys. *J Lipid Res.* 1990; 31:237–247. [PubMed: 2139096]

49. Barceló-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK. Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid. *Am J Clin Nutr.* 2008; 88:801–809. [PubMed: 18779299]
50. Francois CA, Connor SL, Bolewicz LC, Connor WE. Supplementing lactating women with flaxseed oil does not increase docosahexaenoic acid in their milk. *Am J Clin Nutr.* 2003; 77:226–233. [PubMed: 12499346]
51. Su HM, Bernardo L, Mirmiran M, Ma XH, Nathanielsz PW, Brenna JT. Dietary 18:3n-3 and 22:6n-3 as sources of 22:6n-3 accretion in neonatal baboon brain and associated organs. *Lipids.* 1999; 34(Suppl):S347–350. [PubMed: 10419199]
52. Hibbeln JR. Fish consumption and major depression. *Lancet.* 1998; 351:1213.
53. Peet M. International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis. *Br J Psychiatry.* 2004; 184:404–408. [PubMed: 15123503]
54. Noaghiul S, Hibbeln JR. Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am J Psychiatry.* 2003; 160:2222–2227. [PubMed: 14638594]
55. Grosso G, Micek A, Marventano S, Castellano S, Mistretta A, Pajak A, Galvano F. Dietary n-3 PUFA, fish consumption and depression: A systematic review and meta-analysis of observational studies. *J Affect Disord.* 2016; 205:269–281. [PubMed: 27544316]
56. Christensen O, Christensen E. Fat consumption and schizophrenia. *Acta Psychiatr Scand.* 1988; 78:587–591. [PubMed: 3232536]
57. Itomura M, Fujioka S, Hamazaki K, Kobayashi K, Nagasawa T, Sawazaki S, Kirihaara Y, Hamazaki T. Factors influencing EPA+DHA levels in red blood cells in Japan. *In Vivo.* 2008; 22:131–135. [PubMed: 18396795]
58. Sands SA, Reid KJ, Windsor SL, Harris WS. The impact of age, body mass index, and fish intake on the EPA and DHA content of human erythrocytes. *Lipids.* 2005; 40:343–347. [PubMed: 16028715]
59. Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. *J Am Heart Assoc.* 2013; 2:e000513. [PubMed: 24252845]
60. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry.* 2010; 68:140–147. [PubMed: 20452573]
61. McNamara RK, Welge JA. Meta-analysis of erythrocyte polyunsaturated fatty acid biostatus in bipolar disorder. *Bipolar Disord.* 2016; 18:300–306. [PubMed: 27087497]
62. van der Kemp WJ, Klomp DW, Kahn RS, Luijten PR, Hulshoff Pol HE. A meta-analysis of the polyunsaturated fatty acid composition of erythrocyte membranes in schizophrenia. *Schizophr Res.* 2012; 141:153–161. [PubMed: 22981812]
63. McNamara RK, Jandacek RJ, Tso P, Blom TJ, Welge JA, Strawn JR, et al. First-episode bipolar disorder is associated with erythrocyte membrane docosahexaenoic acid deficits: Dissociation from clinical response to lithium or quetiapine. *Psychiatry Res.* 2015; 230:447–453. [PubMed: 26477955]
64. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H. Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiatry.* 2003; 60:1209–1215. [PubMed: 14662553]
65. McNamara RK, Jandacek RJ, Tso P, Blom TJ, Welge JA, Strawn JR, et al. Adolescents with or at ultra-high risk for bipolar disorder exhibit erythrocyte docosahexaenoic and eicosapentaenoic acid deficits: A candidate prodromal risk biomarker. *Early Interv Psychiatry.* 2016; 10:203–211. [PubMed: 26486098]
66. Axelson D, Goldstein B, Goldstein T, Monk K, Yu H, Hickey MB, et al. Diagnostic precursors to bipolar disorder in offspring of parents with bipolar disorder: A longitudinal study. *Am J Psychiatry.* 2015; 172:638–646. [PubMed: 25734353]
67. Berger ME, Smesny S, Kim SW, Davey CG, Rice S, Sarnyai Z, et al. Omega-6 to omega-3 polyunsaturated fatty acid ratio and subsequent mood disorders in young people with at-risk mental states: a 7-year longitudinal study. *Transl Psychiatry.* 2017; 7:e1220. [PubMed: 28850110]

68. Lotrich FE, Sears B, McNamara RK. Elevated ratio of arachidonic acid to long-chain omega-3 fatty acids predicts depression development following interferon-alpha treatment: Relationship with interleukin-6. *Brain Behav Immun*. 2013; 31:48–53. [PubMed: 22926083]
69. Su KP, Huang SY, Peng CY, Lai HC, Huang CL, Chen YC, et al. Phospholipase A2 and cyclooxygenase 2 genes influence the risk of interferon-alpha-induced depression by regulating polyunsaturated fatty acids levels. *Biol Psychiatry*. 2010; 67:550–557. [PubMed: 20034614]
70. Lotrich FE, Sears B, McNamara RK. Anger induced by interferon-alpha is moderated by ratio of arachidonic acid to omega-3 fatty acids. *J Psychosom Res*. 2013; 75:475–483. [PubMed: 24182638]
71. Clayton EH, Hanstock TL, Hirneth SJ, Kable CJ, Garg ML, Hazell PL. Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation. *Eur J Clin Nutr*. 2009; 63:1037–1040. [PubMed: 19156158]
72. Wozniak J, Biederman J, Mick E, Waxmonsky J, Hantsoo L, Best C, et al. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: a prospective open-label trial. *Eur Neuropsychopharmacol*. 2007; 17:440–447. [PubMed: 17258897]
73. McNamara RK, Strimpfel J, Jandacek R, Rider T, Tso P, Welge JA, et al. Detection and treatment of long-chain omega-3 fatty acid deficiency in adolescents with SSRI-resistant major depressive disorder. *PharmaNutrition*. 2014; 2:38–46. [PubMed: 24772386]
74. Grosso G, Pajak A, Marventano S, Castellano S, Galvano F, Bucolo C, et al. Role of omega-3 Fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One*. 2014; 9:e96905. [PubMed: 24805797]
75. Mocking RJ, Harmsen I, Assies J, Koeter MW, Ruhé HG, Schene AH. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Transl Psychiatry*. 2016; 6:e756. [PubMed: 26978738]
76. Sublette ME, Ellis SP, Geant AL, Mann JJ. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J Clin Psychiatry*. 2011; 72:1577–1584. [PubMed: 21939614]
77. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol Psychiatry*. 2012; 17:1272–1282. [PubMed: 21931319]
78. Sarris J, Mischoulon D, Schweitzer I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J Clin Psychiatry*. 2012; 73:81–86. [PubMed: 21903025]
79. Su KP, Lai HC, Yang HT, Su WP, Peng CY, Chang JP, et al. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: Results from a randomized, controlled trial. *Biol Psychiatry*. 2014; 76:559–566. [PubMed: 24602409]
80. Rapaport MH, Nierenberg AA, Schettler PJ, Kinkead B, Cardoos A, Walker R, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol Psychiatry*. 2016; 21:71–79. [PubMed: 25802980]
81. Chen AT, Chibnall JT, Nasrallah HA. A meta-analysis of placebo-controlled trials of omega-3 fatty acid augmentation in schizophrenia: Possible stage-specific effects. *Ann Clin Psychiatry*. 2015; 27:289–296. [PubMed: 26554370]
82. Chen CT, Liu Z, Ouellet M, Calon F, Bazinet RP. Rapid beta-oxidation of eicosapentaenoic acid in mouse brain: an in situ study. *Prostaglandins Leukot Essent Fatty Acids*. 2009; 80:157–163. [PubMed: 19237271]
83. Carver JD, Benford VJ, Han B, Cantor AB. The relationship between age and the fatty acid composition of cerebral cortex and erythrocytes in human subjects. *Brain Res Bull*. 2001; 56:79–85. [PubMed: 11704343]
84. Conklin SM, Runyan CA, Leonard S, Reddy RD, Muldoon MF, Yao JK. Age-related changes of n-3 and n-6 polyunsaturated fatty acids in the anterior cingulate cortex of individuals with major depressive disorder. *Prostaglandins Leukot Essent Fatty Acids*. 2010; 82:111–119. [PubMed: 20060277]
85. McNamara RK, Hahn C-G, Jandacek R, Rider T, Tso P, Stanford K, et al. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biol Psychiatry*. 2007; 62:17–24. [PubMed: 17188654]
86. McNamara RK, Jandacek R, Rider T, Tso P, Stanford K, Hahn C-G, et al. Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and

- saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. *Psychiatry Res.* 2008; 160:285–299. [PubMed: 18715653]
87. McNamara RK, Jandacek RJ, Rider T, Tso P, Richtand NM, Stanford KE. Abnormalities in the fatty acid composition of the postmortem orbitofrontal cortex of schizophrenic patients: Gender differences and partial normalization with antipsychotic medications. *Schizophr Res.* 2007; 91:37–50. [PubMed: 17236749]
 88. McNamara RK, Jandacek R, Tso P, Dwivedi Y, Ren X, Pandey GN. Lower docosahexaenoic acid concentrations in the postmortem prefrontal cortex of adult depressed suicide victims compared with controls without cardiovascular disease. *J Psychiatr Res.* 2013; 47:1187–1191. [PubMed: 23759469]
 89. Tatebayashi Y, Nihonmatsu-Kikuchi N, Hayashi Y, Yu X, Soma M, Ikeda K. Abnormal fatty acid composition in the frontopolar cortex of patients with affective disorders. *Transl Psychiatry.* 2012; 2:e204. [PubMed: 23233023]
 90. Igarashi M, Ma K, Gao F, Kim HW, Greenstein D, Rapoport SI, et al. Brain lipid concentrations in bipolar disorder. *J Psychiatr Res.* 2010; 44:177–182. [PubMed: 19767014]
 91. Lalovic A, Levy E, Canetti L, Sequeira A, Montoudis A, Turecki G. Fatty acid composition in postmortem brains of people who completed suicide. *J Psychiatry Neurosci.* 2007; 32:363–370. [PubMed: 17823652]
 92. Hamazaki K, Choi KH, Kim HY. Phospholipid profile in the postmortem hippocampus of patients with schizophrenia and bipolar disorder: no changes in docosahexaenoic acid species. *J Psychiatry Res.* 2010; 44:688–693. [PubMed: 20056243]
 93. Hamazaki K, Hamazaki T, Inadera H. Fatty acid composition in the postmortem amygdala of patients with schizophrenia, bipolar disorder, and major depressive disorder. *J Psychiatr Res.* 2012; 46:1024–1028. [PubMed: 22572570]
 94. Hamazaki K, Hamazaki T, Inadera H. Abnormalities in the fatty acid composition of the postmortem entorhinal cortex of patients with schizophrenia, bipolar disorder, and major depressive disorder. *Psychiatry Res.* 2013; 210:346–350. [PubMed: 23731984]
 95. Hamazaki K, Maekawa M, Toyota T, Dean B, Hamazaki T, Yoshikawa T. Fatty acid composition of the postmortem prefrontal cortex of patients with schizophrenia, bipolar disorder, and major depressive disorder. *Psychiatry Res.* 2015; 227:353–359. [PubMed: 25858798]
 96. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res.* 2000; 42:7–17. [PubMed: 10706981]
 97. Rapoport SI. Lithium and the other mood stabilizers effective in bipolar disorder target the rat brain arachidonic acid cascade. *ACS Chem Neurosci.* 2014; 5:459–467. [PubMed: 24786695]
 98. McNamara RK, Able JA, Jandacek R, Rider T, Tso P. Chronic risperidone treatment preferentially increases rat erythrocyte and prefrontal cortex omega-3 fatty acid composition: evidence for augmented biosynthesis. *Schizophr Res.* 2009; 107:150–157. [PubMed: 18993032]
 99. Salem N Jr, Vandal M, Calon F. The benefit of docosahexaenoic acid for the adult brain in aging and dementia. *Prostaglandins Leukot Essent Fatty Acids.* 2015; 92:15–22. [PubMed: 25457546]
 100. Wu S, Ding Y, Wu F, Li R, Hou J, Mao P. Omega-3 fatty acids intake and risks of dementia and Alzheimer's disease: a meta-analysis. *Neurosci Biobehav Rev.* 2015; 48:1–9. [PubMed: 25446949]
 101. Zhang Y, Chen J, Qiu J, Li Y, Wang J, Jiao J. Intakes of fish and polyunsaturated fatty acids and mild-to-severe cognitive impairment risks: a dose-response meta-analysis of 21 cohort studies. *Am J Clin Nutr.* 2016; 103:330–340. [PubMed: 26718417]
 102. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev.* 2013; 37:1680–1681. [PubMed: 23769814]
 103. Torres US, Portela-Oliveira E, Borgwardt S, Busatto GF. Structural brain changes associated with antipsychotic treatment in schizophrenia as revealed by voxel-based morphometric MRI: an activation likelihood estimation meta-analysis. *BMC Psychiatry.* 2013; 13:342. [PubMed: 24359128]

104. Lieberman JA, Tollefson GD, Charles C, Zipursky R, Sharma T, Kahn RS, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry*. 2005; 62:361–370. [PubMed: 15809403]
105. Kafantaris V, Spritzer L, Doshi V, Saito E, Szeszko PR. Changes in white matter microstructure predict lithium response in adolescents with bipolar disorder. *Bipolar Disord*. 2017
106. Szeszko PR, Robinson DG, Ikuta T, Peters BD, Gallego JA, Kane J, et al. White matter changes associated with antipsychotic treatment in first-episode psychosis. *Neuropsychopharmacology*. 2014; 39:1324–1331. [PubMed: 24549105]
107. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK. Lithium-induced increase in human brain grey matter. *Lancet*. 2000; 356:1241–1242. [PubMed: 11072948]
108. McNamara RK, Asch RH, Lindquist DM, Krikorian R. Role of polyunsaturated fatty acids in human brain structure and function across the lifespan: An update on neuroimaging findings. *Prostaglandins Leukot Essent Fatty Acids*. 2017
109. Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette S, Pikula A, Decarli C, Wolf PA, Vasan RS, Robins SJ, Seshadri S. Red blood cell ω -3 fatty acid levels and markers of accelerated brain aging. *Neurology*. 2012; 78:658–664. [PubMed: 22371413]
110. Titova OE, Sjögren P, Brooks SJ, Kullberg J, Ax E, Kilander L, et al. Dietary intake of eicosapentaenoic and docosahexaenoic acids is linked to gray matter volume and cognitive function in elderly. *Age (Dordr)*. 2013; 35:1495–1505. [PubMed: 22791395]
111. Yassine HN, Feng Q, Azizkhanian I, Rawat V, Castor K, Fonteh AN, et al. Association of serum docosahexaenoic acid with cerebral amyloidosis. *JAMA Neurol*. 2016; 73:1208–1216. [PubMed: 27532692]
112. Conklin SM, Gianaros PJ, Brown SM, Yao JK, Hariri AR, Manuck SB, et al. Long-chain omega-3 fatty acid intake is associated positively with corticolimbic gray matter volume in healthy adults. *Neurosci Lett*. 2007; 421:209–212. [PubMed: 17574755]
113. Pottala JV, Yaffe K, Robinson JG, Espeland MA, Wallace R, Harris WS. Higher RBC EPA + DHA corresponds with larger total brain and hippocampal volumes: WHIMS-MRI study. *Neurology*. 2014; 82:435–442. [PubMed: 24453077]
114. Raji CA, Erickson KI, Lopez OL, Kuller LH, Gach HM, Thompson PM, et al. Regular fish consumption and age-related brain gray matter loss. *Am J Prev Med*. 2014; 47:444–451. [PubMed: 25084680]
115. Samieri C, Maillard P, Crivello F, Proust-Lima C, Peuchant E, Helmer C, et al. Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. *Neurology*. 2012; 79:642–650. [PubMed: 22855869]
116. Walhovd KB, Storsve AB, Westlye LT, Drevon CA, Fjell AM. Blood markers of fatty acids and vitamin D, cardiovascular measures, body mass index, and physical activity relate to longitudinal cortical thinning in normal aging. *Neurobiol Aging*. 2014; 35:1055–1064. [PubMed: 24332985]
117. Zamroziewicz MK, Paul EJ, Rubin RD, Barbey AK. Anterior cingulate cortex mediates the relationship between O3PUFAs and executive functions in APOE e4 carriers. *Front Aging Neurosci*. 2015; 7:87. [PubMed: 26052283]
118. Quinn JF, Raman R, Thomas RG, Yurko-Mauro K, Nelson EB, Van Dyck C, et al. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA*. 2010; 304:1903–1911. [PubMed: 21045096]
119. Gu Y, Vorburger RS, Gazes Y, Habeck CG, Stern Y, Luchsinger JA, et al. White matter integrity as a mediator in the relationship between dietary nutrients and cognition in the elderly. *Ann Neurol*. 2016; 79:1014–1025. [PubMed: 27129740]
120. Bowman GL, Silbert LC, Howieson D, Dodge HH, Traber MG, Frei B, et al. Nutrient biomarker patterns, cognitive function, and MRI measures of brain aging. *Neurology*. 2012; 78:241–249. [PubMed: 22205763]
121. Bowman GL, Dodge HH, Mattek N, Barbey AK, Silbert LC, Shinto L, et al. Plasma omega-3 PUFA and white matter mediated executive decline in older adults. *Front Aging Neurosci*. 2013; 5:92. [PubMed: 24379780]
122. Nagai K, Koshiba H, Shibata S, Matsui T, Kozaki K. Correlation between the serum eicosapentaenoic acid-to-arachidonic acid ratio and the severity of cerebral white matter

hyperintensities in older adults with memory disorder. *Geriatr Gerontol Int.* 2015; 15(Suppl 1): 48–52. [PubMed: 26671157]

123. Suwa M, Yamaguchi S, Komori T, Kajimoto S, Kino M. The association between cerebral white matter lesions and plasma omega-3 to omega-6 polyunsaturated fatty acids ratio to cognitive impairment development. *Biomed Res Int.* 2015; 2015:153437. [PubMed: 26583090]
124. Virtanen JK, Siscovick DS, Longstreth WT Jr, Kuller LH, Mozaffarian D. Fish consumption and risk of subclinical brain abnormalities on MRI in older adults. *Neurology.* 2008; 71:439–446. [PubMed: 18678827]
125. Witte AV, Kerti L, Hermannstädter HM, Fiebach JB, Schreiber SJ, Schuchardt JP, et al. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb Cortex.* 2014; 24:3059–3068. [PubMed: 23796946]
126. Pawełczyk T, Piłkowska-Janko E, Bogorodzki P, Góbski P, Grancow-Grabka M, Trafalska E, et al. Omega-3 fatty acid supplementation may prevent loss of gray matter thickness in the left parieto-occipital cortex in first episode schizophrenia: A secondary outcome analysis of the OFFER randomized controlled study. *Schizophr Res.* 2017
127. Chhetry BT, Hezghia A, Miller JM, Lee S, Rubin-Falcone H, Cooper TB, et al. Omega-3 polyunsaturated fatty acid supplementation and white matter changes in major depression. *J Psychiatr Res.* 2016; 75:65–74. [PubMed: 26802812]
128. Beltz BS, Tlusty MF, Benton JL, Sandeman DC. Omega-3 fatty acids upregulate adult neurogenesis. *Neurosci Lett.* 2007; 415:154–158. [PubMed: 17240063]
129. Kawakita E, Hashimoto M, Shido O. Docosahexaenoic acid promotes neurogenesis in vitro and in vivo. *Neuroscience.* 2006; 139:991–997. [PubMed: 16527422]
130. Coti Bertrand P, O'Kusky JR, Innis SM. Maternal dietary (n-3) fatty acid deficiency alters neurogenesis in the embryonic rat brain. *J Nutr.* 2006; 136:1570–1575. [PubMed: 16702323]
131. Yavin E, Himovichi E, Eilam R. Delayed cell migration in the developing rat brain following maternal omega 3 alpha linolenic acid dietary deficiency. *Neuroscience.* 2009; 162:1011–1122. [PubMed: 19447164]
132. Rao JS, Ertley RN, Lee HJ, DeMar JC Jr, Arnold JT, Rapoport SI, et al. n-3 polyunsaturated fatty acid deprivation in rats decreases frontal cortex BDNF via a p38 MAPK-dependent mechanism. *Mol Psychiatry.* 2007; 12:36–46. [PubMed: 16983391]
133. Ikemoto A, Nitta A, Furukawa S, Ohishi M, Nakamura A, Fujii Y, et al. Dietary n-3 fatty acid deficiency decreases nerve growth factor content in rat hippocampus. *Neurosci Lett.* 2000; 285:99–102. [PubMed: 10793236]
134. Cao D, Kevala K, Kim J, Moon HS, Jun SB, Lovinger D, et al. Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *J Neurochem.* 2009; 111:510–521. [PubMed: 19682204]
135. McNamara RK, Schurdak JD, Asch RH, Peters BD, Lindquist DM. Deficits in docosahexaenoic acid accrual during adolescence reduce rat forebrain white matter microstructural integrity: An in vivo diffusion tensor imaging study. *Dev Neurosci.* 2018; 40:84–92. [PubMed: 29216635]
136. Harbeby E, Jouin M, Alessandri JM, Lallemand MS, Linard A, Lavialle M, et al. n-3 PUFA status affects expression of genes involved in neuroenergetics differently in the fronto-parietal cortex compared to the CA1 area of the hippocampus: effect of rest and neuronal activation in the rat. *Prostaglandins Leukot. Essent. Fatty Acids.* 2012; 86:211–220. [PubMed: 22579067]
137. Pifferi F, Jouin M, Alessandri JM, Haedke U, Roux F, Perrière N, et al. n-3 Fatty acids modulate brain glucose transport in endothelial cells of the blood-brain barrier. *Prostaglandins Leukot Essent Fatty Acids.* 2007; 77:279–286. [PubMed: 18042368]
138. Ximenes da Silva A, Lavialle F, Gendrot G, Guesnet P, Alessandri JM, Lavialle M. Glucose transport and utilization are altered in the brain of rats deficient in n-3 polyunsaturated fatty acids. *J Neurochem.* 2002; 81:1328–1337. [PubMed: 12068080]
139. Salem N Jr, Moriguchi T, Greiner RS, McBride K, Ahmad A, Catalan JN, et al. Alterations in brain function after loss of docosahexaenoate due to dietary restriction of n-3 fatty acids. *J Mol Neurosci.* 2001; 16:299–307. [PubMed: 11478385]

140. Ahmad A, Murthy M, Greiner RS, Moriguchi T, Salem N Jr. A decrease in cell size accompanies a loss of docosahexaenoate in the rat hippocampus. *Nutr Neurosci.* 2002; 5:103–13. [PubMed: 12004794]
141. Kudas E, Galineau L, Bodard S, Vancassel S, Guilloteau D, Besnard JC, et al. Serotonergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *J Neurochem.* 2004; 89:695–702. [PubMed: 15086526]
142. McNamara RK, Able JA, Liu Y, Jandacek RJ, Rider T, Tso P, et al. Omega-3 fatty acid deficiency during perinatal development increases serotonin turnover in the prefrontal cortex and decreases midbrain tryptophan hydroxylase-2 expression in adult female rats: Dissociation from estrogenic effects. *J Psychiatr Res.* 2009; 43:656–663. [PubMed: 18986658]
143. Aïd S, Vancassel S, Poumès-Ballihaut C, Chalon S, Guesnet P, Lavialle M. Effect of a diet-induced n-3 PUFA depletion on cholinergic parameters in the rat hippocampus. *J Lipid Res.* 2003; 44:1545–1551. [PubMed: 12754277]
144. Moreira JD, Knorr L, Ganzella M, Thomazi AP, de Souza CG, de Souza DG, et al. Omega-3 fatty acids deprivation affects ontogeny of glutamatergic synapses in rats: relevance for behavior alterations. *Neurochem Int.* 2010; 56:753–759. [PubMed: 20172010]
145. McNamara RK, Asch RH, Schurdak JD, Lindquist DM. Glutamate homeostasis in the adult rat prefrontal cortex is altered by cortical docosahexaenoic acid accrual during adolescence: An in vivo 1H MRS study. *Psychiatry Res.* 2017; 270:39–45.
146. Kudas E, Vancassel S, Lejeune B, Guilloteau D, Chalon S. Reversibility of n-3 fatty acid deficiency-induced changes in dopaminergic neurotransmission in rats: critical role of developmental stage. *J Lipid Res.* 2002; 43:1209–1219. [PubMed: 12177165]
147. Zimmer L, Delion-Vancassel S, Durand G, Guilloteau D, Bodard S, Besnard JC, et al. Modification of dopamine neurotransmission in the nucleus accumbens of rats deficient in n-3 polyunsaturated fatty acids. *J Lipid Res.* 2000; 41:32–40. [PubMed: 10627499]
148. Zimmer L, Vancassel S, Cantagrel S, Breton P, Delamanche S, Guilloteau D, et al. The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *Am J Clin Nutr.* 2002; 75:662–667. [PubMed: 11916751]
149. DeMar JC Jr, Ma K, Bell JM, Igarashi M, Greenstein D, Rapoport SI. One generation of n-3 polyunsaturated fatty acid deprivation increases depression and aggression test scores in rats. *J Lipid Res.* 2006; 47:172–180. [PubMed: 16210728]
150. Levant B, Radel JD, Carlson SE. Decreased brain docosahexaenoic acid during development alters dopamine-related behaviors in adult rats that are differentially affected by dietary remediation. *Behav Brain Res.* 2004; 152:49–57. [PubMed: 15135968]
151. McNamara RK, Sullivan J, Richtand NM, Jandacek R, Rider T, Tso P, et al. Omega-3 fatty acid deficiency augments amphetamine-induced behavioral sensitization in adult DBA/2J mice: relationship with ventral striatum dopamine concentrations. *Synapse.* 2008; 62:725–735. [PubMed: 18651642]
152. Bach SA, de Siqueira LV, Müller AP, Oses JP, Quatrim A, Emanuelli T, et al. Dietary omega-3 deficiency reduces BDNF content and activation NMDA receptor and Fyn in dorsal hippocampus: Implications on persistence of long-term memory in rats. *Nutr Neurosci.* 2014; 17:186–192. [PubMed: 24621058]
153. Fedorova I, Hussein N, Baumann MH, Di Martino C, Salem N Jr. An n-3 fatty acid deficiency impairs rat spatial learning in the Barnes maze. *Behav Neurosci.* 2009; 123:196–205. [PubMed: 19170444]
154. Greiner RS, Moriguchi T, Hutton A, Slotnick BM, Salem N Jr. Rats with low levels of brain docosahexaenoic acid show impaired performance in olfactory-based and spatial learning tasks. *Lipids.* 1999; 34(Suppl):S239–43. [PubMed: 10419165]
155. Greiner RS, Moriguchi T, Slotnick BM, Hutton A, Salem N. Olfactory discrimination deficits in n-3 fatty acid-deficient rats. *Physiol Behav.* 2001; 72:379–385. [PubMed: 11274681]
156. Moriguchi T, Greiner RS, Salem N Jr. Behavioral deficits associated with dietary induction of decreased brain docosahexaenoic acid concentration. *J Neurochem.* 2000; 75:2563–2573. [PubMed: 11080210]

157. Moriguchi T, Salem N Jr. Recovery of brain docosahexaenoate leads to recovery of spatial task performance. *J Neurochem.* 2003; 87:297–309. [PubMed: 14511107]
158. Hichami A, Datiche F, Ullah S, Liénard F, Chardigny JM, Cattarelli M, et al. Olfactory discrimination ability and brain expression of c-fos, *Gir* and *Glut1* mRNA are altered in n-3 fatty acid-depleted rats. *Behav Brain Res.* 2007; 184:1–10. [PubMed: 17686536]
159. Calon F, Lim GP, Yang F, Morihara T, Teter B, Ubeda O, et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron.* 2004; 43:633–645. [PubMed: 15339646]
160. He C, Qu X, Cui L, Wang J, Kang JX. Improved spatial learning performance of fat-1 mice is associated with enhanced neurogenesis and neuritogenesis by docosahexaenoic acid. *Proc Natl Acad Sci U S A.* 2009; 106:11370–11375. [PubMed: 19549874]
161. Sakamoto T, Cansev M, Wurtman RJ. Oral supplementation with docosahexaenoic acid and uridine-5'-monophosphate increases dendritic spine density in adult gerbil hippocampus. *Brain Res.* 2007; 1182:50–59. [PubMed: 17950710]
162. Chalon S, Delion-Vancassel S, Belzung C, Guilloteau D, Leguisquet AM, Besnard JC, et al. Dietary fish oil affects monoaminergic neurotransmission and behavior in rats. *J Nutr.* 1998; 128:2512–2519. [PubMed: 9868201]
163. Calon F, Cole G. Neuroprotective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: evidence from animal studies. *Prostaglandins Leukot Essent Fatty Acids.* 2007; 77:287–293. [PubMed: 18037281]
164. Cutuli D, Pagani M, Caporali P, Galbusera A, Laricchiuta D, Foti F, et al. Effects of omega-3 fatty acid supplementation on cognitive functions and neural substrates: A voxel-based morphometry study in aged mice. *Front Aging Neurosci.* 2016; 8:38. [PubMed: 26973513]
165. Kong W, Yen JH, Ganea D. Docosahexaenoic acid prevents dendritic cell maturation, inhibits antigen-specific Th1/Th17 differentiation and suppresses experimental autoimmune encephalomyelitis. *Brain Behav Immun.* 2011; 25:872–882. [PubMed: 20854895]
166. Orr SK, Palumbo S, Bosetti F, Mount HT, Kang JX, Greenwood CE, et al. Unesterified docosahexaenoic acid is protective in neuroinflammation. *J Neurochem.* 2013; 127:378–393. [PubMed: 23919613]
167. Tuzun F, Kumral A, Dilek M, Ozbal S, Ergur B, Yesilirmak DC, et al. Maternal omega-3 fatty acid supplementation protects against lipopolysaccharide-induced white matter injury in the neonatal rat brain. *J Matern Fetal Neonatal Med.* 2012; 25:849–854. [PubMed: 21892882]
168. Yavin E, Brand A, Green P. Docosahexaenoic acid abundance in the brain: a biodevice to combat oxidative stress. *Nutr Neurosci.* 2002; 5:149–157. [PubMed: 12041873]
169. Green P, Glozman S, Weiner L, Yavin E. Enhanced free radical scavenging and decreased lipid peroxidation in the rat fetal brain after treatment with ethyl docosahexaenoate. *Biochim Biophys Acta.* 2001; 1532:203–212. [PubMed: 11470241]
170. Högyes E, Nyakas C, Kiliaan A, Farkas T, Penke B, Luiten PG. Neuroprotective effect of developmental docosahexaenoic acid supplement against excitotoxic brain damage in infant rats. *Neuroscience.* 2003; 119:999–1012. [PubMed: 12831859]
171. Ozyurt B, Sarsilmaz M, Akpolat N, Ozyurt H, Akyol O, Herken H, et al. The protective effects of omega-3 fatty acids against MK-801-induced neurotoxicity in prefrontal cortex of rat. *Neurochem Int.* 2007; 50:196–202. [PubMed: 16971021]
172. Relton JK, Srijbos PJ, Cooper AL, Rothwell NJ. Dietary N-3 fatty acids inhibit ischaemic and excitotoxic brain damage in the rat. *Brain Res Bull.* 1993; 32:223–226. [PubMed: 8374800]
173. Blondeau N, Widmann C, Lazdunski M, Heurteaux C. Polyunsaturated fatty acids induce ischemic and epileptic tolerance. *Neuroscience.* 2002; 109:231–241. [PubMed: 11801360]
174. Belayev L, Khoutorova L, Atkins KD, Bazan NG. Robust docosahexaenoic acid-mediated neuroprotection in a rat model of transient, focal cerebral ischemia. *Stroke.* 2009; 40:3121–3126. [PubMed: 19542051]
175. Carlezon WA Jr, Mague SD, Parow AM, Stoll AL, Cohen BM, Renshaw PF. Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. *Biol Psychiatry.* 2005; 57:343–350. [PubMed: 15705349]

176. Huang SY, Yang HT, Chiu CC, Pariante CM, Su KP. Omega-3 fatty acids on the forced-swimming test. *J Psychiatr Res.* 2008; 42:58–63. [PubMed: 17070845]
177. Lakhwani L, Tongia SK, Pal VS, Agrawal RP, Nyati P, Phadnis P. Omega-3 fatty acids have antidepressant activity in forced swimming test in Wistar rats. *Acta Pol Pharm.* 2007; 64:271–276. [PubMed: 17695151]
178. Laino CH, Fonseca C, Sterin-Speziale N, Slobodianik N, Reinés A. Potentiation of omega-3 fatty acid antidepressant-like effects with low non-antidepressant doses of fluoxetine and mirtazapine. *Eur J Pharmacol.* 2010; 648:117–126. [PubMed: 20826148]
179. Reisbick S, Neuringer M, Gohl E, Wald R, Anderson GJ. Visual attention in infant monkeys: effects of dietary fatty acids and age. *Dev Psychol.* 1997; 33:387–395. [PubMed: 9149918]
180. Reisbick S, Neuringer M, Hasnain R, Connor WE. Home cage behavior of rhesus monkeys with long-term deficiency of omega-3 fatty acids. *Physiol Behav.* 1994; 55:231–239. [PubMed: 8153160]
181. Grayson DS, Kroenke CD, Neuringer M, Fair DA. Dietary omega-3 fatty acids modulate large-scale systems organization in the rhesus macaque brain. *J Neurosci.* 2014; 34:2065–2074. [PubMed: 24501348]
182. Tsukada H, Kakiuchi T, Fukumoto D, Nishiyama S, Koga K. Docosahexaenoic acid (DHA) improves the age-related impairment of the coupling mechanism between neuronal activation and functional cerebral blood flow response: a PET study in conscious monkeys. *Brain Res.* 2000; 862:180–186. [PubMed: 10799683]
183. Pifferi F, Dorieux O, Castellano CA, Croteau E, Masson M, Guillermier M, et al. Long-chain n-3 PUFAs from fish oil enhance resting state brain glucose utilization and reduce anxiety in an adult nonhuman primate, the grey mouse lemur. *J Lipid Res.* 2015; 56:1511–1518. [PubMed: 26063461]
184. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry.* 2010; 67:446–457. [PubMed: 20015486]
185. Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol Psychiatry.* 2013; 74:15–25. [PubMed: 23419545]
186. Upthegrove R, Manzanares-Teson N, Barnes NM. Cytokine function in medication-naïve first episode psychosis: a systematic review and meta-analysis. *Schizophr Res.* 2014; 155:101–108. [PubMed: 24704219]
187. Benedetti F, Poletti S, Hoogenboezem TA, Mazza E, Ambrée O, de Wit H, et al. Inflammatory cytokines influence measures of white matter integrity in Bipolar Disorder. *J Affect Disord.* 2016; 202:1–9. [PubMed: 27253210]
188. Prasad KM, Upton CH, Nimgaonkar VL, Keshavan MS. Differential susceptibility of white matter tracts to inflammatory mediators in schizophrenia: an integrated DTI study. *Schizophr Res.* 2015; 161:119–125. [PubMed: 25449712]
189. Bettcher BM, Wilhelm R, Rigby T, Green R, Miller JW, Racine CA, et al. C-reactive protein is related to memory and medial temporal brain volume in older adults. *Brain Behav Immun.* 2012; 26:103–108. [PubMed: 21843630]
190. Frodl T, Carballedo A, Hughes MM, Saleh K, Fagan A, Skokauskas N, et al. Reduced expression of glucocorticoid-inducible genes GILZ and SGK-1: high IL-6 levels are associated with reduced hippocampal volumes in major depressive disorder. *Transl Psychiatry.* 2012; 13:e88.
191. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR. Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biol Psychiatry.* 2008; 64:484–490. [PubMed: 18514163]
192. Marsland AL, Gianaros PJ, Kuan DC, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. *Brain Behav Immun.* 2015; 48:195–204. [PubMed: 25882911]
193. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. *Neurology.* 2012; 78:720–727. [PubMed: 22357713]

194. Taki Y, Thyreau B, Kinomura S, Sato K, Goto R, Wu K, et al. Correlation between high-sensitivity C-reactive protein and brain gray matter volume in healthy elderly subjects. *Hum Brain Mapp.* 2013; 34:2418–2424. [PubMed: 22438310]
195. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol Psychiatry.* 2009; 66:407–414. [PubMed: 19423079]
196. Slavich GM, Way BM, Eisenberger NI, Taylor SE. Neural sensitivity to social rejection is associated with inflammatory responses to social stress. *Proc Natl Acad Sci U S A.* 2010; 107:14817–14822. [PubMed: 20679216]
197. Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, et al. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. *Mol Psychiatry.* 2016; 21:1358–1365. [PubMed: 26552591]
198. Bagga D, Wang L, Farias-Eisner R, Glaspy JA, Reddy ST. Differential effects of prostaglandin derived from omega-6 and omega-3 polyunsaturated fatty acids on COX-2 expression and IL-6 secretion. *Proc Natl Acad Sci U S A.* 2003; 100:1751–1756. [PubMed: 12578976]
199. Bazan NG, Calandria JM, Serhan CN. Rescue and repair during photoreceptor cell renewal mediated by docosahexaenoic acid-derived neuroprotectin D1. *J Lipid Res.* 2010; 51:2018–2031. [PubMed: 20382842]
200. Groeger AL, Cipollina C, Cole MP, Woodcock SR, Bonacci G, Rudolph TK, et al. Cyclooxygenase-2 generates anti-inflammatory mediators from omega-3 fatty acids. *Nat Chem Biol.* 2010; 6:433–441. [PubMed: 20436486]
201. Serhan CN. Novel lipid mediators and resolution mechanisms in acute inflammation: to resolve or not? *Am J Pathol.* 2010; 177:1576–1591. [PubMed: 20813960]
202. Hong S, Gronert K, Devchand PR, Moussignac RL, Serhan CN. Novel docosatrienes and 17S-resolvins generated from docosahexaenoic acid in murine brain, human blood, and glial cells. Autacoids in anti-inflammation. *J Biol Chem.* 2003; 278:14677–14687. [PubMed: 12590139]
203. Hjorth E, Zhu M, Toro VC, Vedin I, Palmblad J, Cederholm T, et al. Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid- β 42 by human microglia and decrease inflammatory markers. *J Alzheimers Dis.* 2013; 35:697–713. [PubMed: 23481688]
204. Madore C, Nadjar A, Delpech JC, Sere A, Aubert A, Portal C, et al. Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain Behav Immun.* 2014; 41:22–31. [PubMed: 24735929]
205. Rao JS, Ertley RN, DeMar JC Jr, Rapoport SI, Bazinet RP, Lee HJ. Dietary n-3 PUFA deprivation alters expression of enzymes of the arachidonic and docosahexaenoic acid cascades in rat frontal cortex. *Mol Psychiatry.* 2007; 12:151–157. [PubMed: 16983392]
206. McNamara RK, Rider T, Jandacek RJ, Tso P, Cole-Strauss A, Lipton JW. Omega-3 fatty acid deficiency increases constitutive pro-inflammatory cytokine production in rats: Relationship with central serotonin turnover. *Prostaglandins Leukot Essent Fatty Acids.* 2010; 83:185–191. [PubMed: 20817496]
207. Mingam R, Moranis A, Bluthé RM, De Smedt-Peyrusse V, Kelley KW, Guesnet P, et al. Uncoupling of interleukin-6 from its signalling pathway by dietary n-3-polyunsaturated fatty acid deprivation alters sickness behaviour in mice. *Eur J Neurosci.* 2008; 28:1877–1886. [PubMed: 18973601]
208. Dang R, Zhou X, Tang M, Xu P, Gong X, Liu Y, et al. Fish oil supplementation attenuates neuroinflammation and alleviates depressive-like behavior in rats submitted to repeated lipopolysaccharide. *Eur J Nutr.* 2017
209. Shi Z, Ren H, Huang Z, Peng Y, He B, Yao X, et al. Fish Oil Prevents Lipopolysaccharide-Induced Depressive-Like Behavior by Inhibiting Neuroinflammation. *Mol Neurobiol.* 2017; 54:7327–7334. [PubMed: 27815837]
210. Watanabe S, Kanada S, Takenaka M, Hamazaki T. Dietary n-3 fatty acids selectively attenuate LPS-induced behavioral depression in mice. *Physiol Behav.* 2004; 81:605–613. [PubMed: 15178153]

211. Chang PK, Khatchadourian A, McKinney RA, Maysinger D. Docosahexaenoic acid (DHA): a modulator of microglia activity and dendritic spine morphology. *J Neuroinflammation*. 2015; 12:34. [PubMed: 25889069]
212. Black JE, Kodish IM, Grossman AW, Klintsova AY, Orlovskaya D, Vostrikov V, et al. Pathology of layer V pyramidal neurons in the prefrontal cortex of patients with schizophrenia. *Am J Psychiatry*. 2004; 161:742–744. [PubMed: 15056523]
213. Broadbelt K, Byne W, Jones LB. Evidence for a decrease in basilar dendrites of pyramidal cells in schizophrenic medial prefrontal cortex. *Schizophr Res*. 2002; 58:75–81. [PubMed: 12363393]
214. Eastwood SL, Harrison PJ. Synaptic pathology in the anterior cingulate cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin, GAP-43 and the complexins. *Brain Res Bull*. 2001; 55:569–578. [PubMed: 11576753]
215. Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM, et al. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *J Neurol Neurosurg Psychiatry*. 1998; 65:446–453. [PubMed: 9771764]
216. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry*. 2000; 57:65–73. [PubMed: 10632234]
217. Kang HJ, Voleti B, Hajsan T, Rajkowska G, Stockmeier CA, Licznarski P, et al. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. *Nat Med*. 2012; 18:1413–1417. [PubMed: 22885997]
218. Licznarski P, Duman RS. Remodeling of axo-spinous synapses in the pathophysiology and treatment of depression. *Neuroscience*. 2013; 251:33–50. [PubMed: 23036622]
219. Kolluri N, Sun Z, Sampson AR, Lewis DA. Lamina-specific reductions in dendritic spine density in the prefrontal cortex of subjects with schizophrenia. *Am J Psychiatry*. 2005; 162:1200–1202. [PubMed: 15930070]
220. Konopaske GT, Lange N, Coyle JT, Benes FM. Prefrontal cortical dendritic spine pathology in schizophrenia and bipolar disorder. *JAMA Psychiatry*. 2014; 71:1323–1331. [PubMed: 25271938]
221. Bennett MR. The prefrontal-limbic network in depression: A core pathology of synapse regression. *Prog Neurobiol*. 2011; 93:457–467. [PubMed: 21335052]
222. McNamara RK, Ostrander M, Abplanalp W, Richtand NM, Benoit SC, Clegg DJ. Modulation of phosphoinositide-protein kinase C signal transduction by omega-3 fatty acids: implications for the pathophysiology and treatment of recurrent neuropsychiatric illness. *Prostaglandins Leukot Essent Fatty Acids*. 2006; 75:237–257. [PubMed: 16935483]
223. Denys A, Hichami A, Maume B, Khan NA. Docosahexaenoic acid modulates phorbol ester-induced activation of extracellular signal-regulated kinases 1 and 2 in NIH/3T3 cells. *Lipids*. 2001; 36:813–818. [PubMed: 11592732]
224. Holian O, Nelson R. Action of long-chain fatty acids on protein kinase C activity: comparison of omega-6 and omega-3 fatty acids. *Anticancer Res*. 1992; 12:975–980. [PubMed: 1352441]
225. Mirnikjoo B, Brown SE, Kim HF, Marangell LB, Sweatt JD, Weeber EJ. Protein kinase inhibition by omega-3 fatty acids. *J Biol Chem*. 2001; 276:10888–10896. [PubMed: 11152679]
226. Seung Kim HF, Weeber EJ, Sweatt JD, Stoll AL, Marangell LB. Inhibitory effects of omega-3 fatty acids on protein kinase C activity in vitro. *Mol Psychiatry*. 2001; 6:246–248. [PubMed: 11317232]
227. Hains AB, Vu MA, Maciejewski PK, van Dyck CH, Gottron M, Arnsten AF. Inhibition of protein kinase C signaling protects prefrontal cortex dendritic spines and cognition from the effects of chronic stress. *Proc Natl Acad Sci U S A*. 2009; 106:17957–17962. [PubMed: 19805148]
228. Birnbaum SG, Yuan PX, Wang M, Vijayraghavan S, Bloom AK, Davis DJ, et al. Protein kinase C overactivity impairs prefrontal cortical regulation of working memory. *Science*. 2004; 306:882–884. [PubMed: 15514161]
229. Hartwig JH, Thelen M, Rosen A, Janmey PA, Nairn AC, Aderem A. MARCKS is an actin filament crosslinking protein regulated by protein kinase C and calcium-calmodulin. *Nature*. 1992; 356:618–622. [PubMed: 1560845]
230. Calabrese B, Halpain S. Essential role for the PKC target MARCKS in maintaining dendritic spine morphology. *Neuron*. 2005; 48:77–90. [PubMed: 16202710]

231. Wang HY, Friedman E. Enhanced protein kinase C activity and translocation in bipolar affective disorder brains. *Biol Psychiatry*. 1996; 40:568–575. [PubMed: 8886289]
232. Wang HY, Johnson GP, Friedman E. Lithium treatment inhibits protein kinase C translocation in rat brain cortex. *Psychopharmacology (Berl)*. 2001; 158:80–86. [PubMed: 11685387]
233. Johnson SA, Wang JF, Sun X, McEwen BS, Chattarji S, Young LT. Lithium treatment prevents stress-induced dendritic remodeling in the rodent amygdala. *Neuroscience*. 2009; 163:34–39. [PubMed: 19501634]
234. Calabrese B, Halpain S. Lithium prevents aberrant NMDA-induced F-actin reorganization in neurons. *Neuroreport*. 2014; 25:1331–1337. [PubMed: 25304495]
235. Bessa JM, Ferreira D, Melo I, Marques F, Cerqueira JJ, Palha JA, et al. The mood-improving actions of antidepressants do not depend on neurogenesis but are associated with neuronal remodeling. *Mol Psychiatry*. 2009; 14:764–773. [PubMed: 18982002]
236. Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010; 329:959–964. [PubMed: 20724638]
237. Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry*. 1989; 46:243–250. [PubMed: 2784046]
238. Bench CJ, Friston KJ, Brown RG, Scott LC, Frackowiak RS, Dolan RJ. The anatomy of melancholia—focal abnormalities of cerebral blood flow in major depression. *Psychol Med*. 1992; 22:607–615. [PubMed: 1410086]
239. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–827. [PubMed: 9126739]
240. Drevets WC, Bogers W, Raichle ME. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur Neuropsychopharmacol*. 2002; 12:527–544. [PubMed: 12468016]
241. Ho TC, Wu J, Shin DD, Liu TT, Tapert SF, Yang G, et al. Altered cerebral perfusion in executive, affective, and motor networks during adolescent depression. *J Am Acad Child Adolesc Psychiatry*. 2013; 52:1076–1091. [PubMed: 24074474]
242. Wang Y, Zhang H, Tang S, Liu X, O'Neil A, Turner A, et al. Assessing regional cerebral blood flow in depression using 320-slice computed tomography. *PLoS One*. 2014; 9:e107735. [PubMed: 25251476]
243. Hill K, Mann L, Laws KR, Stephenson CM, Nimmo-Smith I, McKenna PJ. Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies. *Acta Psychiatr Scand*. 2004; 110:243–256. [PubMed: 15352925]
244. Umhau JC, Zhou W, Carson RE, Rapoport SI, Polozova A, Demar J, et al. Imaging incorporation of circulating docosahexaenoic acid into the human brain using positron emission tomography. *J Lipid Res*. 2009; 50:1259–1268. [PubMed: 19112173]
245. Hamazaki-Fujita N, Hamazaki K, Tohno H, Itomura M, Terashima Y, Hamazaki T, et al. Polyunsaturated fatty acids and blood circulation in the forebrain during a mental arithmetic task. *Brain Res*. 2011; 1397:38–45. [PubMed: 21616479]
246. Pu S, Nakagome K, Yamada T, Matsumura H, Yokoyama K, Kaneko K, et al. Association between fish consumption and prefrontal function during a cognitive task in male Japanese workers: A multi-channel near-infrared spectroscopy study. *PLoS One*. 2015; 10:e0123972. [PubMed: 25919586]
247. Jackson PA, Reay JL, Scholey AB, Kennedy DO. DHA-rich oil modulates the cerebral haemodynamic response to cognitive tasks in healthy young adults: a near IR spectroscopy pilot study. *Br J Nutr*. 2012; 107:1093–1098. [PubMed: 22018509]
248. Jackson PA, Reay JL, Scholey AB, Kennedy DO. Docosahexaenoic acid-rich fish oil modulates the cerebral hemodynamic response to cognitive tasks in healthy young adults. *Biol Psychol*. 2012; 89:183–190. [PubMed: 22020134]
249. Konagai C, Yanagimoto K, Hayamizu K, Han L, Tsuji T, Koga Y. Effects of krill oil containing n-3 polyunsaturated fatty acids in phospholipid form on human brain function: a randomized

- controlled trial in healthy elderly volunteers. *Clin Interv Aging*. 2013; 8:1247–1257. [PubMed: 24098072]
250. Amen DG, Harris WS, Kidd PM, Meysami S, Raji CA. Quantitative erythrocyte omega-3 EPA plus DHA levels are related to higher regional cerebral blood flow on brain SPECT. *J Alzheimers Dis*. 2017; 58:1189–1199. [PubMed: 28527220]
 251. Gao LG, Cao J, Mao QX, Lu XC, Zhou XL, Fan L. Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: a meta-analysis of randomized controlled trials. *Atherosclerosis*. 2013; 226:328–334. [PubMed: 23153623]
 252. Leslie MA, Cohen DJ, Liddle DM, Robinson LE, Ma DW. A review of the effect of omega-3 polyunsaturated fatty acids on blood triacylglycerol levels in normolipidemic and borderline hyperlipidemic individuals. *Lipids Health Dis*. 2015; 14:53. [PubMed: 26048287]
 253. Birdsill AC, Carlsson CM, Willette AA, Okonkwo OC, Johnson SC, Xu G, et al. Low cerebral blood flow is associated with lower memory function in metabolic syndrome. *Obesity (Silver Spring)*. 2013; 21:1313–1320. [PubMed: 23687103]
 254. Jennings JR, Heim AF, Kuan DC, Gianaros PJ, Muldoon MF, Manuck SB. Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. *Stroke*. 2013; 44:2480–2485. [PubMed: 23881956]
 255. Kristensen SD, Schmidt EB, Dyerberg J. Dietary supplementation with n-3 polyunsaturated fatty acids and human platelet function: a review with particular emphasis on implications for cardiovascular disease. *J Intern Med Suppl*. 1989; 731:141–50. [PubMed: 2650690]
 256. Murray MJ, Zhang T. The incorporation of dietary n-3 polyunsaturated fatty acids into porcine platelet phospholipids and their effects on platelet thromboxane A2 release. *Prostaglandins Leukot Essent Fatty Acids*. 1997; 56:223–228. [PubMed: 9089803]
 257. Wander RC, Patton BD. Comparison of three species of fish consumed as part of a Western diet: effects on platelet fatty acids and function, hemostasis, and production of thromboxane. *Am J Clin Nutr*. 1991; 54:326–333. [PubMed: 1858697]
 258. Berti V, Murray J, Davies M, Spector N, Tsui WH, Li Y, et al. Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals. *J Nutr Health Aging*. 2015; 19:413–423. [PubMed: 25809805]
 259. Nugent S, Croteau E, Pifferi F, Fortier M, Tremblay S, Turcotte E, et al. Brain and systemic glucose metabolism in the healthy elderly following fish oil supplementation. *Prostaglandins Leukot Essent Fatty Acids*. 2011; 85:287–291. [PubMed: 21795034]
 260. Sublette ME, Milak MS, Hibbeln JR, Freed PJ, Oquendo MA, Malone KM, et al. Plasma polyunsaturated fatty acids and regional cerebral glucose metabolism in major depression. *Prostaglandins Leukot Essent Fatty Acids*. 2009; 80:57–64. [PubMed: 19128951]
 261. Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006; 67:1954–1967. [PubMed: 17194275]
 262. Messamore E, McNamara RK. Detection and treatment of omega-3 fatty acid deficiency in psychiatric practice: Rationale and implementation. *Lipids Health Dis*. 2016; 15:1–13. [PubMed: 26728949]
 263. Pottala JV, Talley JA, Churchill SW, Lynch DA, von Schacky C, Harris WS. Red blood cell fatty acids are associated with depression in a case-control study of adolescents. *Prostaglandins Leukot Essent Fatty Acids*. 2012; 86:161–165. [PubMed: 22464051]

Figure 1. Diagram illustrating candidate mediators of the association between omega-3 PUFA deficiency and central pathological features observed in patients with mood and psychotic disorders.