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Review

REVIEW

N-3 Polyunsaturated Fatty Acids through the Lifespan: Implication for Psychopathology

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Abstract

Objective: The impact of lifetime dietary habits and their role in physical, mental, and social well-being has been the focus of considerable recent research. Omega-3 polyunsaturated fatty acids as a dietary constituent have been under the spotlight for decades. Omega-3 polyunsaturated fatty acids constitute key regulating factors of neurotransmission, neurogenesis, and neuroinflammation and are thereby fundamental for development, functioning, and aging of the CNS. Of note is the fact that these processes are altered in various psychiatric disorders, including attention deficit hyperactivity disorder, depression, and Alzheimer's disease.
Design: Relevant literature was identified through a search of MEDLINE via PubMed using the following words, "n-3 PUFAs," "EPA," and "DHA" in combination with "stress," "cognition," "ADHD," "anxiety," "depression," "bipolar disorder," "schizophrenia," and "Alzheimer." The principal focus was on the role of omega-3 polyunsaturated fatty acids throughout the lifespan and their implication for psychopathologies. Recommendations for future investigation on the potential clinical value of omega-3 polyunsaturated fatty acids were examined.
Results: The inconsistent and inconclusive results from randomized clinical trials limits the usage of omega-3 polyunsaturated fatty acids in clinical practice. However, a body of literature demonstrates an inverse correlation between omega-3 polyunsaturated fatty acid levels and quality of life/ psychiatric diseases. Specifically, older healthy adults showing low habitual intake of omega-3 polyunsaturated fatty acids benefit most from consuming them, showing improved age-related cognitive decline.
Conclusions: Although further studies are required, there is an exciting and growing body of research suggesting that omega-3 polyunsaturated fatty acids may have a potential clinical value in the prevention and treatment of psychopathologies.

Keywords: omega-3 polyunsaturated fatty acids (n-3 PUFAs), depression, schizophrenia, bipolar disorder, Alzheimer's disease

Introduction

Despite the improved pharmacological approaches that moderately buffer the worldwide burden of poor mental health, a recent finding suggests that mental illnesses will continue to rise worldwide during the coming decades (Baxter et al., 2013). The general transition to more calorically dense, processed diets and reduced physical activity have had a significant impact on the overall health of individuals in developed nations and are associated with an increased incidence of psychopathologies

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such as anxiety and depression (Logan and Jacka, 2014). Accumulating translational evidence implicates the quality of diet as a crucial and common determinant for mental disorders (McNamara et al., 2015). Within the brain, omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been under the spotlight for decades. However, only recently has research looked into the critical role of n-3 PUFAs in brain function and structure throughout the lifespan. n-3 PUFAs constitute key regulating factors of neurotransmission, neurogenesis, cell survival, and neuroinflammation and are thereby fundamental for development, functioning, and aging of the CNS (Mischoulon and Freeman, 2013). Importantly, these processes are altered in various psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), schizophrenia, major depression, and Alzheimer's disease (Sinn et al., 2010). Despite this evidence, the concept of n-3 PUFAs as a clear therapeutic compound for mental disorders still needs to be clarified. The purpose of this review is to further explore the role of n-3 PUFAs, which have been gaining increasing credence as potential targets for the development of novel strategies for the maintenance of mental health in the prevention and amelioration of psychopathology (Figure 1).

n-3 PUFAs in Early-Life: From Embryogenesis to Adolescence

Brain development is a sequential anatomical process characterized by specific well-defined stages of growth and maturation. It has become more evident that this process is influenced by n-3 PUFAs. Specifically, the levels of docosahexaenoic acid (DHA), the most abundant component of the n-3 PUFAs family, increase sharply along the perinatal period. In rats, the first important step of acquisition of DHA takes place in the embryonic phase and in the first 3 postnatal weeks of life, whereas in humans this period goes between the last trimester of gestation and the first 6 to 10 months after birth (Clandinin et al., 1980a, 1980a). At these stages of life, the foetal metabolic capability to convert the precursor of the n-3 PUFAs family, α-linolenic acid (ALA), to DHA is extremely limited (<0.2% in children). Indeed, it is the mother that guarantees an adequate delivery of DHA to the fetus through the placenta. (Innis, 2007).

The Perinatal Lipid Nutrition Project and The Early Nutrition Programming Project have recently developed consensus recommendations concerning dietary fat intake for pregnant and lactating women. They recommend a minimum DHA intake of 200 mg/d (Koletzko et al., 2007). Interestingly, supplementation of n-3 PUFAs during pregnancy not only increases breast milk DHA content but also results in slightly longer gestation as well as reduced risk of preterm delivery (Singh, 2005). Accordingly, infants born prematurely show less accumulation of DHA in the brain (Barcelo-Coblijn and Murphy, 2009). However, the increased supply of DHA to the developing fetal nervous system leads to a progressive depletion of maternal plasma DHA (Smuts et al., 2003). Of relevance, in a cross-national ecological analysis, reduced levels of maternal milk DHA and lower seafood consumption correlated with higher rates of postpartum depression (Hibbeln, 2002). Therefore, diets enriched in n-3 PUFAs are recommended to both restore the depletion of DHA in the mother as well as to look after the needs of the fetus and suckling infant.

Animal studies reveal n-3 PUFAs as guarantors of proper brain development in early postnatal life (Lei et al., 2013). n-3 PUFA supplementation has been shown to protect from neuronal loss and decreased neurogenesis in the cerebral cortex and hippocampus of neonates (Lei et al., 2013). Furthermore, this effect can be long-lasting and show further benefits in neurocognitive function later in adulthood (Lei et al., 2013). In humans, Jensen et al. (2005) have shown a higher Psychomotor Development Index in breastfed infants of mothers who underwent DHA administration (200 mg/d) for a period of 4 months. Psychomotor development, eye-hand coordination, and visual acuity were all improved after DHA algal-oil treatment. However, these improvements were limited to infants 30 months old and no further advantages on mental development were found. Although of relevance, this study has limitations in terms of treatment duration and assessment instruments. A different study measured IQ in children whose mothers underwent maternal supplementation with cod liver oil (1183 mg/10 mL DHA, 803 mg/10 mL eicosapentaenoic acid [EPA]) started from week 18 until 3 months after delivery (Helland et al., 2003). The scoring of the Mental Processing Composite of the Kaufman Assessment Battery for Children was increased by 4 points in 4-year-old children who were born to mothers who had taken cod liver oil enriched in DHA and EPA. However, only 84 children of the 590 pregnant women enrolled in the study completed

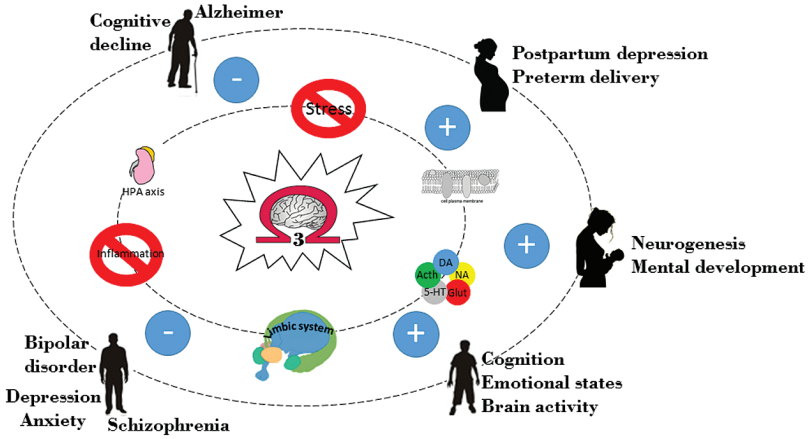


Figure 1. Omega-3 polyunsaturated fatty acids [(n-3) PUFAs] throughout the lifespan. n-3 PUFAs represent essential components of the cellular membrane and constitute key regulating factors of neurotransmission, neurogenesis, stress response, inflammation, and emotional states. Thereby, they are fundamental for development, functioning, and aging of the CNS throughout the lifespan. n-3 PUFAs, mainly acting on the factors mentioned above, contribute to the maintenance of mental health, in the prevention and amelioration of psychopathology.

the Kaufman Assessment Battery for Children at 4 years of age. Another similar study has shown higher mental processing scores and high degree of stereopsis and stereo acuity in children 3.5 years old whose mothers received a DHA-rich diet (Williams et al., 2001). Given the importance to maintain proper DHA levels during the neonatal period of life, the content and kind of fatty acids introduced in the body are of importance. In fact, infants fed formula with 0.4% or 2.4 % energy from ALA had 2.3 ± 0.2 and 2.2 ± 0.3 g/100 g fatty acids as DHA in plasma, respectively, despite the large difference in ALA intake, whereas infants fed formula with only 0.12 % energy from DHA had plasma DHA levels of 5.2 ± 0.2 g/100 g (Innis, 2007).

n-3 PUFAs maintain their importance in brain development and functioning during adolescence (Table 1). At this stage of life, rats fed with an n-3 PUFA-deficient diet tend to have decreased n-3 PUFA mass (82% less) compared with control (Bondi et al., 2014). Such animals show less exploratory behavior, weaker memory performance, and increased tyrosine hydroxylase expression (dopamine [DA] precursor) in the dorsal striatum.

In humans, Kuratko et al. (2013) provided a systematic review based on 15 publications regarding the influence of DHA in learning and behavior in healthy children. The studies differed in purpose and design, and some did not achieve a consistent conclusion regarding DHA's effect on specific cognitive tests. However, the analysis found benefits of DHA supplementation in brain activity and school performance from over one-half of the considered studies. A landmark study showing improved brain activity after DHA supplementation dates back to 2010 (McNamara et al., 2010a). McNamara et al. showed for the first time regulation of cortical metabolic function and cognitive development exerted by DHA concentrations in the grey matter of healthy boys during sustained attention (McNamara et al., 2010a). The study was conducted in 33 subjects (9 years old) who were assigned to receive placebo or 1 of the 2 doses of DHA (400 mg/d; 1200 mg/d) for 8 weeks. A longitudinal study in arctic Quebec has revealed a relation within school-age children with higher DHA cord plasma concentration and memory function (Boucher et al., 2011). Despite this interesting finding, a previous study conducted in DHA-fed healthy children in the UK did not show any improvement on cognitive performance and learning (Kennedy et al., 2009). However, other studies have observed benefits of n-3 PUFAs, particularly in malnourished subjects. For instance, improvements in learning and cognitive performance have been shown in n-3 PUFA-supplemented, malnourished children 7 to 9 years old in South Africa (Dalton et al., 2009) and 8- to 12-year-old Mexican children (Portillo-Reyes et al., 2014), although, no benefits were found in 6- to 10-year-old malnourished children from India (Muthayya et al., 2009) and Indonesia (Osendarp et al., 2007). The discordance between these studies may be accounted for by differences in the extent of malnutrition. Moreover, further discrepancies can be due to differences in the experimental plan such as supplements used, different dosages, and duration of the trials. Overall, the current research supports the view that adequate intake of DHA since prenatal life may have a positive impact on brain activity, learning, and cognition in healthy children. Indeed, being components of cell membranes, n-3 PUFAs are involved in important phases of brain development such as neurogenesis, myelination, synaptogenesis, and dendritic arborisation, which are in continuous flux during development and learning (Wurtman, 2014). Thus, this raises the possibility that n-3 PUFAs may have a beneficial effect on neurodevelopmental psychiatric disorders (McNamara and Carlson, 2006).

n-3 PUFAs: Implication for Childhood Disorders

Deficits in n-3 PUFAs have been associated with higher risk of development of childhood disorders such as ADHD (Richardson and Ross, 2000). In a cross-sectional study, Burgess et al. (2000) observed that 40% of recruited ADHD subjects (53 ADHD 6- to 12-year-old boys) had significantly lower proportions of plasma DHA and EPA and greater frequency of n-3 PUFAsdeficiency syndrome such as thirst, frequent urination, and dry hair. Importantly, such physical signs linked with deficit in n-3 PUFAs are consistent in ADHD (Richardson et al., 2000). Moreover, behavioral and learning problems, such as anomalous visual, motor, attention, and language processing, have been linked to lower n-3 PUFAs plasma levels (Richardson, 2004). The reason for lower n-3 PUFAs levels in ADHD is unknown. Evidence suggests that testosterone can impair the biosynthesis of n-3 PUFAs while estrogens are positively related with the conversion of DHA from ALA both in rodents (Marra and de Alaniz, 1989) and humans (Childs et al., 2008). This may explain the higher prevalence of ADHD in males than in females.

In animal studies the spontaneously hypertensive rat is generally used as a model of ADHD (Meneses et al., 2011). Spontaneously hypertensive rat fed n-3 PUFA (EPA-DHA)-enriched diet (n-6:n-3 PUFAs ratio of 1:2.7), from gestational phase until postnatal day 50, partially ameliorated ADHD-like behavior by improving reinforcer-controlled activity, impulsiveness, and inattention (Dervola et al., 2012). Moreover, such a diet increased the DA and serotonin turnover ratio together with decreased levels of glutamate in the striatum of the same animals (Dervola et al., 2012). These neurotransmitters are thought to be altered in ADHD animal models (Gainetdinov et al., 2001) and ADHD young subjects (Paloyelis et al., 2012).

In humans, supplementation with PUFAs (480 mg DHA, 80 mg EPA, 40 mg arachidonic acid [AA], 96 mg γ-linolenic acids, and 24 mg α-tocopheryl acetate) improved ADHD children's oppositional defiant behavior from a clinical to a nonclinical range (Stevens et al., 2003). In this study, both parents and teachers rated improvement in conduct problems and attention difficulties after 4 months of treatment. However, more than one-half of the patients were prescribed medication for ADHD, making it difficult to attribute the observed improved symptoms to the n-3 PUFA treatment. A similar PUFA mixture (480 mg DHA, 186 mg EPA, 96 mg γ-linolenic acids, 42 mg AA, and 60 IU vitamin E per day), supplemented for 12 weeks, showed improvement in anxiety/shy tests, cognition, inattentiveness, hyperactivity/impulsiveness, total DSM-IV index, and Conners total global index in children with learning difficulties (Richardson and Puri, 2002). However, none of the subjects were formally diagnosed with ADHD and the sample size was small (41 children, 8–12 years old). Although the studies reported above seem to be encouraging, 3 recent systematic reviews have reported only minor n-3 PUFA effect in reducing ADHD symptoms. Grassman et al. (2013) reported mild behavioral and cognitive improvement in ADHD children after treatment with low doses of n-3 PUFAs. However, the studies included in their analysis were heterogeneous, had small sample sizes, and only a limited number were placebo controlled. Bloch and Qawasmi (2011) have reported a modest effect in the treatment of ADHD after treatment with high doses of n-3 PUFAs (especially EPA) in comparison with current pharmacotherapies such as psychostimulants, atomoxetine, or α(2) agonists. Gillies et al. (2012) reported improvement after combined n-3 PUFA and n-6 PUFA supplementation only in a minority of the studies that met the inclusion criteria of their review.

Table 1. n-3 PUFA Impact in Healthy Adolescents

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
6–11 years, low-income iron-deficient children, (n = 321, z n = 288).	(1) Iron + fish oil; (2) Iron + placebo; (3) Fish oil + placebo; (4) Placebo + placebo. Fish oil = 0.5 g/d LC omega-3 (0.42 g DHA + 0.08 g EPA).	8.5 months.	HVLT	LC omega-3 PUFA without iron had negative effects on working memory in children with iron deficiency anemia and long-term memory and retrieval in girls with iron deficiency, whereas boys with iron deficiency performed better.	(Baumgartner et al., 2012)
7–9 years, low-income, marginally nourished indigenous children (n = 183, analysis on n = 155).	Fish flour bread spread provided at school (~0.89 g/week DHA [0.13 g/d]) vs control bread spread.	6 months.	HVLT, spelling test, reading test	↑ Verbal learning ability, memory, and spelling. Effects more pronounced in children with lower baseline performance scores.	(Dalton et al., 2009)
10–12 years (n = 90, analysis on n = 86).	(1) Low-dose algal oil: 0.4 g DHA; (2) High-dose algal oil: 1.0 g/d DHA; (3) Placebo (vegetable oil).	8 weeks.	Cognitive performance	Word recognition task: low dose: faster performance; high dose: slower performance.	(Kennedy et al., 2009)
8–10 years (n = 450, analysis on n = 348).	Fish oil (0.4 g DHA + 0.06 g EPA)/d + micronutrients vs placebo (olive oil).	16 weeks.	KBIT-2, WIAT-2, WMTB-C, creature counting, MFFT, comPET, SNAP-IV, SDQ.	No treatment effects.	(Kirby et al., 2010)
8–10 year boys (n = 38, analysis on n = 33).	(1) Low-dose algal oil: 0.4 g/d DHA; (2) High-dose algal oil: 1.2 g/d DHA; (3) Placebo (corn oil).	8 weeks.	Sustained attention test, fMRI	Both dosages ↑ activation of the dorsolateral prefrontal cortex during sustained attention task. No effect on attention or reaction time of attention.	(McNamara et al., 2010a)
6–10 years, low-income, marginally nourished (n = 598, analysis on n = 550).	(1) High micronutrients + 0.93 g ALA + 0.10 g DHA/d; (2) High micronutrients + 0.14 g/d ALA; (3) Low micronutrients + 0.93 g ALA + 0.10 g DHA/d (4) Low micronutrients + 0.14 g/d ALA.	12 months.	Cognitive test battery	No treatment effects.	(Muthayya et al., 2009)
6–10 years Australia: well nourished, (n = 396, analyzed n = 276) Indonesia: marginally nourished (n = 384, analyzed n = 367).	(1) High micronutrients; (2) DHA + EPA (0.09 g DHA + 0.02 g EPA)/d; (3) Micronutrients + DHA + EPA (as above); (4) Placebo.	12 months.	Cognitive test battery	No treatment effects.	(Osendarp et al., 2007)
3–13 years, indigenous children with low literacy ability (n = 408).	Fish oil 0.75 g LC omega-3 per school day (0.56 g EPA + 0.17 g DHA) plus 0.06 g/d gamma linolenic acid vs placebo (palm oil).	20 weeks.	WRAT4, DAP, MAP, CBRS	Nonverbal cognitive development (Draw-A Person): Improvements with strongest effects in 7- to 12-year olds.	(Parletta et al., 2013)
8–12 years, mild-moderately malnourished (n = 59, analysis on n = 50).	Fish oil 0.45 g/d LC omega-3 (0.18 g EPA + 0.27 g DHA) vs placebo (soybean oil).	3 months.	Anthropometric measures, neuropsychological battery test	↑ Processing speed, visual-perceptive capacity, attention, executive function.	(Portillo-Reyes et al., 2014)
7–9 years, underperforming in reading (≤33rd centile) (n = 362).	Algal oil: 0.6 g/d DHA vs placebo (corn/soybean oil).	16 weeks.	Age-standardized measures of reading, working memory, and parent- and teacher-rated behavior.	Treatment ↑ reading.	(Richardson et al., 2012)

Abbreviations: CBRS, Comprehensive Behaviour Rating Scales; DAP, The Draw-A-Person; HVLT, Hopkins Verbal Learning Test; KBIT-2, Kaufman Brief Intelligence Test, Second Edition; MAP, Matrix Analogies Test; MFFT, Matching Familiar Figures Task; SDQ, Strengths and Difficulties Questionnaire; SNAP-IV, Swanson, Nolan, and Pelham rating scale for ADHD; WIAT-2, Wechsler Individual Achievement Test, Second Edition; WMTB-C, Working Memory Test Battery for Children; WRAT-4, Wide Range Achievement Test: Fourth Edition.

Given its evidence of modest efficacy, it may be reasonable to investigate n-3 PUFAs as a supplement to traditional pharmacologic interventions. Future studies need to be adequately powered and placebo controlled and use adequate dosage, (Table 2).

n-3 PUFAs in Adulthood: Stress Response

In adulthood, full brain development is already achieved. However, at this stage of life stressful life events can alter mood states and cognition, increasing susceptibility to psychopathologies (Cattaneo et al., 2015). n-3 PUFAs seem to play a role in the regulation of the stress-response influencing the activity of the hypothalamic–pituitary–adrenal (HPA) axis. In humans (7 volunteers), the stimulation by 30 minutes of mental stress (mental arithmetic's and Stroop's test) of plasma epinephrine, cortisol, and energy expenditure were all significantly blunted by 3 weeks of 7.2 g/d fish oil administration (Delarue et al., 2003). However, the subjects were tested before and after 3 weeks of n-3 PUFA supplementation; thus, a possible effect of acclimatization due to the repetition of the testing procedure over time should be taken into account. Similarly, ACTH and cortisol plasma levels were blunted by 4 weeks of 7 g/d fish oil supplementation prior lipopolysaccharide (2 ng/kg)-induced neuroendocrine response (Michaeli et al., 2007). In contrast with the n-3 PUFA antiinflammatory effect (Grimm et al., 2002), high levels of cytokines were not reversed by n-3 PUFAs, perhaps due to a too low content of EPA (17%) and DHA (11%) in the fish oil supplement. Indeed, 2.5 g/d of n-3 PUFAs (2 g EPA, 0.35 g DHA) supplementation showed reduction of stimulated interleukin 6 (IL-6) and tumour necrosis factor plasma levels in healthy medical students. Interestingly, this was associated with reduced anxiety symptoms in healthy students without an anxiety disorder diagnosis (Kiecolt-Glaser et al., 2011). This evidence acquires more interest, since stress can exert a pivotal role in memory and cognition (McEwen, 2007). Researchers at the University of Pittsburgh have determined that n-3 PUFAs can enhance cognition in young individuals. Healthy young adults (18–25 years of age) after 6 months of n-3 PUFA supplement, mostly DHA (750 mg/d) and EPA (930 mg/d), experienced improvement in working memory (Narendran et al., 2012). Working memory assessment was performed using a verbal n-back task that used 3 loads of working memory (1-, 2-, and 3-back) (Abi-Dargham et al., 2002). In addition to that, prior to supplementation of n-3 PUFAs, higher red blood cell DHA levels were significantly correlated with working memory in a group of young adults. Interestingly, a similar association between high DHA plasma levels and improved cognitive function was previously observed in a sample of 208 healthy subjects (30–54 years of age; Muldoon et al., 2010). DHA, but not other n-3 PUFAs, was associated with better scores on tests of nonverbal reasoning, mental flexibility, working memory, and vocabulary. Another study conducted in Australia showed 6 weeks of 6 g/d fish oil intake (1.5 g DHA, 360 g EPA) were enough to ameliorate the Perceiving Stress Scale scoring in stressed university staff (Bradbury et al., 2004). Due to a lack of investigation, further research is warranted to elucidate the mechanisms by which n-3 PUFAs enhance cognitive performance in healthy individuals (Table 3).

n-3 PUFAs and Psychopathologies

Major Depressive Disorder

Since the 19th century, the incidence of major depressive disorder (MDD) in Western countries seems to have increased. In contrast, the dietary intake of n-3 PUFAs has dramatically declined in favor of n-6 PUFA intake (Molendi-Coste et al., 2011). Joseph Hibbeln was one of the first investigators to draw attention to the importance of n-3 PUFAs in psychiatric disorders. In 1998, Hibbeln showed a cross-national significant negative correlation between worldwide fish consumption and prevalence of MDD (Hibbeln, 1998). Moreover, higher n-6/n-3 ratios, such as the AA/EPA ratio, has been detected in blood samples (Lin et al., 2010) and red blood cell phospholipids (Logan, 2003) of depressed patients. Accordingly, n-3 PUFA concentrations in the blood reflect an accurate, although not identical, representation of n-3 PUFAs levels in the brain (Horrobin, 2001). Lower DHA levels have been found in the postmortem orbitofrontal cortex of MDD patients (McNamara et al., 2007). Moreover, lower n-3PUFA levels have been found in chronic hepatitis C viral infection patients that developed interferon (IFN)-induced depression after IFN-α intervention. This finding identifies both n-3 PUFA-related genotypes and n-3 PUFA levels as risk factors for IFN-induced depression (Su et al., 2010). However, these findings do not show that fish consumption can cause differences in the prevalence of MDD or that eating fish or fish oils is useful in treatment. One double-blind, placebo-controlled study investigated the effect of EPA as adjunct to antidepressant therapy in a group of 20 MDD diagnosed patients. Although this was a small study (17 women, 3 men), the addition of 2 g of EPA to standard antidepressant medication showed highly significant benefits by week 3 of treatment. Primarily, EPA showed effects on insomnia, depressed mood, and feelings of guilt and worthlessness (Nemets et al., 2002). In 2002, Peet and Horrobin observed that a specific EPA dosage (1 g/d) was effective in ameliorating depressive symptoms in subjects with persistent depression despite ongoing treatment with antidepressant. In this 12-week, randomized, double-blind, placebo-controlled trial, 53% of the subjects who received EPA (17 subjects) achieved a 50% reduction on the Hamilton Depression Rating Scale score. In addition, the EPA had a broad-spectrum positive effect leading to improvements in anxiety, sleep, lassitude, libido, and suicidal ideation (Peet and Horrobin, 2002). Moreover, a 2-week, double-blind, placebo-controlled trial conducted in a group of 162 patients showed n-3 PUFA efficacy in the prevention of IFN-induced depression in hepatitis C virus patients (Su et al., 2014). Both DHA (1.75 g/d) and EPA (3.5 g/d) significantly delayed the onset of IFN-induced depression after 24 weeks of IFN-α treatment. Despite that, only EPA-treated patients showed lower incident rates of IFN-induced depression (10% vs 30% for placebo [oleic oil, 4 g/d], $P = .037$). Although clinical outcomes on the effect of EPA on major depression seem to be promising, trials using DHA are inconclusive. Thirty-six subjects with major depression assigned to receive DHA (2 g/d) for 6 weeks did not show differences in the score of the Montgomery-Asberg Depression Rating Scale compared with the placebo-treated group (Marangell et al., 2003). A recent meta-analysis focused on the hypothesis that EPA represents the key compound of the n-3 PUFA family having effects in the treatment of major depression. Fifteen trials (916 total participants) using n-3 PUFAs as either a mono or adjunctive therapy were analyzed. Studies were selected based on prospective, randomized, double-blinded, placebo-controlled study design, if depressive episode was the primary complaint with or without comorbid medical conditions and, if appropriate outcome measures were used to assess depressed mood. This meta-analysis concluded that n-3 PUFA supplements with >60% of EPA (in a dose range of 200 to 2200 mg/d in excess of DHA) ameliorated the clinical condition. However, doses containing primarily DHA or <60% EPA were not effective against

Table 2. n-3 PUFA Impact on Mental Illnesses in Early Life and Adolescence

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
6–12 year old (78% boys); idiopathic ADHD diagnosis; were being treated successfully with medication (n = 54).	345 mg DHA (algae-derived) or undefined placebo.	16 weeks.	CPRS; CBC; TOVA; CCT.	Treatment = placebo on all measures.	(Voigt et al., 2001)
6–13 year old (78% boys); ADHD diagnosis; high FADS; some on medication (equally allocated to conditions) (n = 50).	96 mg GLA, 40 mg AA, 80 mg EPA, 480 mg DHA, 24 mg Vit E or olive oil placebo.	16 weeks.	DBD; ASQ; CPT; WJPEB-R; FADS.	Treatment > placebo: DBD-Conduct (parents); DBD-Attention (teachers). Other 14 outcome measures nonsignificant.	(Stevens et al., 2003)
6–12 year old (80% boys); ADHD diagnosis; 15% medicated; 82% comorbid conditions (n = 40).	100 mg EPA, 514 mg DHA, or olive oil placebo (supplied in soymilk and bread).	8 weeks.	DTVP; STM; CPT; Other.	Treatment = placebo on all measures (except that placebo > treatment on CPT and STM).	(Hirayama et al., 2004)
8–12 year old (62% boys); normal IQ; low reading ability; above average ADHD scores on Conners' Index; no participants in treatment for ADHD (n = 29).	864 mg LA, 42 mg AA, 96 mg ALA, 186 mg EPA, 480 mg DHA, 60 iμ Vit E or olive oil placebo.	12 weeks.	CPRS.	Treatment > placebo: CPRS; Cognitive problems/ inattention; Anxious/shy; Conners' global index; DSM inattention; DSM hyperactive/impulsive; Conners' ADHD Index.	(Richardson and Puri, 2002)
5–12 year old (77% boys); Developmental Coordination Disorder, one-third with ADHD symptoms in clinical range, not in treatment; IQ > 70 (n = 117).	60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg Vit E or olive oil placebo.	12 weeks active vs placebo; 1-way crossover to active treatment for 12 weeks.	MABC; WORD; CTRS.	Treatment > placebo: WORD; CTRS Oppositional behavior; cognitive problems/ inattention; hyperactivity; anxious/shy; perfectionism; social problems; Conners' index; DSM-IV inattention, hyperactive/impulsive.	(Richardson and Montgomery, 2005)
7–12 year old (74% boys); ADHD symptoms in clinical range; unmedicated (n= 132, questionnaire data available for 104).	60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg Vit E, or palm oil placebo.	15 weeks active vs placebo; 1-way crossover to active treatment for 15 weeks.	CPRS, CTRS Vocabulary, subtests from WISC-III & TEA-ch, Stroop.	Treatment > placebo CPRS: cognitive problems/inattention; hyperactivity; ADHD Index; restless/impulsive; DSM-IV hyperactive/ impulsive; oppositional. Treatment = placebo on other subscales and CTRS. Treatment > placebo on creature counting and vocabulary. Treatment = placebo on other cognitive tests.	(Sinn and Bryan, 2007; Sinn et al., 2008)
8–18 year old with diagnosed ADHD, unmedicated (85% males) (n = 75).	60 mg AA, 10 mg GLA, 558 mg EPA, 174 mg DHA, 9.6 mg Vit E or olive oil placebo.	3 months active vs placebo; 1-way crossover to active treatment for 3 months.	Investigator-rated ADHD Rating Scale-IV; CGI.	Treatment = placebo overall Treatment > placebo in subgroups with inattentive subtype and comorbid neurodevelopmental disorders.	(Johnson et al., 2009)
7–12 year old (79% male) with ADHD/ ADHD symptoms (50% diagnosed) (n = 54, 45 with bloods).	1 g EPA-rich oil, 1 g DHA rich oil or sunflower oil placebo.	3 x 3 crossover (4 months on each treatment).	CPRS, reading, writing, vocabulary, TEA-ch.	Treatment = placebo in 12-month crossover. Over 4 months erythrocyte DHA increases associated with improvements on CPRS - oppositional behavior, anxiety/ shyness – divided attention and reading. In subgroup with learning difficulties (n = 16 with blood) also on CPRS hyperactivity/ impulsivity and spelling.	(Milte et al., 2011)

Table 2. *Continued*

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
5–17 years with Autistic Disorder (81.9% male) (n = 13).	1.5 g/d n-3 PUFA (0.84 g EPA, 0.7 g DHA), Vit E or coconut oil placebo.	6 weeks parallel design.	Aberrant Behavior Checklist.	Treatment > placebo for stereotypy and hyperactivity (trends with large effect sizes). Treatment = placebo on 3 other subscales.	(Amminger et al., 2007)
6–12 year old; 25% girls children with MDD (n = 20).	2 g ethyl-EPA (96% from fish oil) or placebo, Vit E.	4 weeks parallel design, adjunctive therapy.	HDRS.	Treatment > placebo at weeks 2, 3, and 4 on HDRS score and on core depressive symptom subscales.	(Nemets et al., 2006)
Mean-age = 16.4 with ultra-high risk (UHR) for psychosis, (n = 81 individuals, 27 males, 54 females).	~1.2 g ω-3 PUFAs (0.7 g EPA, 0.48 g DHA, 7.6 mg vitamin E).	12 weeks.	Gaussian Process Classification.	Treatment > placebo on GPC	(Sinn et al., 2010)
8–14 year old, (n = 80 boys, 41 ADHD, 39 controls).	10 g of margarine daily, enriched with either 650 mg of EPA/DHA or placebo.	16 weeks.	CBCL, SWAN, TRF, fMRI.	Treatment > parent-rated attention in both ADHD control.	(Bos et al., 2015)

Abbreviations: ASQ, Conners' Abbreviated Symptom Questionnaires; CBC, Child Behaviour Checklist; CCT, Children's Colour Trails test; CGI-S, Clinical Global Impression-Severity; CPRS, Conners' Parent Rating Scales; CPT, Conners' Continuous Performance Test; CTRS, Conners' Teacher Rating Scales; DBD, Disruptive Behaviour Disorders rating scale; FADS, fatty acid deficiency symptoms; GLA, γ-linolenic acids; HDRS, Hamilton Depression Rating Scale; MABC, Movement Assessment Battery for Children; MDD, major depressive disorder; Stroop, Stroop color-word test; STM, Short-term memory; TEA-ch, Test of Everyday Attention for children; TOVA, Test of Variables of Attention; WISC-III, Wechsler Intelligence Scale for Children, version 3; WORD, Wechsler Objective Reading Dimensions; WJPEB-R, Woodstock-Johnston Psycho-Educational Battery – Revised.

primary depression. Moreover, trial duration (4–16 weeks) was not a predictor of outcomes, suggesting that EPA improvements may not be limited to the initial treatment period (Sublette et al., 2011). Albeit, it is not possible to recommend n-3 PUFAs as either a mono or adjunctive therapy in major depression as yet, though the current research is strong enough to justify further studies.

Bipolar Disorder and Schizophrenia

To date, the link between n-3 PUFA levels and bipolar disorder/schizophrenia is poorly understood. n-3 PUFAs can have a slight beneficial effect on depressive symptoms when added to an existing psychopharmacological maintenance treatment for bipolar disorder. For instance, 30 patients with bipolar disorder were randomized to receive 9.6 g/d of n-3 PUFAs (EPA 6.2 g, DHA 3.2 g) or placebo (olive oil) in addition to their ongoing usual treatment. The n-3 PUFAs patient group showed a significantly longer period of remission than the placebo group as assessed by the Kaplan-Meier survival analysis (Stoll et al., 1999). In a second study, patients with bipolar disorder were randomized to receive either 1to 2 g/d ethyl-EPA (n = 24–25, respectively) or placebo (paraffin oil, n = 26) in addition to their ongoing usual treatment (Frangou et al., 2006). The EPA treatment, without apparent benefit of 2 g over 1 g EPA, significantly improved the Hamilton Rating Scale for Depression together with the Clinical Global Impression Scale. Nevertheless, current data on the efficacy of DHA and EPA in the treatment of bipolar disorder are insufficient for us to draw definite conclusions that can guide clinical practice.

Despite the large paucity of data, it seems that n-3 PUFAs may be of help in reducing psychotic-like symptoms (Schlogelhofer et al., 2014). Eighty-one participants with subthreshold psychosis were followed for 12 months to investigate the rate of progression to first-episode psychotic disorder. Previously, one-half of the group underwent a 12-week intervention period of 1.2 g/d n-3 PUFAs or placebo. Only 5% of the n-3 PUFA group had transitioned to psychotic disorder in contrast to a 27.5 % in the control group. Moreover, n-3 PUFA intake ameliorated positive, negative, and general symptoms assessed by the Positive and Negative Syndrome Scale (Amminger et al., 2010). Overall, well-designed and executed randomized controlled trials in this field are clearly lacking, and the need for such high-quality primary research is acute. Study duration should be long enough to ensure that the n-3 PUFAs can be fully absorbed into brain cell membranes and therefore should ideally be 3 months at a minimum. Finally, the dose and composition of the n-3 PUFA supplement should be modelled on current evidence, which suggests that 1 to 2 g/d of EPA or majority EPA supplement may be the most effective form of the treatment, although further research into the efficacy of varied compositions and doses of n-3 PUFA treatment is also necessary (Table 4).

n-3 PUFAs in Elderly

Clinical studies have been carried out to elucidate the role of n-3 PUFAs in healthy older subjects (Table 5). One of the largest randomized, controlled trials to date recruited 867 cognitively healthy subjects (70–79 years old) and did not reveal improved cognitive functioning in the California Verbal Learning Test after 24 months of treatment (200 mg EPA plus 500 mg DHA) (Dangour et al., 2010), even though at the end of the study, the n-3 PUFA serum levels were higher compared with the placebo group (olive oil) and the n-3:n-6 PUFA ratio was relatively high in both groups. Moreover, all the recruited subjects showed a high cognitive functioning at the beginning of the study, as assessed by the Mini-Mental State Examination. This, the authors suggest, is the reason for the negative findings. In another study, higher administration of n-3 PUFAs (900 mg

Table 3. n-3 PUFA Impact in Healthy Adults

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
University students, mean age ~22 years (n = 56, analyzed n = 54).	2.3 g/d fish oil (1.74 g EPA + 0.25 g DHA) vs placebo (olive oil).	4 weeks.	Mini International Neuropsychiatric Interview, neutral and emotional information processing tests.	No effects on attention, memory or reaction time of attention.	(Antypa et al., 2009)
22–51 years (n = 33).	2.8 g/d fish oil (1.6 g EPA + 0.8 g DHA).	35 days.	Zimmermann and Fimm Attention Test procedure, EEG.	Improvements in sustained attention and reaction time of sustained attention.	(Fontani et al., 2005)
18–35 years (n = 159, analyzed n = 140).	(1) DHA-rich fish oil (0.45 g DHA + 0.09 g EPA)/d; (2) EPA-rich fish oil (0.2 g DHA + 0.3 g EPA)/d; (3) Placebo (olive oil).	12 weeks.	Cognitive performance and mood battery test.	No treatments effects.	(Jackson et al., 2012a)
18–29 years (n = 65).	(1) Low-dose DHA fish oil (0.45 g DHA + 0.09 g EPA)/day; (2) High-dose DHA fish oil (0.9 g DHA + 0.18 g EPA)/d; (3) placebo (olive oil).	12 weeks.	COMPASS, spatial working memory, numeric working memory, 3-back task, simple reaction time, Choice reaction time, Stroop task, RVIP.	Increased cerebral blood flow; cognitive tasks only assessed at end of study using comprehensive computerized cognitive test battery (episodic memory, working memory, attention, reaction time, executive function). Both dosages improved reaction times on 2 attention tasks, but effects were lost when correcting for multiple testing.	(Jackson et al., 2012b)
College students (mean age ~20 ± 2 years) (n = 43, analyzed n = 41).	Fish oil (0.72 g EPA + 0.48 g DHA)/d vs placebo (coconut oil).	4 weeks.	RAVLT, SCWT, TMT, PANAS.	No effects on verbal learning and memory, inhibition and executive control.	(Karr et al., 2012)
Mildly depressed adults, 18–70 years (average ± SD age 38 ± 14 years) (n = 218, analyzed n = 190).	Fish oil 1.5 g/d LC omega-3 (0.85 g DHA + 0.63 g EPA) vs placebo (olive oil).	12 weeks.	DASS, BDI, GHQ, STAXI-2.	No treatment effects.	(Rogers et al., 2008)
18–45 years (n = 228, analyzed n = 176).	Fish oil (1.2 g DHA + 0.17 g EPA)/d vs placebo (high oleic acid sunflower oil).	6 months.	Computerized cognitive test battery (episodic and working memory, attention, reaction time (RT) of episodic and working memory, and attention and processing speed).	Improvement in reaction times and working memory. RBC DHA increased by 2.6% (to ~7.9%); RBC EPA increased by 0.2% (to ~0.81%).	(Stonehouse et al., 2013)

Abbreviations: BDI, Beck Depression Inventory; DAS, Differential Ability Scales; GHQ, General Health Questionnaire; PANAS, Positive and Negative Affect Schedule; RAVLT, Rey Auditory Verbal Learning Test; RBC, red blood cell; RVIP, Rapid Visual Information Processing; SCWT, Stroop Color Word Test; STAXI-2, State-Trait Anger Expression Inventory-2; TMT, treadmill test.

DHA) for 24 weeks showed improvements in verbal recognition memory and visuospatial learning in elderly subjects with low habitual intake of DHA (Yurko-Mauro et al., 2010). Accordingly, higher concentration (1.3 g DHA and 0.45 g EPA) and longer duration (12 months) of n-3 PUFAs showed improvement in different cognitive domains of a neuropsychological battery (Lee et al., 2013). In this study, the choice of subjects could have been critical. Thirty-five healthy elderly women with mild cognitive impairment (MCI) from a low socioeconomic background were recruited. Moreover, in this group the habitual intake of n-3 PUFAs was inadequate for financial reasons. These findings are in agreement with a double-blind, randomized control trial conducted by Sinn et al. (2012) in which 40 MCI subjects (over 65 years old) with low fish intake were divided into 3 experimental groups to receive a supplement rich in EPA (1.67 g EPA plus 0.16 g DHA), DHA (1.55 g DHA + 0.40 g EPA), or LA (2.2 g). After 6 months of n-3 PUFA supplementation, depressive symptoms, assessed by the Geriatric Depression Scale, verbal fluency (Initial Letter Fluency), and self-reported physical health,were improved, especially in the DHA group. It is likely that MCI and low n-3 PUFA consumption offer the best prospect of cognitive improvement. Interestingly, DHA seems to

Table 4. n-3 PUFA Impact on Mental Illnesses in Adulthood

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
18–70 years depressed (>15 on HDRS), medicated (n = 70).	Ethyl-EPA – 1, 2, or 4 g/d or placebo.	12 weeks parallel design, adjunctive therapy.	HDRS, MADRS, BDI.	Treatment > placebo on all 3 rating scales with 1 g/d EPA – strong effects for core depressive symptoms. Treatment = placebo on 2 g and 4 g/d (nonsignificant trends).	(Peet and Horrobin, 2002)
28–73 years diagnosed MDD (85% women) HDRS score > 18 (n = 20).	2g ethyl-EPA (96% from fish oil) or placebo, Vit E.	4 weeks parallel design, adjunctive therapy.	HDRS.	Treatment > placebo at weeks 2, 3, and 4 on HDRS score and on core depressive symptom subscales.	(Nemets et al., 2002)
18–60 years outpatients with MDD; HDRS score > 18, medicated, (n = 22).	3.3 g/d n-3 PUFA (2.2 g DHA, 1.1 g EPA).	8 weeks parallel design, adjunctive therapy.	HDRS.	Treatment > placebo on HDRS.	(Su et al., 2003)
18–65 years MDD diagnosis; HDRS score > 16 (80% female) (n = 35).	2 g/d DHA or placebo.	6 weeks parallel.	MADRS, HDRS, GAFS.	Treatment = placebo on outcome measures.	(Marangell et al., 2003)
18–65 years recruited, (mean age 38), treated for current depressive episode (53% female) (n =77).	3 g/d n-3 PUFA (2.4 g DHA; 0.6 g EPA) + Vit E or olive oil placebo.	12 weeks parallel, adjunctive therapy.	HDRS short form, BDI.	Treatment = placebo on outcome measures (improvements in both groups at week 2).	(Silvers et al., 2005)
18–72 years outpatients with major depression diagnosis (n = 83, 45 males).	3 g/d n-3 PUFA (2.2 g DHA, 0.6 g EPA) + Vit E or olive oil placebo.	4 month parallel design, adjunctive therapy.	HDRS, BDI, GAFS.	Treatment = placebo on outcome measures (improvements in both groups).	(Grenyer et al., 2007)
18–40 years with MDD during pregnancy (n = 24).	2.2 g EPA + 1.2 g DHA or placebo, both with tocopherols and orange flavor.	8 weeks, parallel design.	HDRS, EPDS, GDI.	Treatment > placebo on outcome measures.	(Su et al., 2008)
18–70 years recruited, (mean age = 38); people from GP surgeries or public with mild-moderate depression (77% female) (n = 190).	630 mg EPA, 850 mg DHA, 870 mg olive oil, or olive oil placebo (both with tocopherols and orange oil).	12 weeks parallel design.	DASS, BDI, STAEI, mood using diary and visual probe task, cognitive function.	Treatment = placebo on outcome measures (improvements in both groups).	(Rogers et al., 2008)
40–55 years recruited, (mean age 49) postmenopausal women with psychological distress and depressive symptoms (n = 120).	1.5 g ethyl-EPA, 0.5 g ethyl-DHA.	8 weeks parallel design.	PGWB, HSCL-D-20, HDRS.	Treatment = placebo on all measures (improvements in both groups). Treatment > placebo in women without MDE (major depressive episode diagnosis).	(Lucas et al., 2009)
Major depression + coronary heart disease (n = 122).	930 mg ethyl-EPA + 750 mg ethyl DHA/d or corn oil placebo.	10 weeks parallel design, adjunctive therapy.	BDI-II, HDRS.	Treatment = placebo on outcome measures (improvements in both groups).	(Carney et al., 2009)
18–65 years inpatients with bipolar disorder (n = 30).	9.6 g/d n-3 PUFA (6.2 g EPA, 3.4 g DHA) or olive oil esther placebo.	4 month parallel design; adjunctive therapy.	HDRS, YMRS, CGI-S, GAS.	Treatment > placebo on GAS, HDRS and CGI; treatment = placebo on YMRS.	(Stoll et al., 1999)
57 Bipolar depressed and 59 rapid cycling (mean age 45) (n = 116, 51% male).	6 g/d ethyl-EPA or liquid paraffin placebo.	4 month parallel design; adjunctive therapy.	IDS, YMRS, CGI-BP (bipolar disorder).	Treatment = placebo on outcome measures.	(Keck et al., 2006)
Outpatients with bipolar depression + scores > 17 on HDRS, (mean age 47) (n = 75, 76% female).	1 g/d ethyl EPA (n = 24); 2 g/d ethyl EPA (n = 25) or paraffin placebo.	12 week parallel design, adjunctive therapy.	HDRS, YMRS, CGI.	Treatment > placebo on HDRS & CGI on 1 g and 2 g/d. Treatment = placebo on YMRS.	(Frangou et al., 2007)

Table 4. *Continued*

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
16–64 years presenting after act of repeated self-harm (n = 49, 65% women).	1.2 g/d EPA + 0.9 g DHA or corn oil placebo (with 1% EPA/DHA).	12 weeks parallel design in addition to standard care.	BDI, HDRS, OAS-M, IMT/DMT, PSS, DHUS.	Treatment > placebo on BDI, HDRS, PSS, DHUS. Treatment = placebo on OAS-M and IMT/DMT (hostility/aggression, memory).	(Hallahan et al., 2007)
Study 1: schizophrenic patients, PANSS score > 40, mean age 44 (n = 45). Study 2: diagnosed schizophrenia, untreated, mean age 35, (n = 30).	2 g/d EPA or corn oil placebo.	3 months parallel, single therapy unless drugs needed.	PANSS; need for antipsychotic medication.	Treatment > placebo, particularly on positive subscale; 12/12 placebo and 8/14 EPA patients took medication.	(Peet et al., 2001)
(18–65 years, M = 40; 61% male) diagnosed schizophrenia or schizoaffective disorder (n = 30).	3 g/d ethyl EPA + Vit E or mineral oil + Vit E placebo.	16 weeks parallel design, adjunctive therapy.	PANSS, CGI, MADRS, RBANS, AIMS, SARS.	Treatment = placebo on outcome measures (some showed improvements in both groups).	(Fenton et al., 2001)
18–55 years schizophrenic, treatment resistant patients, PANSS score > 10 (n = 40, mean age 45).	3 g/d ethyl-EPA or liquid paraffin placebo.	12 weeks parallel design, adjunctive therapy.	PANSS, ESRS.	Treatment > placebo on PANSS and dyskinesia subscale of ESRS. Treatment = placebo on other ESRS subscales.	(Emsley et al., 2002)
20–62 years treatment-resistant schizophrenia; PANSS > 50, (n = 115, mean age 37, 66% male).	1, 2, or 4 g/d ethyl-EPA or liquid paraffin placebo.	12 weeks parallel design, adjunctive therapy.	PANSS, LUNSERS, MADRS, AIMS, BAS, SARS.	Treatment = placebo on all rating scales; 2 g treatment > placebo for patients on clozapine (associated with ↑AA).	(Peet et al., 2002)
First-episode psychosis patients (n = 69, mean age 21, 76% male).	2 g/d ethyl-EPA or mineral oil placebo not absorbed by intestinal tract (both with Vit E).	12 weeks parallel design, adjunctive therapy.	BPRS, SANS, CDSS, CGI, GAF, SOFAS.	Treatment = placebo on all outcome measures. Treatment > placebo on CGI co-varying for duration of untreated psychosis; treatment > placebo at weeks 4–6.	(Berger et al., 2007)
13–25 years met defined risk factors for psychosis (n = 81, mean age 16, 40% male).	1.2 g/d n-3 PUFAs 0.7 g EPA, 0.48 g DHA, and 7.6 mg of vitamin E).	12 weeks.	PANSS, MADRS, GAF.	Treatment > placebo on PANSS and GAF at 12 weeks, 6 and 12 months.	(Amminger et al., 2010)
19–30 years university students (study measured aggression and executive function) (n= 41, 70% female).	1.5–1.8 g/d DHA or 97% soybean oil + 3% fish oil placebo capsules.	3 months parallel design.	P-F Study; Stroop; Dementia-detecting test.	Treatment > placebo on aggression (increased in placebo group during exam time); treatment = placebo on other measures.	(Hamazaki et al., 1996)
18–40 years females with moderately severe borderline personality disorder (n= 30, mean age 26).	1 g/d ethyl-EPA or mineral oil placebo.	8 weeks parallel design.	OAS-M; MADRS.	Treatment > placebo aggression and depressive symptoms	(Zanarini and Frankenburg, 2003)
MDD patients (n= 154).	(1) EPA 1 g/d; (2) DHA 1 g/d; (3) Placebo.	8 weeks.	HDRS-17, QIDS-SR-16, CGI-S.	Treatments and placebo improved HDRS-17, QIDS-SR-16, CGI-S.	(Mischoulon et al., 2015)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CBC, Child Behaviour Checklist; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression-Severity; DASS, Depression & Anxiety Stress Scale; DHUS, Daily Hassles & Uplifts Scale; DMT, Delayed Memory Task; ESRS, Extrapyramidal Symptom Rating Scale; GAFS, Global Assessment of Functioning Scale (revised GAS); GAS, Global Assessment Scale; HDRS, Hamilton Depression Rating Scale; HSCL-D-20, 20-item Hopkins Symptom Checklist Depression Scale; IDS, Inventory for Depressive Symptomology; IMT, Immediate Memory Task; LUNSERS, Liverpool University Neuroleptic Side-Effects Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; MDD, major depressive disorder; OAS-M, The Overt Aggression Scale, Modified; PANSS, Positive and Negative Syndrome Scale; PGWB, Psychological General Well-Being Schedule; PSS, Perceived Stress Scale; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SANS, Scale for the Assessment of Negative Symptoms; SARS, Simpson-Angus Rating Scale; SOFAS, Social and Occupational Functioning Assessment Scale; STAEI, State-Trait Anger Expression Inventory; YMRS, Young Mania Rating Scale.

Table 5. n-3 PUFA Impact in Healthy Elderly

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
70–75 years, cognitively healthy, MMSE ≥ 24 (median = 29) (n = 867, analysis on n =748).	Ethyl ester fish oil (0.2 g EPA + 0.5 g DHA)/d vs placebo (olive oil).	24 months.	CVLT.	No effect on global cognitive function, memory, processing speed, executive function, global delay score.	(Dangour et al., 2010)
60–80 years, stable MI patients, MMSE >21 (average ± SD 28 ± 1.6 points).	(1) 0.4 g/d EPA + DHA; (2) 2 g/d ALA; (3) EPA + DHA + ALA; (4) Placebo.	40 months.	MMSE.	No effect on MMSE.	(Geleijnse et al., 2012)
60–80 years, healthy women (n = 57, analyzed n = 49).	(1) 0.8 g/d DHA (algal oil); (2) 12 mg/d lutein; (3) DHA + lutein; (4) Placebo.	4 months.	Cognitive test battery measuring verbal fluency, memory, processing speed and accuracy.	Treatments (1), (2), (3) improved verbal fluency. DHA + lutein improved rate of learning and memory in 1 of 6 recall tests.	(Johnson et al., 2008)
≥60 years, MCI, MMSE = 26.4 (25–28), middle to low-socioeconomic status (n = 36, analyzed n = 35).	Fish oil (1.3 g DHA + 0.45 g EPA)/d vs placebo (corn oil).	12 months.	MMSE, RAVLT.	Improved memory (short-term memory, working memory, immediate visual memory, delayed recall).	(Lee et al., 2013)
51–72 years, healthy (n = 44, analyzed n = 38.	Fish oil (1.05 g DHA + 1.50 g EPA)/d vs placebo.	5 weeks.	Working memory.	Improved working memory. TNF-α inversely related to working memory performance.	(Nilsson et al., 2012)
>65 years, MCI, MMSE ≥ 22 (average ~27 ± 2.5) (n = 50).	(1) EPA-rich fish oil (1.67 g EPA + 0.16 g DHA)/d); (2) DHA-rich fish oil: (1.55 g DHA + 0.40 g EPA)/d; (3) Placebo (safflower oil).	6 months.	Cognitive battery.	DHA improved verbal fluency (test of fluid thinking/semantic memory). Only 1 of 11 cognitive assessments affected.	(Sinn et al., 2012)
45–77 years (average ~56 ± 8.7 years), healthy (n = 112, analyzed n = 75).	Tuna oil (0.25 g DHA + 0.06 g EPA)/d vs placebo (soybean oil).	90 days.	CDR, visual acuity.	No treatment effects.	(Stough et al., 2012)
≥65 years, cognitively healthy, median (25, 75 percentile) MMSE = 28, ranged from 23 to 30 (n = 302).	(1) Low-dose fish oil (0.26 g EPA + 0.18 g DHA)/d; (2) High dose fish oil (1.09 g EPA + 0.85 g DHA)/d; (3) Placebo (oleic acid).	26 weeks.	Cognitive test battery.	Treatment improved attention in APOE4 allele carriers. Treatment–gender interactions: Attention improved in men.	(van de Rest et al., 2008a)
50–90 years, nondemented participants with memory complaints, MMSE ≥ 27 (average ~28.5 ± 1.11) (n = 157, analyzed n = 122).	PS containing LC omega-3: 300 mg PS + 0.08 g (DHA + EPA)/d.	15 weeks.	Immediate and delayed verbal recall, learning abilities, and time to copy complex figure.	Improved verbal immediate recall. A subset of participants with higher baseline cognitive status performed better on immediate and delayed verbal recall, learning abilities and time to copy a complex figure.	(Vakhapova et al., 2010)

Table 5. *Continued*

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
50–75 years, MMSE < 26 (average ~29 ± 1.0, ranged from 26 to 30) (n = 80, z n = 65).	Fish oil 2.2 g/d LC omega-3 (1.32 g EPA + 0.88 g DHA) vs placebo (sunflower oil).	26 weeks.	Stroop Color-Word test, TMT, AVLT.	Improved executive function. Subset who showed greatest increase in n-3 index showed improved memory. Improved white matter microstructural integrity, grey matter volume in frontal, temporal, parietal and limbic areas. Improvements in executive function associated with peripheral BDNF and inversely with fasting insulin.	(Witte et al., 2014)
≥55 years (average ~70 ± 9 years), subjective memory complaints with ARCD, MMSE >26 (n = 485).	0.9 g/d DHA from algal oil vs placebo (corn + soy oil).	24 weeks.	CANTAB PAL, MMSE.	Improved visuospatial learning and episodic memory, immediate and delayed verbal recognition memory.	(Witte et al., 2014)

Abbreviations: AVLT, Auditory Verbal Learning Test; CANTAB-PAL, Cambridge Neuropsychological Test Automated Battery - Paired Associates Learning; CDR, Clinical Dementia Rating; CVLT, California Verbal Learning Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; TNF- α, tumour necrosis factor-α.

be more of benefit in both memory and cognition than EPA, or their combination, as observed in adulthood. This discrepancy could be due to the phospholipid degradation occurring at this last stage of life. Since DHA constitutes the most abundant fatty acid in the brain and due to its importance in the formation and functionality of the CNS, it is plausible to think that DHA can ameliorate cognitive performance more than other PUFAs in older subjects.

n-3 PUFAs and Alzheimer's Disease

Postmortem analysis of AD subjects shows lower n-3 PUFAs levels in the hippocampus and frontal lobe together with decreased hippocampal size (Soderberg et al., 1991; Yehuda et al., 2002). Moreover, reduced risk of senile dementia and AD has been reported to be related to higher fish consumption (Morris et al., 2003). However, no cognitive improvements were observed in subjects affected by moderate AD after 24 weeks of n-3 PUFAs (EPA 1080 mg plus DHA 720 mg) (Chiu et al., 2008). Neither has a longer trial, up to 1 year of n-3 PUFA supplementation, shown neuropsychiatric improvements in AD subjects (Freund-Levi et al., 2008). On the other hand, Yehuda et al. (1996) have shown improvements in mood, cooperation, appetite, sleep, ability to navigate in the home, and short-term memory after only 4 weeks of an ALA:LA mixture (1:4). Furthermore, within 174 AD subjects that underwent n-3 PUFA administration for a total period of 1 year, only 15% of them showed reduction in cognitive decline (Freund-Levi et al., 2006). The impact of n-3 PUFAs on mental illnesses in elderly are reported in Table 6.

n-3 PUFAs: Mechanisms of Action

Inflammation

As outlined in the previous sections, n-3 PUFAs have multiple implications in several conditions. Therefore, they are likely to act via multiple mechanisms (Figure 2). The antiinflammatory effect exerted by n-3 PUFAs represents one of the most investigated mechanisms. Moreover, chronic inflammation is now considered to be central to the pathogenesis of stress-related disorders such as depression (Barnes et al., 2016). Primarily EPA and in part DHA metabolize into antiinflammatory compounds such as leukotrienes (5 series), prostaglandins (3 series), resolvins, lipoxins, and neuroprotectin D1. Competing with n-6 PUFAs for metabolism, both EPA and DHA may interfere with the production of the n-6 PUFA arachidonic acid-derived proinflammatory eicosanoids such as prostaglandins (series 2), leukotrienes (series 4), and thromboxanes (series 2) (Das, 2006). DHA and EPA have been also shown to inhibit the release of proinflammatory cytokines, such as interferon-γ, tumour necrosis factor-α, IL-1β, IL-2, and IL-6, directly acting on the transcriptional factor NF-kB (Kang and Weylandt, 2008).

HPA Axis

n-3 PUFAs seem to play a role in the regulation of the stress-response influencing the activity of the HPA axis. It has been proposed that n-3 PUFA deficiency may induce a chronic stress state by disruption of glucocorticoid receptors (GR)-mediated negative feedback (Larrieu et al., 2014, 2016). Controversially, the same authors observed that supplementation of n-3 PUFAs (9 weeks) prevented detrimental chronic social defeat

Table 6. n-3 PUFA Impact on Mental Illnesses in Elderly

Participants	Treatment	Length of Trial	Measurements	Outcomes	References
>65 years nondepressed community dwelling adults (n = 302, mean age 70, 55% male).	1.8 g/d EPA + DHA, 400 mg/d EPA + DHA.	26 weeks.	CES-D, MADRS, GDS-15, HADQ.	Treatment = placebo on outcome measures.	(van de Rest et al., 2008b)
People with AD living in own homes, on stable treatment with acetylcholine esterase inhibitors, (n = 204, mean age 73).	1.72g DHA + 600mg EPA/ day.	6 months parallel + 1-way crossover to fish oil for 6 months.	NPI, MADRS, CGB, DAD.	Treatment > placebo on MADRS in non-apoE-4 carriers and agitation in apoE-4 carriers.	(Freund-Levi et al., 2008)
50–73 years AD patients, (n = 100, 21% females).	0.5 g ALA:LA, 1:4 ratio.	4 weeks, adjunctive therapy.	12-item quality of life questionnaire (caregiver), clinician interview.	Treatment > placebo on 12-item QOL questionnaire.	(Yehuda et al., 1996)
Nursing home residents with mild-moderate vascular dementia (n = 20, mean age 83).	4.32 g/d DHA.	12 months.	MMSE; HDS-R; clinical evaluation.	Treatment > placebo on outcome measures after 3 and 6 months, associated with DHA increases.	(Terano et al., 1999)
n = 21, mean age 68; 57% male.	240 mg/d AA+DHA or olive oil placebo.	3 months.	RBANS (Japanese version).	Treatment > placebo on immediate memory and attention.	(Kotani et al., 2006)
n = 178, mean age 74.	1.72 g DHA + 600 mg EPA/d.	6 months, adjunctive therapy.	MMSE, ADAS-cog; global function on [b]CDRS.	Treatment > placebo on MMSE in mild MCI group (n = 27).	(Freund-Levi et al., 2006)
n = 35, mean age 74, 57% female.	1.08g EPA + .72 g DHA or olive oil placebo.	6 months.	CIBIC-plus; ADAS-cog; MMSE; HDRS.	Treatment > placebo on CIBIC-plus. Treatment > placebo on ADAS-cog in MCI sub-group.	(Chiu et al., 2008)
n = 302 (mean age 70, 55% male.	1.8 g/d EPA+DHA; 400 mg/d EPA + DHA.	26 weeks.	Word Learning Task; Digit Span; Trail Making; Stroop; Verbal Fluency.	Treatment = placebo on outcome measures; treatment > placebo on attention for apoE-4 carriers and males.	(van de Rest et al., 2008a)

Abbreviations: ADAS-cog, cognitive portion of the Alzheimer's Disease Assessment Scale; CES-D, Centre for Epidemiologic Studies Depression Scale; CGB, Caregivers Burden Scale; CIBIC-plus, Clinician's Interview-Based Impression of Change Scale; DAD, Disability Assessment for Dementia scale; GDS, Geriatric Depression Scale; HADQ, Hospital Anxiety and Depression Questionnaire; HDRS, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

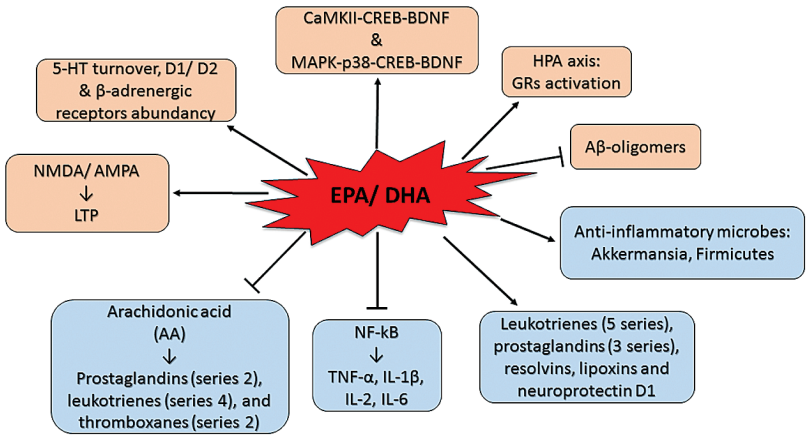


Figure 2. Omega-3 polyunsaturated fatty acid [(n-3) PUFA] mechanisms of action. Schematic representing the possible mechanisms of action of n-3 PUFAs.

stress-induced emotional and neuronal impairments by attenuating HPA dysfunction (Larrieu et al., 2014). Similarly, n-3 PUFA (EPA 12%, DHA 18%; 16 weeks) supplementation decreased stress-induced high plasma corticosterone levels and decreased anxiety- and depressive-like behaviors, as assessed by the elevated plus maze and the forced swim test, while increasing cognition as assessed by the Morris water maze in rats that underwent restrain stress (Ferraz et al., 2011). Accordingly, a study from our laboratory recently revealed n-3 PUFA (EPA 80%, DHA 20%; 12 weeks)-induced hippocampal GR activation correlated with cognitive and mood state improvements in adult female rats assessed by the novel object recognition, elevated plus maze, and forced swim test (Pusceddu et al., 2015b) (Table 7). Another study from our laboratory showed the protective effects of DHA against corticosterone-induced neuronal death as well as astrocyte overgrowth in cortical primary cultures (Pusceddu et al., 2015c). Furthermore, in the same study, we observed that the DHA was able to reverse the corticosterone-induced down-regulation of GR expression levels in neurons. The regulation of GRs may represent a novel mechanism exerted by n-3 PUFAs which is worth to investigate further.

BDNF

DHA regulation of BDNF protein levels has gotten the attention of several researchers. This is of importance, since stress-related pathologies are strongly associated with decreased levels of BDNF (Lee and Kim, 2010). Accordingly, decreased BDNF levels are found in rats fed a diet containing inadequate n-3 PUFAs (Rao et al., 2007). Indeed, DHA supplementation to cortical astrocytes cells increased cAMP response element-binding protein and BDNF protein levels via a p38 mitogen-activated protein kinase-dependent mechanism (Rao et al., 2007). Likewise, DHA-induced hippocampal calcium–calmodulin protein kinase II-cAMP response element-binding protein-BDNF pathway activation enhanced synaptic plasticity, memory, and learning in rats (Wu et al., 2008).

Monoaminergic System

Associations between monoaminergic dysfunction in stress-related pathologies and lower dietary levels of n-3 PUFAs have been observed. Male rats with a 61% decrease in brain DHA, induced by feeding a diet deficient in n-3 PUFAs from birth, exhibited lower expression of the serotonin-synthesizing enzyme tryptophan hydroxylase in the midbrain and higher serotonin turnover in the prefrontal cortex compared with controls (McNamara et al., 2010b). Controversially, feeding a diet containing ALA reversed the effect on serotonin turnover (McNamara et al., 2010b). Consistent with this, adult rats supplemented with DHA and EPA exhibited increased concentrations of serotonin in the frontal cortex and hippocampus (Vines et al., 2012). Similarly, in mice, the decrease in brain serotonin levels induced by unpredictable chronic mild stress was reversed by an n-3 PUFA diet supplementation (Vancassel et al., 2008). Likewise, the role of n-3 PUFAs in modulation of noradrenergic neurotransmission has recently received attention. Studies in cultured SH-SY5Y neuroblastoma cells suggest that either brief exposure to, or incorporation of, DHA increased basal, but not KCl-evoked release of [3H]- norepinephrine by a mechanism involving enhanced exocytosis (Mathieu et al., 2010). DHA treatment also increased the density of β-receptors on rat astrocytes in primary culture (Joardar et al., 2006). Also, the DA system is affected by variation in dietary n-3 PUFA content. Virgin females with lower tissue DHA levels had altered abundancy of D1 and D2 DA receptors in the caudate nucleus relative to virgin females with normal DHA (Davis et al., 2010). These receptor alterations have been found in rodent models of depression and are consistent with the proposed hypodopaminergic basis for anhedonia and motivational deficits in depression (Kram et al., 2002). The effects of n-3 PUFAs on adult rodents' behavior are reported in Table 7.

Glutamatergic System

It has been observed that n-3 PUFAs can regulate the functionality of the glutamatergic system, which can undergo dysregulation during aging. Indeed, n-3 PUFAs are involved in the regulation of the post-synaptic 2-amino-3-propionic acid and N-methyl-d-aspartate receptors (Nishikawa et al., 1994). This suggests that n-3 PUFAs may play an important role in the genesis of long-term potentiation, which is involved in memory formation and restoration of synaptic plasticity (Dyall et al., 2007; Lynch et al., 2007; Kelly et al., 2011). Excess glutamate can lead to excessive release of AA, which initiates a proinflammatory cascade of events involving the production of eicosanoids via the activation of inducible cyclooxigenase and lipoxigenases and the production of proinflammatory cytokines (Bazan, 2007; Farooqui et al., 2007).

Aβ Oligomers and Antiapoptosis

In vitro studies have shown DHA preventive effects against Aβ oligomer-induced neurotoxicity both in cortical and hippocampal cultures (Florent et al., 2006; Wang et al., 2010). Moreover, DHA has been found to promote cellular survival and prevent cortical neuronal apoptosis in primary cultures in a physiological condition (Cao et al., 2005) and after chronic corticosterone treatment (Pusceddu et al., 2015c). Moreover, similar results have been found in animal models of AD fed with n-3 PUFA-enriched diet (Lim et al., 2005a; Green et al., 2007). Interestingly, learning memory performance improved in Aβ-infused adult rats supplemented upon DHA intervention (Hashimoto et al., 2002; Hashimoto et al., 2005, 2009) (Table 8). These findings indicate that n-3 PUFAs decrease Aβ levels and have antioxidative stress and antiapoptosis effects, leading to neuron protection and maintenance of learning memory ability.

New Horizons: The Gut Microbiome

Parallel with these findings, we recently shed light on the role of n-3 PUFAs in regulating the gut microbiome, which is involved in a bidirectional communication with and influence over the brain both in rodents and humans (Cryan and Dinan, 2012). Indeed, there is a corpus of evidence to support the view that the gut microbiome plays an important role in stress-related psychopathologies such as depression (Dinan and Cryan, 2016). A first study conducted in our laboratory showed that EPA/DHA combination (1 g/kg/d) was able to normalize early-life stress-induced disruption of female rat gut microbiome (Pusceddu et al., 2015a). This microbial disruption seems to be mainly due to a shift in Bacteroidetes:Firmicutes, the alteration of which in human stool specimen has been revealed in depressed individuals (Jiang et al., 2015). The early-life stress-induced microbial disruption also altered abundance of members of the gut microbiome known to have inflammatory effects such as Akkermansia (Stecher et al., 2007) and Flexibacter (Frank et al., 2007), and this was correlated with alteration of the corticosterone response to acute stress. Notably, EPA/DHA administration

Table 7. Effect of n-3 PUFAs on Adult Rodent Behavior

Animals	Treatment	Length of Treatment	Measurements	Outcomes	References
C57Bl6/J mice 2nd generation.	(1) control; (2) n-3 def diet; (3) n-3 suppl diet.	3 months old.	Chronic social defeat test, open field, forced swim test.	(3) ameliorated chronic social defeat stress-induced emotional and neuronal impairments by impeding HPA axis hyperactivity.	(Larrieu et al., 2014)
C57BL6/J female mice.	(1) n-3 def diet; (2) n-3 suppl diet.	After weaning, both groups were fed with a control diet.	Social investigation, forced swim test, open field.	Anxiety-like behaviour induced by (1) was abolished by the cannabinoid agonist WIN55,212-2.	(Larrieu et al., 2012)
C57Bl/6 mice.	(1) control; (2) n-3 def diet + (1) after weaning.	Until 14 weeks old.	Open-field, object recognition, light-dark transition, elevated plus maze, social interaction tests.	(2) reduced anxiety-like behavior compared to (1).	(Palsdottir et al., 2012)
Wistar rats 2nd generation.	(1) n-3 adeq diet; (2) n-3 def diet.	Until 60 days old.	Inhibitor avoidance task, flinch-jump task, open-field, elevated plus maze.	(1) Improved inhibitor avoidance task and elevated plus maze performances compared to (2).	(Moreira et al., 2010)
Long Evans rats.	3 generations (F): (1) n-3 adeq diet; (2) n-3 def diet; (3) n-3 def till birth of 3F; (4) n-3 def till weaning of 3F; (5) n-3 def till 7 weeks of 3F.	Until 9 or 13 weeks of age.	MWM, motor activity.	(3), (4) similar MWM outcomes and DHA brain levels to (1).	(Moriguchi and Salem, 2003)
Wistar rats, 2nd generation.	(1) Control; (2) n-3 def diet; (3) same as (2) + DHA/AA at weaning.	After lactation all groups received (1).	Passive-avoidance test.	(3) reversed learning impairments observed in (2).	(Garcia-Calatayud et al., 2005)
Wistar Imamichi rats, 2nd generation.	(1) Control; (2) n-3 def diet; (3) same as (2) + DHA (300mg/kg/d).	DHA was administrated 1 week prior behavioral test.	Elevated plus maze, fear conditioning.	(3) reversed behavioral impairments observed in (2).	(Takeuchi et al., 2003)
Wistar rats, 2nd generation.	(1) Control; (2) fish oil.	2 months.	Elevated plus maze, ambulatory activity test.	(2) improved animal behaviors.	(Chalon et al., 1998)
Long Evans rats.	(1) def diet; (2) adeq diet.	15 weeks.	Forced swim test, resident intruder test, open field.	(2) Improved forced swim and resident intruder test.	(DeMar et al., 2006)
Long Evans rats.	(1) Control; (2) artificial rearing: n-3 def diet; (3) artificial rearing: n-3 adeq diet.	Until 9 weeks.	Motor activity, elevated plus-maze, Morris water maze.	(3) Improved spatial learning compared to (2).	(Lim et al., 2005b)
Long Evans rats.	(1) Control; (2) n-3 def diet; (3) same as (2) + DHA enriched diet after weaning.	56 days.	Locomotor activity, thermal stimulus.	(3) reversed behavioral impairment compared to (2).	(Levant et al., 2004)

Table 7. *Continued*

Animals	Treatment	Length of Treatment	Measurements	Outcomes	References
Long Evans rats, 2nd and 3rd generation.	(1) n-3 def diet; (2) n-3 adeq diet.	8 weeks.	Motor activity, elevated plus maze, Morris water maze.	(2) reversed behavioral impairment compared to (1).	(Moriguchi et al., 2000)
Donryu rats, 2nd generation.	(1) Control; (2) n-3 def diet; (3) same as (2) + DHA after weaning.	7 wks.	Brightness-discrimination learning test.	(3) reversed behavioural impairment compared to (2).	(Ikemoto et al., 2001)

Table 8. Effect of n-3 PUFAs in Aged Rodents

Animals	Treatment	Length of Treatment	Measurements	Outcomes	References
C57BL/6 mice.	(1) n-3: n-6 = 1: 29 ratio; (2) n-3: n-6 = 1: 3.6 ratio; (3) n-3: n-6 = 2: 1 ratio.	From age 3 to 7 months.	Open field, Barnes maze; Serum and hippocampal cytokines; Hippocampal Ki67, DCX, GFAP, IBA-1, oxo8dG/oxo8G staining.	(3) ↑ Anxiety, hippocampal dependent spatial memory vs (1); (3) ↑ hippocampal PUFA, ↓ hippocampal and serum TNF-α, ↑ KI67 and DCX vs (1);	(Grundy et al., 2014)
C57B6/J mice.	Gavage: (1) n-3 PUFA mixture (440 mg/kg); (2) olive oil; (3) Control.	From 19 to 27 months.	MWM, NOR, SYM, CFC, EPM; BrdU, DCX, GFAP, Ki67, Iba-1; DG, CA1, CA3 volume, cell numbers, neurons, dendrites.	(1) ↑ NOR, MWM, SYM, CFC; (1) ↑ neurogenesis, dendritic arborization of DG newborn neurons, hippocampal volumes and cell density, microglia. (1) ↓ apoptosis, astrocytosis.	(Cutuli et al., 2014)
Sprague-Dawley rats.	Gavage: (1) Control (2) Control + fish oil; (3) Deficient; (4) Deficient + fish oil.	Max 140 days.	MWM.	(3) ↓ MWM performance; (4) partially ↑ MWM; (2) ↑ MWM.	(Chung et al., 2008)
SAMP8 mice 2nd generation.	(1) n-3 def diet; (2) n-3 enriched diet.	Until 28 weeks old.	Sidman active avoidance task, light and dark discrimination learning test.	(2) ↑ Performance in discrimination learning test.	(Umezawa et al., 1995)
Wistar rats.	(1) control; (2) DPA or EPA enriched diet.	56 days.	Morris water maze; LTP, caspase-3, microglial activity.	(2) ↑ Spatial learning, ↓ microglial activation.	(Kelly et al., 2011)
C57B6/J mice.	(1) control; (2) DHA enriched diet. (3) n-3 def diet + DHA enriched at age 8 months.	Entire lifespan.	Open field, light/dark test, Morris water maze	(2) ↑ Anxiety-like behavior and memory compared to (3).	(Carrie et al., 2002)
CD1 mice 2nd generation.	(1) n-3 def diet; (2) n-3 enriched diet.	Until 23 months.	Forced swim test, Y-maze test, cytokines.	(2) ↓ Depressive-like behavior.	(Moranis et al., 2012)
Wistar rats 3rd generation.	(1) n-3 def diet; (2) n-3 def diet + oral DHA for 10 weeks prior behavior.	10 weeks.	8-arm radial maze	(2) ↑ Memory compared to (1).	(Gamoh et al., 2001)

Abbreviations: LTP, long-term potentiation; MWM, Morris water maze; NOR, novel object recognition; EPM, elevated plus maze; CFC, contextual fear conditioning; SYM, spatial Y-maze; DCX, doublecortin; DG, dentate gyrus; CA1, cornu ammonis 1; CA3, cornu ammonis 3.

was beneficial for restoring members of the gut microbiome with immunoregulatory functions, suggesting a possible prevention to an overly robust stress-induced inflammatory response that may contribute to the onset of mental illnesses. Subsequent to this first evidence, a second study revealed a correlation between neurobehavioral outcomes and gut microbiome composition in mice fed with diets containing altered n-3 PUFA status (Robertson et al., 2016). Although the impact of n-3 PUFAs

on the gut microbiome is still at its infancy, understanding the mechanisms behind their potential interplay may open up novel attractive strategies to prevent the onset of psychopathologies.

Conclusions

Despite strong evidence pointing out an inverse correlation between n-3 PUFAs levels and quality of life/psychiatric diseases, the introduction of n-3 PUFAs in clinical practice is still in its infancy. The primary reason for this is largely because of inconsistent and inconclusive randomized clinical trials. Inadequate dosing, inadequate duration, and lack of placebo control are major weaknesses in many studies. Use of insensitive and inappropriate clinical rating measures is another cause for concern. Nonetheless, there are some clear recommendations emerging. Low habitual intake of n-3 PUFAs is associated with poorer mental health and, in children, low literacy ability. A major finding is the positive evidence within older healthy adults with age-related cognitive decline. They benefit most from consuming n-3 PUFAs, particularly DHA. However, with the development of senile dementia or Alzheimer's disease, n-3 PUFAs lose efficacy. While MDD still remains one of the most discussed and investigated forms of psychopathology, a clear identification of n-3 PUFAs as a treatment or adjunct therapy has not yet emerged. The evidence base is still weak and RCTs have been inconsistent with many study design limitations. Hence, a major challenge ahead is to design and conduct rigorous RCTs to provide proper evidence of n-3 PUFA application in clinical conditions, such as MDD. Further studies are also required to definitively demonstrate that n-3 PUFAs reduce the risk of transit from a prepsychotic state to overt schizophrenia. On the other hand, n-3 PUFAs are safe and well-tolerated supplements with only mild transient side effects. Moreover, being considered as a "natural remedy" and due to their relatively low cost, n-3 PUFAs represent an appealing option for individuals. While the evidence is not entirely conclusive to make specific recommendations for dietary intake of n-3 PUFAs, the limited ability of synthesis of n-3 PUFAs de novo and their critical role in brain development and functioning make it reasonable to include n-3 PUFAs in a balanced daily diet.

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