

*Current Perspective***Possibility of Polyunsaturated Fatty Acids for the Prevention and Treatment of Neuropsychiatric Illnesses**Michio Hashimoto<sup>1,\*</sup>, Motoko Maekawa<sup>2</sup>, Masanori Katakura<sup>1</sup>, Kei Hamazaki<sup>3,4,5</sup>, and Yutaka Matsuoka<sup>4,5,6</sup><sup>1</sup>Department of Environmental Physiology, Shimane University Faculty of Medicine, Izumo, Shimane 693-8501, Japan<sup>2</sup>Laboratory for Molecular Psychiatry, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako City, Saitama 351-0198, Japan<sup>3</sup>Department of Public Health, Faculty of Medicine, University of Toyama, 2630 Sugitani, Toyama City, Toyama 930-0194, Japan<sup>4</sup>Department of Clinical Epidemiology, Translational Medical Center, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Tokyo 187-8551, Japan<sup>5</sup>CREST, Japan Science and Technology Agency, 3256 Midoricho, Tachikawa, Tokyo 190-0014, Japan<sup>6</sup>Department of Psychiatry, National Disaster Medical Center, 3256 Midoricho, Tachikawa, Tokyo 190-0014, Japan

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**Abstract.** Increasing evidence from the fields of neurophysiology and neuropathology has uncovered the role of polyunsaturated fatty acids (PUFA) in protecting neuronal cells from oxidative damage, controlling inflammation, regulating neurogenesis, and preserving neuronal function. Numerous epidemiological studies have shown that deficits in the dietary PUFA docosahexaenoic acid and eicosapentaenoic acid are associated with the onset and progression of neuropsychiatric illnesses such as dementia, schizophrenia, depression, and posttraumatic stress disorder (PTSD). Recent clinical trials have offered compelling evidence that suggests that n-3 PUFA could reduce depressive, psychotic, and suicidal symptoms, as well as aggression. Although many studies have had the validity of their results questioned because of small sample size, several studies have indicated that n-3 PUFA are useful therapeutic tools for the treatment of dementia, major depression, bipolar disorder, and PTSD. These findings suggest that the pharmacological and nutritional actions of n-3 PUFA may be beneficial in certain neuropsychiatric illnesses. This review article outlines the role of PUFA in neurodevelopment and the regulatory mechanisms in neuronal stem cell differentiation and also the possible use of PUFA as a prescription medicine for the prophylaxis or treatment of neuropsychiatric illnesses such as dementia, mood disorder, and PTSD.

**Keywords:** n-3 polyunsaturated fatty acid, docosahexaenoic acid, eicosapentaenoic acid, neuropsychiatric illness

**1. Introduction**

The brain contains large amounts of fatty acids, 50% of which are polyunsaturated fatty acids (PUFA) and predominantly docosahexaenoic acid (DHA, C22:6n-3) and arachidonic acid (AA, C20:4n-6). Owing to their long carbon chains and high degree of unsaturation, DHA and AA confer specific properties on the lipid bilayer that make it dynamic and flexible, implying that

these fatty acids affect brain functions by altering the biophysical properties of cell membranes. DHA and AA can be synthesized from other n-3 and n-6 precursor fatty acids, namely,  $\alpha$ -linolenic acid (ALA, C18:3n-3) and linoleic acid (LA, C18:2n-6), respectively, which must be obtained from our diet since humans lack the enzymes required for their synthesis. ALA and LA, as well as eicosapentaenoic acid (EPA, C20:5n-3), are found only in trace amounts in the brain (< 1.0%) and the amount of DHA that is synthesized from ALA is limited.

Because most DHA and AA are incorporated into brain structures during the third trimester of prenatal development and the early post-natal period, they are

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vital for neurological development. In addition, there is a growing body of evidence indicating a role for these fatty acids in mental health throughout life. The half-life of DHA in the human brain is approximately 2.5 years (1), suggesting that dietary n-3 PUFA deprivation for only a few months might lead to functional brain changes and the pathophysiology of several major psychiatric disorders. This is supported by evidence from epidemiological surveys, case-control n-3 PUFA composition studies, prospective observational and n-3 PUFA intervention studies, and neurological studies. Furthermore, an acute change in dietary DHA may selectively affect the composition of newly formed neuronal membranes in discrete regions of the adult brain or influence synaptic remodeling and neurogenesis. In the adult human, the newly formed neurons may help to shape existing neural circuitry, thereby permitting rapid changes in neuropsychiatric function in response to n-3 PUFA prescription. This review article will focus on the role of PUFA in neurodevelopment and in the regulation of neural stem cell (NSC) differentiation and also review the possible benefits of PUFA for the prophylaxis and treatment of neuropsychiatric illnesses, including dementia, mood disorder, and posttraumatic stress disorder (PTSD).

## **2. Brain development origin hypothesis for psychoses caused by PUFA deficiency**

The “neurodevelopmental hypothesis of schizophrenia” attributes subtle insults that occur during the early brain developmental period as increasing the risk for the subsequent manifestation of clinical symptoms. In this neurodevelopmental theory, the abnormal brain development is caused by a combination of genetic and environmental factors. The well-known epidemiological data supporting this neurodevelopmental hypothesis are those of the “Dutch Hunger Winter” (1944 – 1945) and the Chinese famine of 1959 – 1961. In the Dutch Hunger Winter, the cohort, who were in the second trimester of their mother’s pregnancy during the famine, showed an increased incidence of schizophrenia in later life (2). Data from the Chinese famine have bolstered the connection between malnourishment in pregnant women and increased risk of schizophrenia in their offspring (3). Several candidate micronutrients have thus been suggested as potential risk factors for schizophrenia. These nutrients include folate, essential fatty acids, retinoids, vitamin D, and iron (4).

We are particularly interested in the possibility that essential fatty acids play critical roles in brain development. DHA is the primary structural fatty acid in the brain, comprising 25% – 30% of the structural fatty acids in the gray matter. Therefore, a deficiency in essential

fatty acids during development may cause some functional impairment in brain development. In addition, Yoshikawa’s group recently reported that the *Fabp7* gene (coding fatty acid binding protein 7) is associated with dampened “sensorimotor gating” function, which is reflected by an impaired prepulse inhibition status in mice (5) and is genetically associated with schizophrenia (5). FABP proteins constitute a family of small, highly conserved, cytoplasmic proteins that bind long-chain fatty acids and other hydrophobic ligands. FABPs are thought to play roles in fatty acid uptake, transport, and metabolism (6). Of the FABPs/Fabps, FABP7/*Fabp7* is known to be abundantly expressed in the neurons of early differential stages. Therefore, FABP7/*Fabp7* could be one of the molecules connecting nutrients (fatty acids) and phenotypic outcome.

## **3. Regulatory mechanisms of PUFA in neural stem and progenitor cell differentiation**

The enhancement of hippocampal neurogenesis is an important tool for treating neuropsychiatric illnesses such as schizophrenia, depression, PTSD, and Alzheimer’s disease (AD) (7). PUFA, especially n-3 PUFA, have been reported to prevent or treat these illnesses, as we discuss below. Therefore, we hypothesized that n-3 PUFA could at least partially affect neuropsychiatric illness through neurogenesis.

Long-term DHA oral administration has prevented or ameliorated learning and memory ability loss in AD model rats and aged rats (8). Furthermore, it has increased the neuronal differentiation of both newborn cells in the rat hippocampus and cultured NSCs (9). Several research groups have subsequently reported n-3 PUFA-induced neurogenesis. On the other hand, AA, an n-6 PUFA, was reported to increase the number of newborn cells in the dentate gyrus of the hippocampus (10) and the number of neurospheres of neurogenic NSCs (11). However, the exact mechanisms of action are not fully understood.

Katakura et al. (12) reported the effects of DHA, EPA, and AA on the differentiation, expression of basic helix-loop-helix transcription factors (*Hes1*, *Hes6*, and *NeuroD*), and cell cycle of cultured NSCs. DHA decreased the mRNA levels of *Hes1* (an inhibitor of neuronal differentiation) and increased *NeuroD* and *Map2* mRNA and *Tuj-1* (a neuronal marker)-positive cells, indicating that DHA induced neuronal differentiation. EPA increased the mRNA levels of *Hes1*, *Hes6* (an inhibitor of *Hes1*), *NeuroD*, and *Map2*, as well as *Tuj-1*-positive cells, indicating that EPA also induced neuronal differentiation. Treatment with AA decreased *Hes1* mRNA, but did not affect *NeuroD* and *Map2* mRNA levels, and also did not affect the number of

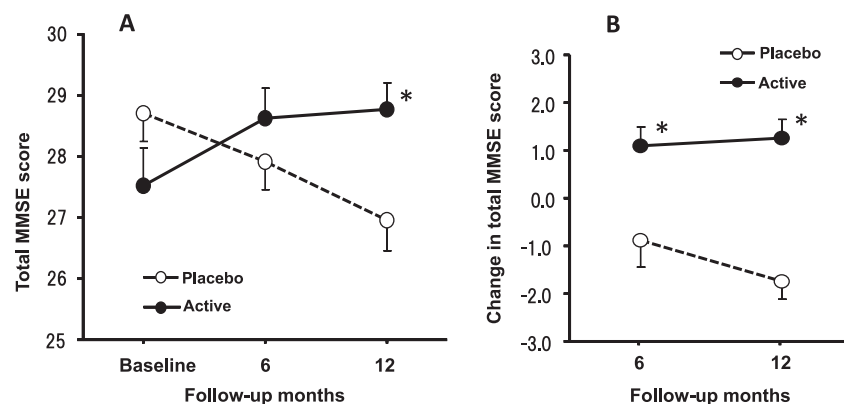
Tuj-1-positive cells. DHA and EPA, but not AA, increased the mRNA levels of the cyclin-dependent kinase inhibitors p21 and p27, indicating that DHA and EPA induced cell cycle arrest. Taken together, these results suggest that EPA is involved in neuronal differentiation in NSCs by mechanisms distinct from those of DHA, while AA does not affect this neuronal differentiation. Little is known, however, about upstream mechanisms regulating helix-loop-helix transcription factors by n-3 PUFA. Therefore, the possible role of the activation of PUFA-interacting proteins, such as receptors or binding proteins, and/or PUFA metabolite formation in PUFA-induced neuronal differentiation of NSCs needs to be further investigated.

#### 4. Role of n-3 PUFA in dementia

Growing evidence from observational studies suggests that moderate fish consumption as a proxy for n-3 PUFA intake is associated with a reduced risk of impaired cognitive function. Moreover, low DHA and n-3 PUFA levels have been detected in the plasma and brains of the elderly and patients with AD (13). Despite the promising findings of epidemiological studies, little effect of n-3 PUFA on AD has been observed in clinical studies. In a randomized control trial of n-3 PUFA supplementation, beneficial effects on cognitive performance were not observed between the treated and placebo groups; however, analyses of subgroups of mildly affected individuals [Mini-Mental State Examination (MMSE) score > 27] did show a benefit from n-3 PUFA treatment (14). In a preliminary randomized, double-blind, placebo-

controlled study, Chiu et al. (15) showed improvement of cognitive function in patients with dementia treated with n-3 PUFA. Additionally, in a 2-year randomized, double-blind, placebo-controlled trial of n-3 PUFA supplementation, Hashimoto et al. (16) reported that even in healthy elderly Japanese ( $n = 111$ ,  $72.4 \pm 7.7$  years) with very mild dementia, who consume more fish than elderly people in the West, long-term daily dietary DHA (1720 mg/day) and EPA (407 mg/day) supplementation had beneficial effects against age-related cognitive decline. According to their responses to the MMSE, the subjects were also grouped as responders (47.5%) and nonresponders (52.5%), and the mean changes in the total MMSE scores from baseline to month 12 were significantly greater in the active group of responders (Fig. 1). These results suggest that long-term dietary n-3 PUFA supplementation was effective for some, but not all, healthy elderly people with very mild dementia.

Several mechanisms have been postulated for the possible protective role of n-3 PUFA in dementia. DHA is a key component of membrane phospholipids in the brain, and dietary DHA has been suggested to improve neuronal development; restore and enhance cognitive functions including neuronal plasticity, synaptogenesis, and neurogenesis; and increase neuronal resistance to various types of insults such as amyloid-induced oxidative stress (8). Nonesterified DHA and/or the oxidative products of n-3 PUFA, such as protectin D1 and resolvins, act as key cellular inhibitory mediators of oxidative stress, bronchial constrictions, vascular response, thrombosis, inflammation, allergy, and immunity and may thereby influence risks for vascular dementia and/or



**Fig. 1.** Time course of total Mini-Mental State Examination (MMSE) scores (A) and mean changes in total MMSE (B) scores from baseline to the 12th month in the placebo and active groups of the responders (16). \* $P < 0.05$  vs. the placebo group. Bars denote standard error. Participants in both groups were instructed to consume two fish sausages daily for 12 months. Each fish sausage for the active group ( $n = 20$ ) contained 860 mg DHA and 204 mg EPA, whereas each fish sausage for the placebo group ( $n = 28$ ) contained olive oil in addition to 48 mg DHA and 12 mg EPA. Both groups were subdivided according to the mean changes in total MMSE scores over 12 months as follows: responders, an increased or unchanged total MMSE score; nonresponders, reduced total MMSE score.

AD (8, 17, 18). DHA might also modify the expression of genes that regulate a variety of biological functions potentially important for cognitive health, including those related to neurogenesis and neuronal function (8). Furthermore, DHA directly inhibits the formation of the neurotoxic A $\beta$  oligomer in vitro (19), and in vivo studies have demonstrated that oral administration of DHA decreases the amyloid burden in the cortico-hippocampal tissues of Amyloid  $\beta$  (A $\beta$ )-infused AD model rats (20) and in the hippocampus of the APPsw (Tg2576) transgenic AD model mice (21), suggesting that chronic dietary DHA supplementation could alter the amyloid burden in the brain.

In a more recent study using induced pluripotent stem cells (iPSC) from familial and sporadic AD patients, DHA treatment alleviated intracellular A $\beta$  oligomer-induced cellular oxidative stress in the iPSC-derived neurons. Interestingly, one of two sporadic AD neural cell lines accumulated intracellular A $\beta$  oligomers and showed cellular phenotypes that could respond to DHA (22). This result may explain why DHA treatment was effective for some AD patients, those with the intracellular A $\beta$  oligomer-associated AD type, and why dietary n-3 PUFA supplementation was effective for responders in our 2-year clinical trial (16, Fig. 1). However, the timing (i.e., the stage of disease development) for starting the treatment would be another critical factor to consider.

## 5. The role of n-3 PUFA in mood disorder

In 1998, Hibbeln (23) discovered an inverse association between fish consumption and the annual prevalence of major depression in an ecological study. Since this discovery, many epidemiological (24) and clinical studies (25, 26) into n-3 PUFA and depression have been reported.

Abnormal fatty acid compositions in the peripheral tissues (e.g., plasma, serum, and red blood cells) of patients with depression have been reported extensively, and a meta-analysis revealed that n-3 PUFA levels are significantly lower in depressive patients (24). Interestingly, patients with depression who are diagnosed by the Diagnostic and Statistical Manual of Mental Disorders (DSM) system seem to have much lower n-3 PUFA than individuals with less strictly defined depressive symptoms.

Many scientists have also searched for alterations in fatty acids in postmortem brains from patients with psychiatric disorders (see our review, ref. 27). The frontal cortex is of particular interest in this field, and it seems to show a significant decrease in DHA in patients with major depression and bipolar disorder,

specifically in the orbitofrontal cortex. Other regions, including the anterior cingulate cortex, hippocampus, amygdala, caudate, and entorhinal cortex, showed almost no changes in DHA. However, due to the cross-sectional nature of the study, the cause and effect relationship could not be established.

A few large cohort studies have been performed to investigate the relationship between fish intake and depression. Fish intake appears to help prevent depression in women, but not in men. The most recent meta-analysis of randomized controlled trials revealed that patients with DSM-defined major depressive disorder were successfully treated with supplements containing  $\geq 60\%$  EPA, but not with those containing EPA  $< 60\%$  (25). According to a recent meta-analysis of the pooled results from five clinical trials of bipolar disorder, significant favorable effects of n-3 PUFA were observed on bipolar depression, but not on bipolar mania (26).

The reason why EPA is more effective than DHA in combating major depressive disorder is still unknown. However, one of the mechanistic underpinnings may involve anti-inflammation. Inflammation is known to be an important biological event that may increase the risk of major depressive episodes (28). EPA has a stronger anti-inflammatory effect than DHA (29). To support this view, three of the five studies listed in the category “EPA  $< 60\%$ ” in the meta-analysis mentioned above (25) contained more than 70% DHA. Furthermore, a recent study comparing the efficacy of EPA with that of DHA revealed greater efficacy of the former than the latter or placebo as an adjunctive treatment in combating mild-to-moderate depression (30).

In summary, n-3 PUFA seem to be beneficial in preventing and ameliorating depression. However, due to the considerable heterogeneity of the studies, additional large cohort studies and well-conducted clinical trials into depression are warranted.

## 6. Possibility of preventing PTSD with n-3 PUFA

Kitamura et al. (31) showed that the level of hippocampal neurogenesis could be modulated and was associated with a causal relationship between adult neurogenesis and the hippocampus-dependent period of fear memory in adult rodents. Administration of DHA promotes both the maturation of neurons and hippocampal neurogenesis in adult rats (9). Moreover, fat-1 transgenic mice, which have enriched levels of DHA in the brain because they can convert n-6 to n-3 PUFA, exhibit enhanced hippocampal neurogenesis (32). Taking these findings together, we have proposed that promoting adult neurogenesis by n-3 PUFA supplementation early in the transition period might facilitate



clearance of fear memory from the hippocampus and consequently minimize PTSD symptoms (33).

Support for the ability of n-3 PUFA to minimize subsequent PTSD symptoms comes from two studies by Matsuoka's group (34, 35). First, they recruited 15 consecutive patients admitted to the intensive care unit of a Japanese general hospital immediately after accidental injury (34). Patients received n-3 PUFA capsules containing 1470 mg DHA and 147 mg EPA daily for 12 weeks. The primary efficacy variable was scored on the Clinician-Administered PTSD Scale (CAPS). n-3 PUFA administration was well tolerated and resulted in a significantly increased DHA concentration in erythrocytes. Compared with the hypothetical mean in their previous cohort study, n-3 PUFA resulted in a significantly reduced mean CAPS total score (11 vs. 25,  $P = 0.03$ ) over the 12-week period. Significant differences in erythrocyte DHA concentrations were confirmed between weeks 0 and 12 (mean percentage of total fatty acids:  $5.9 \pm 1.4$  vs.  $8.4 \pm 1.7$ ,  $P < 0.001$ ). We also found that the increased changes seen in serum brain-derived neurotrophic factor (BDNF) levels during the trial might be associated with reduced PTSD symptoms on follow-up (36).

Second, the group (35) emergently conducted a single-blind, randomized, parallel-group trial in April 2011 in 172 rescue workers who were deployed during the acute disaster phase of the Great East Japan Earthquake to determine whether n-3 PUFA supplementation can attenuate PTSD symptoms. Participants were randomly assigned to an n-3 PUFA (1568 mg DHA and 157 mg EPA daily for 12 weeks) plus psychoeducation group or a psychoeducation alone group. The primary outcome was total score on the Impact of Event Scale-Revised (IES-R) at 12 weeks. When adjusted for age, sex, and IES-R score at baseline, no significant difference in

primary outcomes were seen between the two groups. Remarkably, the change in the IES-R score for women in the two groups from baseline to 12 weeks was  $-3.9$  (95% CI:  $-7.5$  to  $-0.3$ ;  $P = 0.04$ ) when adjusted for the IES-R scores at baseline. In contrast, that for men was  $0.2$  (95% CI:  $-2.2$  to  $2.7$ ;  $P = 0.86$ ).

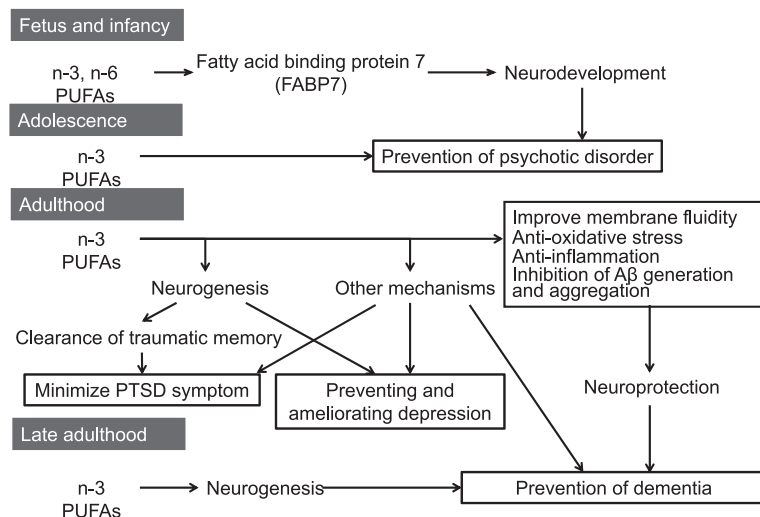
No definitive conclusion can be drawn from these trials because of their design. However, n-3 PUFA may offer a safe strategy for preventing PTSD in women that does not require individualized care by psychiatric professionals.

## 7. Summary

Most evidence suggests that n-3 PUFA act on some mechanism involved in the pathophysiology of neuropsychiatric illness (Fig. 2). However, at the moment, those involved in the neuropsychiatric field cannot yet say whether PUFA deficiency is the cause of these conditions themselves or whether the n-3 PUFA are truly effective drugs for neuropsychiatric illnesses. Likewise, the issue of whether DHA, EPA, or a combination of the two is more effective in the treatment of neuropsychiatric illness remains to be clarified. The mechanism of action of the n-3 PUFA, particularly its neurodevelopmental and regulatory actions on the differentiation of NSCs, merits further investigation. Future experimental studies should aim to identify the specific molecular mechanism and clinical research should aim to conduct preventive intervention studies with large sample sizes.

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**Fig. 2.** Preventive effects of PUFAs for neuropsychiatric illnesses in each life stage. Other mechanisms include vasodilatation, anti-thrombotic effects, cerebral blood flow increase, synaptogenesis promotion, BDNF increase, and neurotransmitter release regulation. Aβ, Amyloid β; PTSD, posttraumatic stress disorder; PUFA, polyunsaturated fatty acids.

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