Review

Dietary ω-3 fatty acid supplementation for optimizing neuronal structure and function

Stephen C. Heinrichs

Department of Psychology, Regis College, Weston, MA, USA

Direct actions of ω-3 polyunsaturated fatty acids (PUFAs) on neuronal composition, neurochemical signaling and cognitive function constitute a multidisciplinary rationale for classification of dietary lipids as "brain foods." The validity of this conclusion rests upon accumulated mechanistic evidence that ω-3 fatty acids actually regulate neurotransmission in the normal nervous system, principally by modulating membrane biophysical properties and presynaptic vesicular release of classical amino acid and amine neurotransmitters. The functional correlate of this hypothesis, that certain information processing and affective coping responses of the central nervous system are facilitated by bioavailability of ω-3 fatty acids, is tentatively supported by developmental and epidemiological evidence that dietary deficiency of ω-3 fatty acids results in diminished synaptic plasticity and impaired learning, memory and emotional coping performance later in life. The present review critically examines available evidence for the promotion in modern society of ω-3 fatty acids as adaptive neuromodulators capable of efficacy as dietary supplements and as potential prophylactic nutraceuticals for neurological and neuropsychiatric disorders.

1 Introduction

The statement that dietary supplementation with ω-3 fatty acids confers significant benefits as a neuromodulatory nutraceutical has achieved the status of truism as a consequence of extensive repetition and dissemination in scientific, news and trade journals. The validity of this claim as it applies to healthy children and adults is largely untested, however, and is based upon extension and elaboration of the very well documented neurotropic actions of ω-3 fatty acids and their highly reproducible recovery-of-function actions in the context of neurological disorders of the brain as well as in instances of prior ω-3 fatty acid deficiency. Accordingly, the present review compiles and examines critically recent pre-clinical and clin-ical evidence of putative cognitive enhancing actions of ω-3 fatty acids exerted in the normal, undamaged, and nutritionally replete nervous system as well as therapeutic efficacy of ω-3 fatty acid supplementation in recovery-of-function and ω-3 fatty acid repletion-following-deprivation studies.

Three experimental contexts within which the biological relevance of fatty acids are typically explored have been clearly delineated in the schematic diagram of Fig. 1. The first classification into which relevant findings and literature can be grouped is labeled "dietary deficiency" in order to describe a set of findings in which the key independent variable is imposed deficiency of ω-3 fatty acids in the diet. Well-known dietary deficiency findings include the demonstration that inadequate intake of thiamine (vitamin B_1) leads to the wasting disorder, beriberi, and that inadequate intake of sodium leads to salt hunger. The second cluster of experimental findings that can be labeled "neurological deficiency" (Fig. 1) describes pathological depletion of ω-3 fatty acids from the neural tissue depots themselves. A well-researched example of the neurological deficiency scenario is reflected in Parkinson's disease wherein a decline in brain dopamine content is transiently reversible by dietary supplementation

Correspondence: Dr. Stephen C. Heinrichs, Regis College Psychology Department, SB103 235 Wellesley Avenue, Weston, MA 02390, USA
E-mail: stephen.heinrichs@regiscollege.edu
Fax: +1-781-768-8339
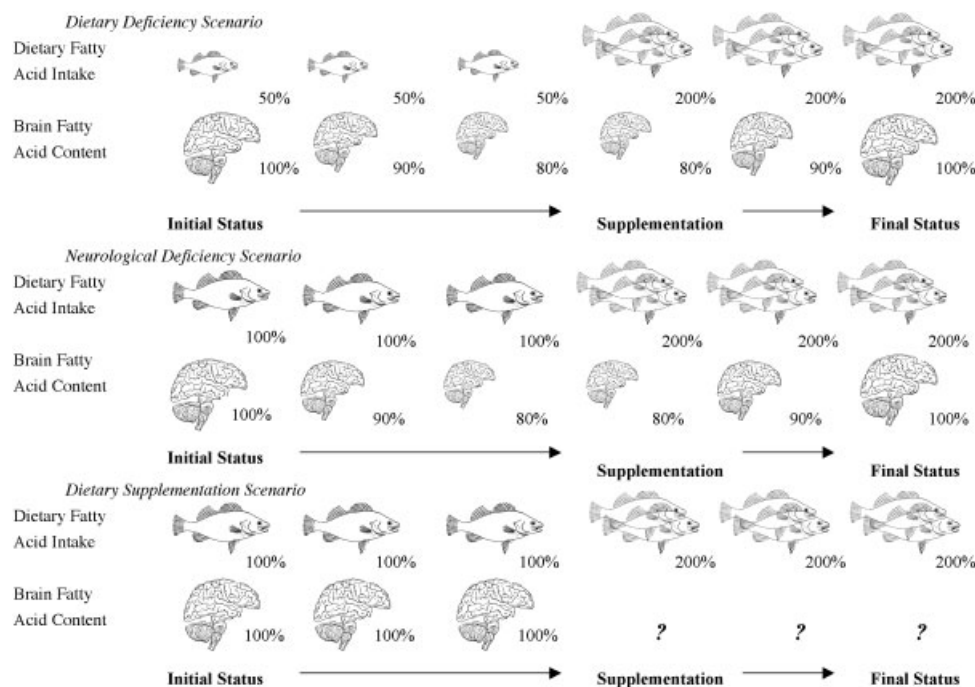
Figure 1. Schematic diagram depicting three separate experimental strategies for assessing the biological relevance of dietary ω-3 fatty acid supplementation. The first row exhibits a hypothetical scenario in which restriction of proper fatty acid intake provokes a neuro-biological deficiency that is reversed subsequently by dietary ω-3 fatty acid supplementation. Dietary fatty acid deficiency, depicted in the diagram as a small fish which provides only 50% of the recommended daily requirement, depletes the brain of fatty acid content depicted in the diagram as neural surface area, which shrinks from 100>90>80% over time; following dietary fatty acid supplementation depicted as two full sized fish which provide 200% of the recommended daily requirement, neural fatty acid content recovers from 80<90<100% over time. The second row exhibits a hypothetical scenario in which idiopathic depletion of ω-3 fatty acid components necessary for neurobiological integrity and signaling is reversed subsequently by dietary ω-3 fatty acid supplementation at supraphysiological levels well above those necessary for dietary repletion. Depletion of brain fatty acid content is depicted in the diagram as neural surface area which shrinks from 100>90>80% over time while dietary fatty acid repletion is maintained as depicted by a full-sized fish, which provides 100% of the recommended daily requirement; following dietary fatty acid supplementation depicted as two full sized fish which provide 200% of the recommended daily requirement, neural fatty acid content recovers from 80<90<100% over time. The third row exhibits a hypothetical scenario in which the focus is on potential biological consequences of dietary ω-3 fatty acid supplementation at supra-physiological levels in normal, healthy organisms. Initial state dietary and brain fatty acid repletion at 100% of normal, healthy levels is depicted in the diagram as full sized fish and neural surface areas; in this repletion context, dietary fatty acid supplementation over time has uncertain consequences for brain fatty acid content as depicted in the diagram by question marks. The fish image proportions and corresponding percentages reflect dietary fatty acid levels with 100% constituting repletion. The brain image proportions and corresponding percentages reflect neural fatty acid content with 100% constituting the unadultered norm in healthy organisms.

with dopamine precursors (*e.g.* dopa). The third context in which efficacy of dietary fatty acids is commonly assessed is the so-called "dietary supplementation" context (Fig. 1) in which normal, health adults incorporate increased amounts of lipid in the diet in the absence of explicit fatty acid or neurological deficiencies. A well-studied example of efficacious dietary supplementation in the context of cognitive enhancement is the timely intake of glucose or other simple sugar in conjunction with performance of an episodic learning/memory task. The present review evaluates evidence for neuromodulatory efficacy of dietary fatty acids within these three separate dietary deficiency, neurological deficiency and dietary supplementation contexts.

Having defined three dietary deficiency, neurological deficiency and dietary supplementation categories of experimental evidence of ω-3 biological efficacy, it is a daunting task to

assign clinical findings unambiguously to a single scenario. There is certainly no standardized practice of assessing plasma or tissue fatty acid levels which would be necessary to assess baseline ω-3 repletion relative to the consequences of the experimental manipulation at a later, post-treatment time point [1]. Similarly, the lack of standardization of dose of fatty acid administered, formulation of fatty acids within a foodstuff, duration of fatty acid administration or developmental stage during which fatty acids are first introduced raises the possibility that false-negative results could result from sub-optimal conditions [2]. Moreover, blinding may be compromised in randomized, placebo-controlled studies if participants are able to detect the flavor of fish extract, for example [3]. Accordingly, evidence derived from relevant animal models in which circumstances of ω-3 exposure are well controlled will introduce many of the following sections.

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1.1 Neurobiology of essential fatty acids

The brain contains a higher concentration of lipids than any other organ, excluding adipose tissue. The majority of dry weight in an adult brain is composed of lipids, 35% of which are polyunsaturated fatty acids (PUFAs) such as ω-3 and ω-6 long chain fatty acids [4]. Certain fatty acids are termed "essential" when animals cannot synthesize the nutrient which is nevertheless required for proper nutrition [5]. Ingested essential fatty acids can be progressively lengthened and desaturated by enzymes (Fig. 2) in order to form many other fatty acids required by the body [4]. ω-3 and ω-6 fatty acids are
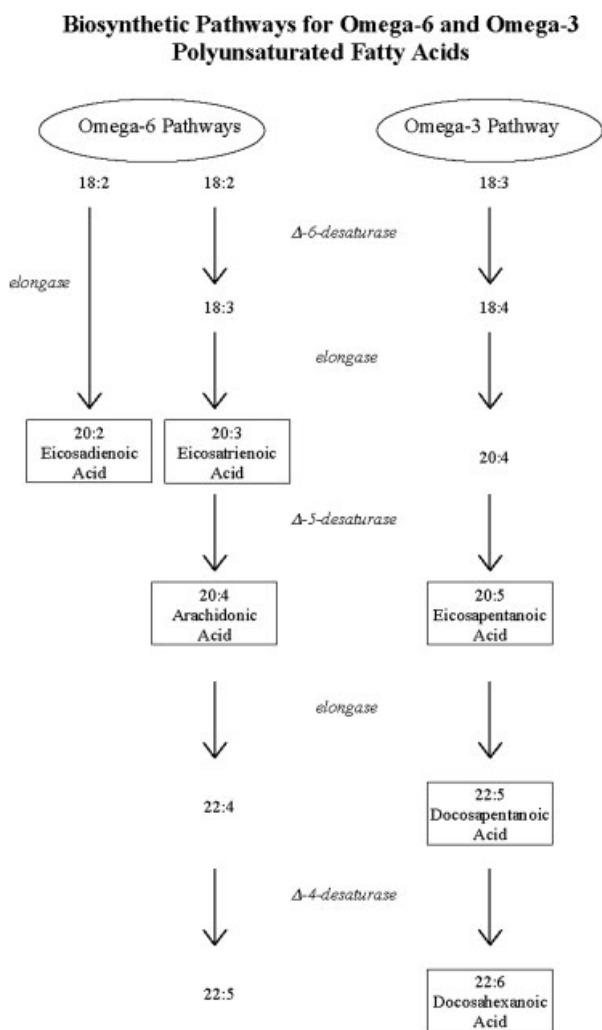
Figure 2. Schematic diagram depicting biosynthesis of ω-6 and ω-3 fatty acids. Essential, ingested precursors at top are modified through a series of enzyme (italics) mediated reactions (arrows) to form the variants below. In the shorthand notation used here, the first number denotes the number of carbon atoms in the fatty acid molecule, and the digit after the colon denotes the number of double bonds contained in the fatty acid molecule. The six boxed fatty acids include corresponding chemical names and are quantified in Fig. 4.

used in the construction of the lipid bilayer in cell membranes, and dietary intake is actually reflected in membrane levels [6]. The cell membrane plays a particularly important role in the brain by contributing to membrane fluidity. The kinked chains of PUFAs take up more space in the membrane, making it more fluid in contrast to the straight chains of saturated fatty acids that make the membrane rigid. Considering that neurotransmission relies on ion channels embedded in membranes, neurons composed of membranes with insufficient amounts of PUFAs would be expected to exhibit signaling abnormalities [7]. While such dietary ω-3 fatty acid-induced changes in membrane fluidity certainly impact mature adults [8] as well as aged adults [9], a number of reports also document the deleterious impact of dietary ω-3 fatty acid deficiency imposed during gestation and lactation on nerve cell myelination and second messenger functioning in developing organisms [10–12].

Besides membrane function, PUFAs also play a role in various cellular signaling pathways including activation of second messenger systems in response to neurotransmitter binding at extracellular receptors. Both ω-3 and ω-6 fatty acids have been shown to increase levels of adenylate cyclase, as well as levels of protein kinase A, in neuronal tissue cultures *in vitro* [4]. Adenylate cyclase and protein kinase A are both involved in the metabotropic-receptor mediated signaling pathways that are used by serotonin (5-HT$_1$ receptor), norepinephrine (á-2 and beta receptors) and dopamine (D$_1$ and D$_2$ receptors). These metabotropic receptors work through a G protein-adenylate cyclase coupled mechanism, whereby the final product of the pathway is an activation of protein kinase A which phosphorolates ion channels, opening them up. As a concrete example of how fatty acids could modulate neurotransmission, consider the fact that a ligand-bound D$_1$ receptor activates and, therefore, increases levels of adenylate cyclase and protein kinase A. A deficiency of PUFAs in the neuron would likely result in a lower level of adenylate cyclase and protein kinase A activity. Therefore, less ion channels in the neuron would open when the D$_1$ receptor is activated, and a greater amount of dopamine agonist activity would be needed to depolarize the cell.

Evolutionary perspectives on fatty acid contributions to selection pressures suggest that the long-chain PUFAs may have played a role in the enlargement of the human brain. The increased size of the hominid cerebral cortex over the last two million years when Homo first emerged is correlated with a large increase in fish consumption, a food source rich in PUFAs. Early hominid development is believed to have taken place in the Rift Valley of Eastern Africa, an area that was filled with freshwater lakes at the time, providing plenty of fish for human ancestors [13]. Other researchers have proposed that long-chain PUFAs were crucial in the development of human intellect [14].

This conclusion is consistent with evidence from crucial experiments documenting in close human ancestors, rhesus monkeys, the fact that dietary ω-3 fatty acid deficiency

depletes brain fatty acid composition [15] in a manner which is reversible by fatty acid consumption [16]. The fact that such dietary fatty acid deficiencies also lead in primates to serious behavioral derangements [17] have prompted additional study of fatty acid intake levels which may be necessary for growth and development of motor and cognitive skills in human infants [18].

2   Impact of ω-3 fatty acid deficiency

The current western diet likely does not contain the same levels of ω-3 and ω-6 fatty acids as the diet of human ancestors. The estimated ratio of ω-6 to ω-3 fatty acid intake in hunter-gatherer ancestors based on 35% of calories being supplied by animal sources and 65% being supplied by plant sources ranges from 0.8 (ω-6):1 (ω-3) to 1:1. Estimates of current United States intake ratios based on the same percentage of calories *per* source range from 17:1 to 20:1 [19]. Although hunter-gatherer ancestors consumed large amounts of wild plants, the development of agricultural societies about 10 000 years ago produced cultivated plants that provided cereal grains. While wild plants (and many green, leafy vegetables today) are an excellent source of ω-3 and ω-6 fatty acids, cereal grains provide high levels of ω-6, but very little ω-3. Therefore, this aspect of diet has changed very recently in terms of evolutionary development. In addition to this, livestock are typically fed cereal grains, and the high ratio of ω-6 to ω-3 fatty acids in the grains these animals eat is reflected in the meat that they provide [19]. Wild game animals have much higher levels of ω-3 fatty acids than do domesticated grain-fed animals. This effect is also seen in farm-raised fish unless they are provided a diet sufficient in ω-3 fatty acids [20]. Thus, the average modern western diet has increased in levels of ω-6 fatty acids, while the level of ω-3 fatty acids consumed has declined. Based on their role in biosynthetic pathways, one could forecast that a modern diet would be more vulnerable to ω-3 insufficiency than that of our forebears.

### 2.1   Consequences of ω-3 fatty acid deficiency during development

PUFAs are essential to brain development and accordingly the gestating organism is nourished with ω-3 fatty acids from the placenta, as well as from breast milk [4]. Docosahexaenoic acid (DHA), an ω-3 fatty acid found mainly in fish, accrues rapidly in grey matter of the brain during development [10] and is incorporated into nerve growth cones in events leading to synaptogenesis [21]. Deletion of ω-3 fatty acid intake among dams and offspring during the perinatal, post-weaning and post-pubertal stages of development produces a graded 10–60% decline in forebrain serotonin and serotonin transporter content [22]. Similarly, inadequate ω-3 fatty acid nutrition from conception results in depletion in number and function of brain dopamine source neurons [23]. Deficits in spatial learning ability are exhibited by rats maintained on an ω-3 fatty acid deficient diet from birth and subsequent supplementation of ω-3 fatty acids restores normal learning capabilities [24]. In particular, rats maintained on the deficient diet for 6 wk after birth and then supplemented with ω-3 fatty acids for 1 wk before testing show impaired learning abilities compared to rats that were maintained on the deficient diet for 2 wk and then supplemented with ω-3s for 1 wk before testing [24]. These findings illustrate the importance of maintaining adequate levels PUFAs in order to ensure unimpaired brain development. In particular, dietary fatty acid insufficiency is forecast to confer particular vulnerability to poor infant neural development, as well as neurological disorders and age-related cognitive decline in some individuals with low ω-3 intakes [25].

While it would not be ethical to impose ω-3 dietary deficiency in humans, some clues regarding the potential consequences of fatty acid deficiency emerge from regions of the world in which children are under-nourished. In particular, school-aged children in Jakarta, Indonesia, were found by The NEMO Study Group to be marginally nourished based upon low weight-for-height *z*-scores [26]; in this

Table 1. Representative clinical and pre-clinical literature addressing efficacy of dietary polyunsaturated fatty acid deficiency and supplementation

Dietary deficiency scenario		Neurological deficiency scenario		Dietary supplementation scenario	
Relevant citations	Findings	Relevant citations	Findings	Relevant citations	Findings
Clinical literature					
Osendarp *et al.* [26]	PUFA ineffective	Bromfield *et al.* [63]	PUFA ineffective	Kennedy *et al.* [64]	DHA ineffective
Dalton *et al.* [1]	PUFA↑memory	Richardson *et al.* [40]	PUFA↓DCD signs	Hamazaki *et al.* [60]	PUFA↓plasma NE
Pre-clinical literature					
McNamara *et al.* [22]	65%↓brain 5-HT	Ferrari *et al.* [42]	PUFA↓pathology	Robson *et al.* [9]	PUFA↑neurite growth
Ahmad *et al.* [23]	30%↓brain DA	Lim *et al.* [45]	PUFA↓ß-amyloid	Wu *et al.* [65]	DHA↑learning/BDNF

Twelve representative fatty acid bioefficacy studies involving both human participants and animal models are listed in the table cells. Selected studies are not exhaustive but rather represent the blend of positive and negative findings that characterize the literature and also the three fatty acid deficiency/supplementation scenarios that are fully detailed in Fig. 1. BDNF, brain-derived neurotrophic factor; DA, dopamine; DCD, developmental coordination disorder; DHA, docosahexanoic acid; NE, norepinephrine; PUFA, polyunsaturated fatty acid 5-HT, serotonin.

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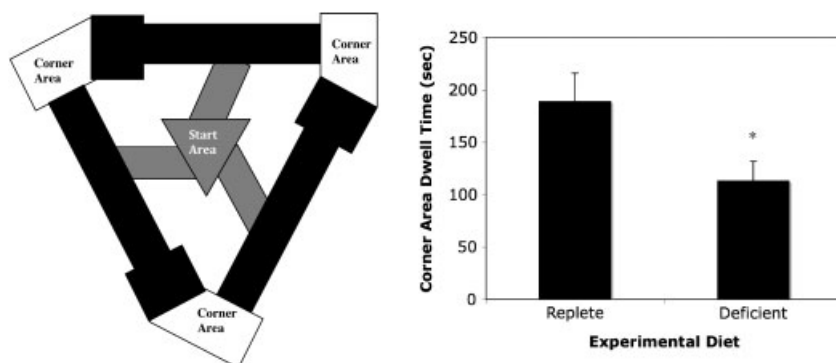
Figure 3. ω-3 Fatty acid deficiency produces anxiogenic-like behavior in an animal model of anxiety. A maze apparatus sensitive to novelty-induced inhibition of exploration (left hand panel) was employed to investigate the impact of ω-3 fatty acid deficiency on emotionality. Consumption of ω-3 replete (flax seed supplemented) and deficient diets over a 4-wk period resulted in greater inhibition of exploration, an anxiogenic-like characteristic, among ω-3 fatty acid deficient rats (right hand panel). *$p < 0.05$ relative to replete controls.

population, no cognitive enhancing effects of ω-3 fatty acid supplementation were observed. In contrast, 7- 9-year-old children in Northern Cape Province of South Africa exhibited both evidence of stunting and underweight as well as efficacy of ω-3 supplementation for verbal learning, spelling and reading test performance [1]. Findings of this sort have led some investigators to hypothesize that marginally nourished children would benefit more from ω-3 fatty acid supplementation than would well-nourished children [26].

## 2.2 Impact of ω-3 fatty acid deficiency in the healthy adult

Animal research imposing PUFA deprivation suggests a role for these lipids in the behavior of healthy adult organisms. In terms of learning and memory performance, mice maintained on an ω-3 deficient diet are slower to habituate, a simple form of learning, than mice maintained on an ω-3 adequate diet [27]. Similarly, mice maintained on an ω-3 deficient diet show deficits in their ability to learn the correct pathway to exit a maze [8]. These results indicate that ω-3 deficiency can have adverse consequences on learning ability. Relevant studies which exhibit some of the pre-clinical and clinical consequences of dietary fatty acid deficiency are listed in the left column of Table 1.

Other research has examined the impact of ω-3 deficiency on emotionality and an example of such a finding is exhibited in Fig. 3. One study [28] tested ω-3 deficient rats in the elevated plus-maze, as well as in a conditioned-fear task. Deficient rats were found to spend significantly less time in the open arms of the plus-maze than ω-3 supplemented rats, indicating an anxiogenic-like profile of exploration in deficient rats. One week of ω-3 supplementation in the deficient rats resulted in an increase in time spent in the open arms of the plus-maze, restoring performance comparable to that of rats never fed a deficient diet [28]. In the conditioned freezing task, ω-3 fatty acid supplementation produced a progressive decrease in the amount of time spent freezing in response to the conditioned stimulus, while the deficient rats did not show such an effect, again suggesting that an anxiogenic-like profile accompanies ω-3 deficiency. These

researchers also tested the reaction of ω-3 deficient and supplemented rats to intracerebroventricular injections of corticotropin releasing factor, a stress neuropeptide. They found that rats deficient in ω-3 showed significantly higher levels of anxiogenic-like behavior, such as an increase in face washing as well as decreases in rearing, sniffing and feeding [28]. Consistent with these pre-clinical findings, an abnormally low level of ω-3 fatty acids relative to high levels of ω-6 fatty acids has been implicated in susceptibility to psychological stress in human studies [29].

It is typically the case with essential nutrients that animals consuming a deficient diet sense the resulting nutritional deficiency and mount the appropriate appetitive coping response. The self-selection of ω-3 fatty acid foods can only be inferred at the present time and requires explicit experimental demonstration in order to bolster the claims assigning important neurodevelopmental and neurobiological functions to PUFAs [30]. It was therefore hypothesized that rats fed a diet deficient in ω-3 fatty acids would show lower levels of ω-3 fatty acids in neural tissue than rats fed an ω-3 fatty acid replete diet, and that the ratio of ω-6 fatty acids to ω-3 fatty acids would increase in rats fed a deficient diet. Indeed, dietary fatty acid deficiency manifested decreased forebrain lipid content (Fig. 4). ω-3 fatty acid deficient rats exhibited significantly lower levels of two ω-3 fatty acids, eicosapentaenoic acid and docosapentaenoic acid, compared to rats consuming the ω-3 fatty acid replete diet (Fig. 4). This finding is consistent with previous studies showing that another ω-3 fatty acid, DHA, is highly concentrated in the frontal cortex of the rat [31], and that deletion of all ω-3 fatty acids from the diet results in brain depletion of DHA, which is reversed by subsequent DHA refeeding [32]. The acquired hunger allowed malnourished rats consuming an unsafe, nutritionally deficient diet to increase consumption of a safe, nutritionally replete alternative diet [33]. In particular, rats maintained on an ω-3 deficient diet learned to select a novel food containing ω-3 fatty acids over repeated exposures to this novel food (Fig. 4). The ability of postingestional factors to guide long-term preference behavior of rats for lipid-adultered diets has been reported previously [34]. In that study, rats titrated their intake of fat or oil-supplemented foods within 2–4 days of
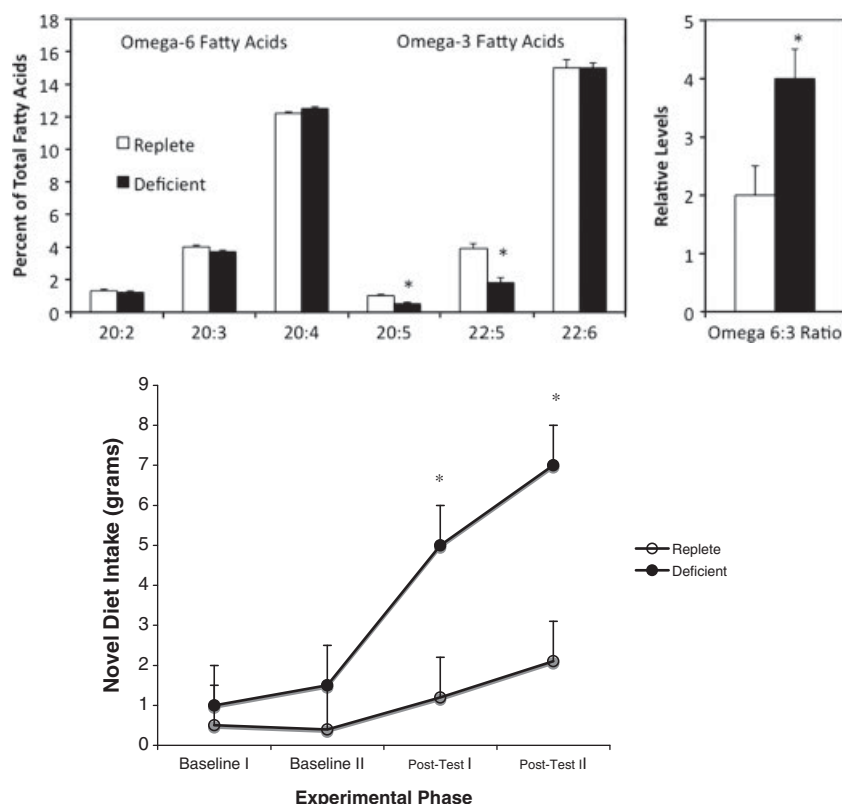
Figure 4. Diminished brain ω-3 fatty acid levels in rats fed an ω-3 deficient diet provokes dietary neophilia. Levels of three ω-6 (20:2 – eicosadienoic acid, 20:3 – eicosatrienoic acid, 20:4 – arachidonic acid) and three ω-3 (20:5 – eicosapentanoic acid, 22:5 – docosapentanoic acid, 22:6 – docosahexaenoic acid) fatty acids, as well as the ratios of ω-6: ω-3 fatty acids, are exhibited among rats fed either an ω-3 deficient diet or an ω-3 replete diet over a 4-wk period (top panel). Enhanced preference for a novel ω-3 fatty acid replete diet among rats fed an ω-3 deficient maintenance diet during daily 1 h preference tests conducted prior to, and following onset of dietary deficiency is exhibited in the bottom panel. *p<0.05 relative to replete controls.

daily 1 h preference tests in a manner which was independent of the sensory properties of the diets [34]. While precise regulation of lipid intake does not appear to occur in the rodent due to the multitude of factors which guide dietary self-selection [35, 36], the principle of acquired hunger can be invoked to explain a dietary self-selection preference for any nutrient which has deleterious consequences if absent from the maintenance diet [37]. In an often cited experiment, thiamine deficient rats were allowed to chose between several alternative diets only one of which contained adequate thiamine [37]. The resulting overall preference for this thiamine replete diet was interpreted as an adjustment in food selection resulting from consumption of a novel food source that acts to alleviate a nutritional deficit. The adaptive advantages of this long delay nutritional coping mechanism have been suggested to constitute a specialized form of learning [33].

3   Impact of ω-3 fatty acid supplementation

This section confronts the issue of biological relevance of increased intake of ω-3 fatty acids without presupposing a prior history of ω-3 fatty acid deficiency. Strong skepticism in the presumption of ω-3 efficacy as a dietary supplement is reflected in the conclusion of Innis that "Because an

increased intake of an essential nutrient cannot have benefit in individuals with an intake above their needs, [individuals] without deficiency cannot benefit from additional DHA" [25]. This conclusion is supported by the observation that there are non-responders within a treatment group exposed to DHA supplementation to the extent that prior DHA intake has been sufficient to meet biological needs. Indeed, the pattern of heterogeneous (*i.e.* inconsistent) results derived from a meta-analysis of human ω-3 fatty acid supplementation studies [2] may be constructively advanced by assaying the degree of fatty acid repletion of the sampled individual, or the mother who gestated and breast fed the weanling, with the expectation that a history of prior ω-3 fatty acid deficiency would confer efficacy of dietary ω-3 fatty acid supplementation.

3.1   Consequences of ω-3 fatty acid supplementation during development

High levels of ω-3 in the diet of infants are associated with improved mental development scores and better visual acuity [38]. Complementary evidence for this statement is provided by the fact that several common childhood neurodevelopmental disorders, including attention-deficit/hyperactivity disorder and developmental coordination disorder are accompanied by fatty acid deficiencies or

imbalances [39, 40]. A randomized, controlled trial of dietary ω-3 and ω-6 supplementation in 5–12 year old children with developmental coordination disorder revealed significant improvement in reading, spelling and behavior [40]. Among school aged children of normal ability levels, some degree of improvement in scholastic performance was observed in a group supplemented with ω-3 fatty acids [41].

3.2　Impact of ω-3 fatty acid supplementation on adult neurological and psychological disorders

Animal models of neurological disorders such as epilepsy and Alzheimer's disease provide a valuable context of neuronal damage and reorganization in which to assess potential therapeutic actions of ω-3 fatty acid supplementation. In particular, adult supplementation with ω-3 fatty acids prevents status-epilepticus associated neuropathological changes in the hippocampal formation of rats with epilepsy [42] and reduces the duration and frequency of seizures [43, 44]. Similarly, administration of a diet high in DHA produced 70% reduction in β-amyloid, 40% reduction in overall plaque burden and ameliorated the impairment of spatial learning ability in animal models of Alzheimer's disease [45, 46]. These pre-clinical findings are consistent with an epidemiologic study of fish consumption in relation to cognitive decline in the elderly which described a protective effect of ω-3 supplementation [47]. Finally, traumatic brain injury in rats induces oxidative stress and learning disabilities which are counteracted by dietary ω-3 supplementation [48]. Notably, both dementia and brain injury disorders are accompanied by degradation of brain membranes [49, 50],] so efficacy of ω-3 supplementation in the context of neurological disorders conforms well to the neurological deficiency scenario of Fig. 1. Accordingly, brain fatty acid derangements are hypothesized by some investigators as potential causal factors in human dementia and affective disorders [51, 52].

ω-3 fatty acids derangements have also been implicated in various psychological disturbances. One set of researchers examined the relation of plasma ω-3 and ω-6 levels to various behavioral problems in boys 6–12 years of age and found no significant behavioral abnormality associated with low levels of ω-6 fatty acids, but they did find that low ω-3 fatty acid plasma levels correlated with frequency as well as severity of the behavioral problem [53]. Low plasma concentrations of ω-3 correlated with impulsivity and hyperactivity, anxiety, temper tantrums, and sleep disturbances, and the lower the level of ω-3, the greater the frequency of these problems. Furthermore, other researchers have looked at ω-3 and ω-6 levels in the adult population and found that a high ratio of plasma ω-6 to ω-3 fatty acids is predictive of depressive symptoms and that higher ratios indicate a higher level of depressive symptoms [54].

One debilitating psychiatric disorder characterized by ω-3 fatty acid irregularities is schizophrenia. A large body of data that suggesting that ω-3 fatty acids play a role in this syndrome has led to the emergence of the phospholipid or membrane hypothesis of schizophrenia. Broadly, this hypothesis states that phospholipid metabolism is abnormal in schizophrenics, leaving the neuronal membranes of patients deficient in PUFAs, especially ω-3 [55]. This hypothesis has been extended by various researchers in terms of the exact mechanism whereby a neuronal membrane deficient in ω-3 fatty acids could contribute to the disorder. One study examined post-mortem levels of fatty acids in the brains of schizophrenics and non-psychiatric controls [56]. These researchers found an abnormally low level of ω-3 fatty acids in the frontal cortex of schizophrenics, but in no other regions of the brain, an interesting finding since frontal lobe abnormalities have been implicated in schizophrenia. Other researchers have looked at efficacy of ω-3 fatty acids in the treatment of schizophrenia and reported that chronically medicated schizophrenics who were supplemented with a combination of ω-3 fatty acids and antioxidants (vitamins E and C) showed significant improvement in both negative and positive symptoms [57]. In addition to other reports along these same lines, a case study of a schizophrenic who had never before been medicated for the disorder has been published. These researchers report that treatment with eicosapentaenoic acid (an ω-3) significantly improved both positive and negative symptoms in this patient, and also significantly raised the level of ω-3 fatty acids in the blood plasma of this individual [58]. A meta-analysis of available literature confirmed that promising protective effects of ω-3 fatty acid supplementation are apparent for individuals with schizophrenia, unipolar depression and bipolar disorders [59]. Relevant studies which exhibit some of the pre-clinical and clinical consequences of neurological neuropsychiatric fatty acid deficiency are listed in the middle column of Table 1.

3.3　Impact of ω-3 fatty acid supplementation in the healthy adult

Research suggests that consumption of dietary fish oil increases serotonin and dopamine concentrations in the frontal cortex of rats [7, 22]. Similarly, ω-3 supplementation lowered plasma norepinephrine concentrations in healthy volunteers [60]. These authors propose that the peripheral catecholamine reducing action of dietary ω-3 fatty acids is consistent with the well-known preventive effect of fish oil for lethal arrhythmia [61].

Fatty acid levels have been implicated in susceptibility to psychological stress [29] and investigators have studied the effects of ω-3 fatty acids on the adrenal stress response in humans. Researchers induced mental stress in subjects by having them take a 30 min stress test that included mental arithmetic and the Stroop test. Baseline measures of plasma cortisol and catecholamines, blood pressure, heart rate and

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levels of fatty acids in adipose tissue were taken before the subjects participated in the mental stress task. These same measures were then taken immediately after the subjects completed the mental stress task. These subjects were then supplemented with fish oil for 3 wk before returning to the lab where the same procedures were carried out again. These researchers found that in the non-supplemented condition, mental stress significantly raised heart rate, blood pressure, plasma epinephrine and plasma cortisol levels. Three weeks of supplementation with fish oil blunted the stress response as determined by non-significant changes in of all of these measures after taking the mental stress test. Relevant studies which exhibit some of the pre-clinical and clinical consequences of dietary fatty acid supplementation are listed in the right hand column of Table 1.

4   Concluding remarks

(i) ω-3 Fatty acids are critical components of brain membrane lipids such that fatty acid impoverished diets contribute to poor central nervous system development and function [25].

(ii) Although the totality of evidence is still inconclusive, there are promising indications that supplementation with DHA and other ω-3 fatty acids during pregnancy, lactation and infancy may benefit cognitive development early in life [2].

(iii) ω-3 Fatty acids play a major role in determining whether the brain ages successfully or experiences neurodegenerative disorders [62].

5   References

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