

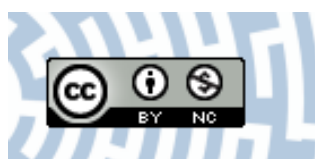


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Nutritional Modulators of Neuropsychiatric Dysfunction

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Abstract: This review article gathers evidence on the potential relationship between dietary intake of ω 3 polyunsaturated fatty acids (ω 3 PUFAs) and mental function. Several pieces of evidence that ω 3 PUFAs influence affective and cognitive function are presented.

Although published data and results available in the field remain limited and sometimes ambiguous, they have shed a new light on the role of proper diet in general, ω 3 PUFAs in particular, in many mental disorders and dysfunctions, including depression and cognitive decline in aging. The analysis of the influence of fatty acids on human health allows us to formulate a new, more holistic approach to both prevention and treatment of psychological disorders and dysfunctions. What is more, it appears that ω 3 PUFAs have a beneficial influence on mental function in healthy people as well.

The currently available data concerning the influence of fatty acids on behaviour and mental function are still insufficient and suffer so far from lack of standard determination of background, intermediary and endpoint omega-6/3 ratios in plasma lipids of patients involved in both epidemiological and intervention studies. There is a great need for further refined trials in the field.

Keywords: Diets, food, nutrients, nutraceuticals, depression, anxiety, type A behaviour.

INTRODUCTION

It is known that brain function is highly sensitive to dietary nutrients. One of the probably best known examples is caffeine, which is contained in tea, coffee, chocolate etc. Caffeine is a stimulant that improves mental alertness and performance. Many other dietary elements – from vitamins to macro-elements – influence brain biochemistry and function. Some silently while others have been reported to have behavioural and functional effects. As the study of brain nutrition and, in particular, its impact on brain function and behaviour is relatively new, it is not surprising that gaps remain to be filled in our knowledge of the biochemical, physiological, psychological and behavioural aspects of the effects of diet on brain function. However, accurate and relevant data are available from where functional effects appear obvious though underlying mechanisms are still poorly understood. The aim of this article is to review and discuss the effects of essential nutrients (particularly ω 3 PUFAs) on psychological function and mental health.

NUTRIENTS AND BRAIN FUNCTION

Polyunsaturated fatty acids (PUFAs) constitute key structural components of phospholipid membranes in body

tissues. They are highly concentrated in the central nervous system (CNS) and human brain [1]. They play a role in nervous system activity, neuroplasticity of nerve membranes [2], synaptogenesis [3], synaptic transmission [4] and neurotransmitter uptake. Most neurotransmitters, i.e. catecholamines, acetylcholines and serotonin, also affect the function of the cardiovascular system, in addition to their effects on neuropsychiatric dysfunctions [5-8]. The synthesis of neurotransmitters has been shown to also depend on a number of other essential nutrients such as tryptophan, tyrosine, arginine. and choline [6, 7]. There is evidence that ω 3 fatty acids and other nutrients can affect cognitive function, mood, type-A behaviour, and depression [6-14]. In this respect, excess intakes of linoleic acid (C18: 2 ω 6), saturated fat and trans-unsaturated fats, refined carbohydrates, are pro-inflammatory leading to increased plasma levels of activating protein-1 (AP-1) and early response growth protein-1 (ERGP-1), which are transcription factors for pro-inflammatory cytokines. These latter cytokines appear to be positively associated with depression and type-A behaviour which are also risk factors for heart disease. On the other hand, ω 3 fatty acids, monounsaturated fatty acids, antioxidant vitamins, flavonoids, coenzyme Q10, potassium, magnesium, calcium and moderate alcohol seem to have beneficial effects on brain and heart function as well as on mental function (Table 1).

The brain is responsible for approximately one fifth of the basal metabolism, which is fuelled by glucose and oxygen. Protein and lipids material are essential to the

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Table 1. Nutrients Having Possible Effects on Brain and Psychological Function

Beneficial Effects	Adverse Effects
Omega 3 fatty acids	
Monounsaturated fatty acids	Excess of Total fat
Vegetable proteins	Excess of Saturated fat
Soluble fiber	Trans fat
Vitamins; A,E,C, beta-carotines	Excess of Linoleic acid
B vitamins and folic acid	Excess of Sodium
Coenzyme Q10	
Flavonoids	
Potassium	
Magnesium	
Calcium	
Zinc	
Copper	
Selenium	
Chromium	

growth and regeneration of myelin sheaths and axis cylinders as well as for enzyme systems needed for cellular metabolism and neuroprotection. Vitamins, minerals and electrolytes, ω 3 fatty acids and coenzyme Q10 in the neurons may influence the excitability of nerve centres. These vitamins, minerals, antioxidants, flavonoids and ω 3 fatty acids should be adequately available as these nutrients can affect glucose metabolism, which is necessary for neuronal functions. Deficiencies in B vitamins, including folic acid, may be connected with psychological disorders. Epidemiological studies indicate that consumption of diets rich in antioxidants and anti-inflammatory compounds such as those found in fruits and vegetables (i.e. polyphenols), may lower the risk of developing age-related, neurodegenerative diseases, such as Alzheimer's or Parkinson's diseases [15].

POLYUNSATURATED FATTY ACIDS (PUFAS)

Omega-6/3 PUFAs are essential to mammals, including humans; they cannot be synthesized *in vivo* and have to be obtained from the diet. PUFAs are composed of a hydrocarbon chain of variable lengths with a methyl group at one end (omega end), a carboxyl group at the opposite end, and several double bonds in between. The position of the first double bond differentiates ω 3 fatty acids (i.e. C18:3 ω 3 or ALA or alpha-linolenic acid) and ω 6 fatty acids (i.e. C18:2 ω 6 or LA or linoleic acid) [10]. ω 3 PUFAs have their first double bond at the third carbon, while ω 6 PUFAs at the sixth carbon from the omega end. In the wild, ALA, often referred to as short chain ω 3 PUFA, can be metabolized to longer chain ω 3 PUFA, mainly eicosapentaenoic acid (EPA, C20: 5 ω 3) and docosahexaenoic acid (DHA, C22:6 ω 3), whereas LA can be converted into arachidonic acid (AA, C20:4 ω 6). ALA is present in greens, chia, flax, perilla, mustard seeds and oils, walnuts, soy beans, wheat; EPA and DHA are typically present in wild meat and eggs, and fish (salmon, tuna, her-

ring etc.); LA is present in maize, sunflower, soy bean and sesame oil; ARA is typically present in modern meat and eggs.

Biochemical data show that ω 3 PUFAs play an important role in neural structure and function. The brain and CNS contain high concentrations of ω 3 PUFAs and several studies suggest a role for ω 3 PUFAs in neurotransmitter synthesis, degradation, release, reuptake and binding [16-18]. Fatty acids and phospholipids are part of all biological membranes. The membrane's fluidity, of crucial importance for its functioning, depends on its lipid components; PUFAs increase membrane fluidity according to their number of double bonds, whereas free cholesterol (CHL) increases membrane viscosity so that the end result depends on the PUFAs/CHL desaturation index [19]. DHA deficit is associated with dysfunctions of neuronal membrane stability and transmission of serotonin, norepinephrine and dopamine, which might be related to the aetiology of mood and cognitive dysfunction and depression. On the other hand, EPA is essential to balancing the immune function and physical health by reducing the proportion of arachidonic acid (AA, C20:4 ω 6) in cell membrane and prostaglandin E2 (PGE2) synthesis. A diet based on a high proportion of PUFAs allows for a higher incorporation of cholesterol in cell membranes to balance their fluidity, which, in turn, appear to contribute to lower blood cholesterol levels.

The types of fatty acids available for the make-up of cell membranes depend upon their relative presence in the diet. The retina and brain, in particularly the cerebral cortex, are rich in ω 3 PUFAs [3, 20], and the role of ω 3 in visual and cognitive development has been described [21-24]. Any dietary deficiency in ω 3 PUFAs has consequences for cerebral development, modifying the activity of enzymes imbedded in cerebral membranes. In addition, it has been reported that maternal intake of ω 3 PUFAs during pregnancy and lactation may have a favourable effect on the later mental development of children [24, 25].

The critical factor in fatty acids' efficacy does not seem to be their absolute dietary intakes, but rather the ratio between their various types (C18, 20, 22- ω 6/3). It is known that the relative amounts of ω 6 and ω 3 PUFAs in cell membranes guide their function [26, 27]. PUFAs are precursors of prostaglandins and leukotrienes, which are involved in inflammation and immune response. A diet rich in fish oil (ω 3 PUFAs) reduces production of inflammatory cytokines PGE2, helps in the treatment of chronic inflammatory diseases such as rheumatoid arthritis and prevents the onset of hormone-dependent tumours (i.e. prostatic cancer) by antagonizing the formation of cancerogenic factors [28].

In conclusion, ω 3 PUFAs play a crucial role in numerous cellular functions, including membrane fluidity, membrane enzyme activities and eicosanoid synthesis; in such respect they are essential for brain development in infants and also required for maintaining normal brain function [29]. Early reports suggested that large amounts of ω 3 PUFAs could cause prolonged bleeding times, possibly resulting in hemorrhagic stroke, and oxidative damage to various tissues [30]. For this reason it is often suggested to accompany ω 3 PUFAs supplementation with various antioxidants such as vitamins E, A and C, flavonoids, polyphenols etc. In fact,

many pieces of evidence indicate that antioxidants are also essential for maintaining a healthy neurophysiology.

NUTRIENTS AND AFFECTIVE FUNCTION

Omega-3 long chain polyunsaturated fatty acids appear beneficial in the treatment of several human conditions and diseases, including depression, schizophrenia and dementia. . Omega-3 treatment of these diseases often shows positive effects [31-35]. Discussion of its effects on depression, although it might be considered controversial, has led to the conclusion that ω 3 PUFAs can affect both affective and cognitive function, and may even act as a “mood stabilizer” [34].

Over the last decades since the 1940s, the age of onset of major depression in the western world has declined, and its incidence, on the whole, has increased up to twenty-fold. According to the World Health Organisation, depression is one of the most important diseases in the world, a fact reflected in the huge increase in the prescription of anti-depressive drugs in the western world, now about three times as many as just two decades ago. Clinical manifestations of depression are fatigue, loss of vigour, anger, hostility, confusion, and anxiety. WHO data indicate that the prevalence of depression in modern societies is relatively high – about 5-10%. Among the ten most important disorders in developed countries ranked according to the “years lived with disability” index (YLD), major depressive disorder termed 'unipolar major depression', clearly turned out to be ahead of all others. In addition, 'bipolar disorder', a condition in which periods of depression alternate with periods of mania, ranks sixth on the list. To put that into perspective, diabetes was tenth. In terms of “years lost due to premature death” (YLPD), 'unipolar major depression' ranked second only to cardiovascular diseases (CVD). In a further analysis, WHO predicted a clear-cut increase in the relative prominence of depression over the next 20 years. Depression is the most frequent psychiatric disorder and it affects well-being in a more fundamental way than other disorders. It is a life-threatening disorder, as about 15% of people with severe depression commit suicide.

Several lines of evidence suggest that there is a relation in humans between dietary intake of ω 3 PUFAs and depressed mood. There is epidemiologic evidence that ω 3 PUFAs play a role in affective function. Numerous studies have shown a clear link between the drop in ω 3 PUFAs consumption (i.e. fish) and the risk of depression, particularly as the incidence of this disorder varies, depending on the country, parallel with fish consumption. In this regard, numerous negative correlations have been demonstrated between worldwide fish consumption and rates of depression. One of the most famous and the most spectacular studies in this area was conducted by Joseph R. Hibbeln [35]. They showed a strong negative association ($r=-0,84$) between fish intake and depression across 13 countries (among 35000 citizens). Silvers and Scott [36] found that the personal perception of good mental and physical health varies with the consumption of fish (rich in ω 3 PUFAs) in New Zealand. Timonen *et al.* [37] showed an increased risk of developing depression in persons who rarely ate fish compared with regular fish eaters. Other analysis [38] reported a connection between dietary seafood intake and protection against bipolar disorder

and against seasonal affective disorder [39]. Similar results have been reported by Parker *et al.* [40].

Here, it is worthwhile to emphasize that the studies cited above are cross-sectional and that significant correlations may always reflect associations with other uncontrolled factors (i.e. smoking).

A relationship between ω 3 intake and depressed mood has also been found in clinical studies. However, only a few studies have focused on dietary factors, a fact which shows their underestimated recognition in research on depression. Lower concentrations of ω 3 have been reported in the plasma/red blood cell membranes of persons with major depressive disorder diagnosis compared with matched non-depressed control subjects [41-43]. Tiemeier *et al.* [44] found in a group of 567 participants statistically significant lower ω 3 PUFAs levels, and higher ω 6/ ω 3 ratios in blood serum in individuals with depressive disorder than in the non-depressed control group. Stoll *et al.* [34] observed improvements in the depressive symptoms associated with bipolar disorder after supplementation with ω 3 PUFAs compared with placebo, and Nemets *et al.* [45] reported benefits of ω 3 PUFAs compared with placebo for treating unipolar disorder.

The role of ω 3 PUFAs in major depressive disorder has been studied by Su *et al.* [69]. They conducted an 8-week double-blind, placebo controlled trial comparing ω 3 PUFAs (9,6g/d) with placebo, on top of the usual treatment. Interestingly, participants in the ω 3 PUFAs group had significant differences in HRSD (Hamilton Rating Scale for Depression) score from the fourth week after treatment (and this difference kept growing up to week 8) – though it was a preliminary trial and small sample.

Tanskanen *et al.* [46, 47] in research on a random sample, found that frequent fish consumption might be coupled with a reduced risk of suicidal ideation. In the Huan *et al.* study [48] there was nearly eightfold difference in the number of suicide attempts between the lowest and highest red blood cells EPA level quartiles.

Very interesting results on ω 3 PUFAs effects on mood, cognitive and physiological function have been reported by researchers from the University of Siena [49]. The study aimed to examine the effects of ω 3 supplementation on healthy volunteers performing a series of attention tests (tests involving different types of attention were used). The tests were accompanied by neurophysiological recordings (electroencephalogram «EEG» and electromyography «EMG») to evaluate the possible modification of neuroelectrical parameters. In each test the participants' mood was diagnosed (involving The Profile of Mood States «POMS») and the reaction time was recorded. Subjects were tested at the beginning of the experiment and after thirty five days. Blood samples were taken on day 1 and day 35 to analyze specific parameters: AA/EPA ratio, cholesterol, triglycerides, High-density lipoprotein (HDL), Low-density lipoprotein (LDL) and glycaemia. Over a period of 35 days they were supplemented with ω 3 PUFAs. A control group was supplemented with placebo (olive oil). After 35-day supplementation, blood analyses showed that the AA/EPA ratio was strongly reduced by ω 3 treatment. Supplementation with ω 3 PUFAs was associated with clear variations in mood. The POMS

analysis showed an increase in vigour and decrease in such mood states as: anger, anxiety, fatigue, depression and confusion. The reaction time in attention tests decreased after ω 3. An EEG frequency distribution showed a shift towards low frequencies in all recordings after ω 3 supplementation. In particular, after ω 3 the percentage of the beta-2 band decreased significantly in all tests and in the relaxation period. Its reduction was accompanied by a concomitant increase of the theta and alpha bands. Though it was a relatively small sample, the results strongly suggest that ω 3 PUFA supplementation has a beneficial influence on general psychological state, including mood and cognitive function, non-specific for depressive disorders. Data supplied by Fontani *et al.* reinforce the hypothesis of the direct action of ω 3 fatty acids on the central nervous system. The authors assume that the importance of these results is strengthened by the fact that they occur within subjects in good health and leading a physically active life in whom ω 3 PUFAs improved an already good condition of well-being.

Omega-3 PUFA supplementation is reported to be beneficial in psychological distress [50]. Based on the evidence from epidemiological data, case-control studies of phospholipid PUFA levels in human tissues, and antidepressant effect in clinical trials, it can be concluded that ω 3 PUFAs could help to decipher the unsolved enigma of depression and connect the body and mind. The deficit of ω 3 PUFAs has been reported to be associated with neurological, autoimmune, cardiovascular, cerebrovascular and metabolic diseases, cancers, and psychological conditions and diseases. Animals fed with high ARA diet or treated with PGE2 were observed to show symptoms of low activity, anorexia, change in sleep pattern and attention, which are similar to somatic symptoms of depression in humans. The deficit of EPA and DHA in depression may be linked with cognitive dysfunction, mood disturbance, medical co-morbidity and somatic symptoms in depression. The role of ω 3 PUFAs in immunity and mood function supports the promising psycho-neuro-immunological hypothesis of depression and provides an excellent example of body and mind interface [11].

It has not been precisely determined how ω 3 PUFAs affect psychological function. There are several possible mechanisms by which EPA and DHA could improve mood in affective disorders. EPA and DHA are intrinsic to the molecular structure of the phospholipids of cell membranes. The fatty acids are crucial to their role in modulating the functioning of proteins in the membrane. PUFAs lend fluidity to cell membranes and have specific functional interactions with membrane enzymes, receptors and other proteins. EPA and DHA can inhibit protein kinase C signal transduction enzyme complex, block calcium influx into the cell through the L-type calcium channel, similar to the calcium channel blockers verapamil or nimodipine [31]. Omega-3 fatty acids are often employed in conjunction with conventional medicine. That is because some psychiatric patients with depression or persistent anxiety are dissatisfied with the apparent ineffectiveness of traditional treatments and seek a more holistic approach with fewer side effects. The role of ω 3 PUFAs as an adjunct to antipsychotics and melatonin as a treatment or prophylactic agent for side effects remains ambiguous, requiring further trials with sound methodology [51].

In order to compile and compare data from different trials, Appleton *et al.* [52, 53] conducted a study which aimed to systematically review several published randomized controlled trials investigating the effects of ω 3 PUFAs on depressed mood.

Eight medical and health databases were thoroughly searched for all years on record up to June 2006 for trials that exposed participants to ω 3 PUFAs or fish, measured depressed mood, and were conducted on human participants with inclusion of a reference group.

Twelve randomized controlled trials were identified and included in the meta-analysis. The participants either had diagnosis of various different clinical conditions or were healthy volunteers. The pooled standardized difference in mean outcome (fixed-effect model) was 0.13 SDs (95% CI: 0.01; 0.25) in those receiving ω 3 PUFAs compared with placebo, with strong evidence of heterogeneity. A sensitivity analysis that excluded one large trial increased the effect size but did not reduce heterogeneity. Meta-regression provided some evidence that the effect was stronger in trials involving populations with major depression – the difference in the effect size was 0.73 (95% CI: 0.05; 1.41; $P=0.04$), but there was still significant heterogeneity when trials that involved populations with major depression were pooled separately.

Appleton and associates' research indicates that trial evidence which examines the effects of ω 3 PUFAs on depressed mood is limited and difficult to summarize and evaluate, due to its considerable heterogeneity. Most trials were small in scale, short in duration, and used different combinations of different doses of ω 3 in varied groups of subjects. The evidence analyzed provides some support for the use of ω 3 PUFAs in improving depressed mood. Larger trials with adequate precision to detect clinically important benefits are still required.

Indeed, the effects of ω 3 PUFAs on depressed mood and cognitive function remain unclear. In fact, there is a number of studies showing the lack of therapeutically important effects of ω 3 PUFA supplementation on mood and psychological states.

Silvers *et al.* [54] conducted a placebo-controlled trial of fish oil in the treatment of depression. They found no evidence that fish oil improved mood when compared to placebo oil. A study by Hakkarainen *et al.* [55] examined a total of 29,133 men aging from 50 to 69 years in a population-based trial in Finland and did not find associations between the dietary intake of ω 3 PUFAs or fish consumption and depressed mood, major depressive episodes or suicide. However, we must take under consideration that mean fish consumption is much higher in Finland than in many other European countries (i.e. Poland). British researchers [56] conducted a large double-blind randomised controlled trial to evaluate the effects of EPA+DHA supplementation (1,5 g/d) on mood and cognitive function in mildly to moderately depressed individuals (190 participants completed 12 weeks intervention). Compliance, confirmed by plasma fatty acid concentrations, was good, but there was no evidence of a difference between supplemented and placebo groups in the depression subscale of DASS (Depression, Anxiety and Stress Scales) at 12 weeks (adjusted difference in mean: -1,0; 95%

CI; $P=0,27$). Other measures of mood, mental health and cognitive function, including Beck Depression Inventory (BDI) score and attention bias toward threat words, were similarly little affected by the intervention. Substantially increasing EPA+DHA intake for 3 months was found not to have beneficial or harmful effects on mood in mild to moderate depression

Table 2 presents the findings of available articles. It includes: authors, year of publication, type and size of research group, daily dose applied in research and obtained results [see 57-84]. The table shows different effects of $\omega 3$ on depressed mood.

NUTRIENTS AND COGNITIVE FUNCTION

It seems $\omega 3$ PUFA intake may be associated with human cognitive function. However, the majority of studies conducted in this field have considered only pathological situations. Many investigations have ascertained that dietary intake of fish and $\omega 3$ PUFAs is associated with lower risk of cognitive impairment, Alzheimer disease, dementia and stroke [i.e. 32, 84-89]. Relatively few studies have examined the beneficial role of $\omega 3$ PUFAs on cognitive performance in healthy adults.

Assessments of the cognitive benefits in adults are limited because of a lack of information on the characteristics and diets of food supplement users and the fact that those who seem healthier are also more likely to watch their diet, use supplements, etc. The relationship between better retention of cognitive function in later life and diet might be explained by better lifelong cognitive function informing health choices in old age.

The studies in this field also use observational design and relatively few studies of the cognitive benefits of proper diet and food supplement use have adjusted the results for the possible role of mental ability in earlier life, mainly because this information is usually not available. There is strong suggestion that $\omega 3$ PUFA intake affects cognitive performance in adults.

Whalley *et al.* [90, 91] conducted an observational study of 350 mentally efficient subjects born in 1936 whose mental ability was tested in 1947 and who were followed up to in 2000/01, at which point cognition, supplement use, diet, and risk factors for vascular disease were assessed. This investigation showed that use of food supplements in late adulthood can influence cognitive performance. This influence does not depend on differences in cognitive ability present in childhood. Specific cognitive advantages at the age of 64 were found in users of food supplements, including fish oils - compared with non-users. Cognitive advantages were found in the digit symbol subtest, which is highly sensitive to cognitive aging and Alzheimer disease. The blood samples of fish oil users and nonusers were examined; there were significant correlations between childhood IQ and erythrocyte $\omega 3$ PUFAs in 2000/01. This means that higher childhood IQ is probably related to higher $\omega 3$ PUFA / fish oil consumption in later adulthood. IQ at age 64 y was significantly correlated in the total sample with erythrocyte $\omega 3$ PUFA content and with the ratios of DHA/AA and $\omega 6/\omega 3$ PUFAs. Whalley *et al.* conclude that greater dietary fish oil consumption is related to higher cognitive function in late adulthood.

The results coincide with those of the investigation conducted by Nurk *et al.* [92]. A large cross-sectional study with 2031 healthy subjects over 70 y showed a similar relation between intake of different amounts of seafood and cognitive performance.

It was found that fish eaters have significantly better results on all six cognitive tests used (Kendrick Object Learning Test «KOLT», Trial Making Test Part A «TMT-A», Digit Symbol Test Modified «m-DST», Block Design «m-BD», Modified version of the Mini-Mental State Examination «m-MMSE», Abridged version of the Controlled Oral Word Association «S-task») than non-consumers. People who declared mean daily intake of fish and fish products $\geq 10\text{g/d}$ had significantly better mean results in cognitive tests and a lower prevalence of poor cognitive performance than did those whose intake was $< 10\text{g/d}$. The associations between total intake of seafood and cognition strongly depended on dose and the type of fish. The maximum effect was reported at an intake of about 75g/d and with fatty fish (a richest source of $\omega 3$ PUFAs).

The association between plasma $\omega 3$ PUFA proportions and cognitive performance in older adults was also shown in another longitudinal study [93]. Researchers found that higher plasma proportions of $\omega 3$ PUFA predicted significantly less decline in such cognitive domains as sensory motor speed and complex speed over three years than did lower proportions of $\omega 3$ PUFAs.

It has not been determined whether cognitive decline is pathological or the result of a normal aging process. Nonetheless, current scientific data indicates that fish / $\omega 3$ PUFA consumption may be associated with slower decline; which seems a valuable piece of information.

The results above ought to be considered with a dose of scepticism. As in all observational studies, the direction of associations between cognitive scores in late life, self-reported supplement use, and blood $\omega 3$ PUFAs, remains uncertain. In example, participants with higher mental ability may be better informed about healthy nutritional habits, and eat a diet rich in $\omega 3$, vitamins etc.

Randomized controlled trials offer much greater degree of control of experimental variables, such as composition and quantity of taken PUFAs, than do observational studies. Such design allows us to avoid many of the potential problems that often render more difficult the interpretation of observational study.

The effects of $\omega 3$ supplementation on some cognitive and physiological parameters in healthy subjects (22 to 51 y) have been examined in controlled trials conducted by Fontani *et al.* [49]. Different types of attention have been measured in a 35-day $\omega 3$ PUFA supplementation group vs placebo group. Omega-3 PUFA supplementation has been found to be associated with a positive effect on reactivity, i.e. reduction of reaction time in the Go/No-Go and Sustained Attention tests. The latency of EMG activation was concomitantly reduced in the same test plus Choice. EEG frequency shift to the alpha and theta band were recorded in all the tests after $\omega 3$ PUFA supplementation. These results indicate a beneficial influence of $\omega 3$ PUFAs on cognitive functions (attention) in healthy humans. It is possible that

Table 2. Chronological List of Clinical Trials Investigating Effects of Omega-3 PUFA on Depressed Mood and other Affective Manifestations

No.	Study	Year	Group	No. of subjects, total: treatment/placebo	Intervention		Outcome measures	Statistical significant difference
					Daily dose	Duration (d)		
1	Behan et al.	1990	chronic fatigue syndrome	63:39/24	0,14g EPA 0,09g DHA	90	Likert scale	Yes
2	Warren et al.	1999	chronic fatigue syndrome	50:24/26	0,14g EPA 0,09g DHA	90	BDI	No
3	Stoll et al.	1999	bipolar disorder	30:14/16	6,2g EPA 3,4g DHA	112	HDRS YMRS CGI GAS	Yes
4	Keck et al.	2002	bipolar disorder	116:59/57	6,0g E-EPA	120	IDS YMRS	No
5	Nemets et al.	2002	unipolar depressive disorder	20:10/10	2,0g E-EPA	28	HDRS	Yes
6	Peet and Horrobin	2002	major depression	70:17 _ 1g/d 18_ 2g/d 17_ 4g/d	1,2,4g EPA	84	HDRS MADRS BDI	Yes
7	Llorente et al.	2003	postpartum depression	99:44/45	ok 0,2g DHA	120	BDI	No
8	Marangell et al.	2003	major depression	36:18/18	2,0g DHA	42	MADRS HDRS	No
9	Su et al.	2003	major depression	28:14/14	4,4g EPA 2,2g DHA	56	HDRS	Yes
10	Zanarini and Frankenburg	2003	borderline personality disorder	30:20/10	1,0g E-EPA	56	MADRS MOAS	Yes
11	Post et al.	2003	bipolar disorder	121	6g EPA	112	-	No
12	Fux et al.	2004	obsessive compulsive disorder	11	2,0g E-EPA	42	HDRS YBOCS	No
13	Hirashima et al.	2004	bipolar disorder	21:12/9	5,0-5,2g EPA 3,0-3,4 DHA or 1,3g EPA 0,7g DHA	28	T2 time HDRS	Yes
14	Silvers et al.	2005	major depression	77:40/37	0,6g EPA 2,4 g DHA	84	HDRS-SF BDI	No
15	Fontani et al.	2005	healthy subjects	49:33/16	1,6g EPA 0,8g DHA 0,4g other-3 PUFAs	35	POMS	Yes
16	Osher et al.	2005	bipolar disorder	12	1,5-2g EPA	up to 168	HDRS	Yes
17	Freeman et al.	2005	postpartum depression	16: 6_ 0,5g EPA+DHA 3_ 1,4g EPA+DHA 7_ 2,8g EPA+DHA	0,5g EPA+DHA 1,4g EPA+DHA 2,8g EPA+DHA ratio EPA:DHA_ 1,5:1	56	EPDS CGI HRSD	(lack of placebo-control group)
18	Frangou et al.	2006	bipolar disorder	75:24_ 1g/d 25_ 2g/d 26_ placebo	1,2g/d E-EPA	84	HDRS CGI YMRS	Yes
19	Nemets et al.	2006	(children)[6-12y] major depression	28:13/15	0,38-0,4g EPA 0,18-0,2g DHA	112	CDRS CDI CGI	Yes
20	Hallahan et al.	2007	patients with recurrent self-harm	49:22/27	1,2g EPA + 0,9g DHA	84	BDI HDRS MOAS IMT/DMT PSS	Yes
21	Rogers et al.	2008	mild to moderate depressive disorder	190:96/94	0,63g EPA 0,85g DHA	84	DASS BDI GHQ STAI	No
22	van de Rest et al.	2008	older subjects (≥65 y) independently living	302	1,8g EPA+DHA or 0,4g EPA+DHA	182	CES-D MADRS GDS-15 HADS-A	No
23	Buydens-Branchey et al.	2008	substance abusers	22:11/11	2,25g EPA + 0,5g DHA + 0,25 other PUFAs	84	POMS	Yes
24	Lucas et al.	2009	middle aged women with moderate-to-severe psychological distress (with and without MDE diagnosis)	120:59/61	1,05g E-EPA 0,15g E-DHA	56	PGWB HSCL-D-20 HDRS	No
			middle aged women with moderate-to-severe psychological distress (without MDE diagnosis)	91:46/45	1,05g E-EPA 0,15g E-DHA	56	PGWB HSCL-D-20 HDRS	Yes

they improve an already healthy level of cognitive function. The authors definitely ascribe changes in the reaction time and psychological parameters to the action of ω 3 on the central nervous system. These results are in line with the above mentioned effects of ω 3 PUFAs in pathological circumstances.

In a double-blind, randomized and placebo-controlled study involving 30 young women, results indicate that supplementation with zinc may be effective in reducing anger and depression (94). The women were randomized to one of two groups for a period of 10 weeks: 1) zinc group: (n=15) received multivitamins + zinc (7 mg/day); control group: (n=15) received multivitamins daily. Women in the zinc group showed significant reduction in anger-hostility score and depression-dejection score (P=0.011) in the Profile of Moods State (POMS). Thus, the authors of this study conclude, "Our results suggest that Zn supplementation may be effective in reducing anger and depression"[94].

CONCLUSIONS

In this work we have outlined the evidence that particular nutrients influence the structure, the biochemistry and the functioning of the central nervous system. Fatty acids of the ω 3 family probably have a beneficial effect on both affective and cognitive function, probably more in long term prevention and in acute treatment. Although some lines of investigation showed negative results, the data available shed new light on potential nutrition issues relative to the modern diet, and open the field to further studies.

The data concerning ω 3 PUFAs effects on affective and cognitive function remain rather limited and often ambiguous in interpretation. However, the available evidence forces us to lend thorough consideration to the issue of dietary management in treating depression and other mental disorders. These data provide topics for interpretation and further research, which seems crucial. Indeed, the role of ω 3 PUFAs in affecting immunity and affective function may support the promising psycho-neuro-immunological hypothesis of depression and appears to reveal the interface of body and mind (holistic approach). It seems that polyunsaturated fatty acids may become useful for prophylactic and/or therapeutic treatment of mood disorders and even for cognitive decline in senescence. What is more, it has been suggested that ω 3 PUFAs might play a similarly beneficial role also in healthy humans' mental function. Data indicate that high ω 3 PUFA dietary consumption might stabilize one's mood by reducing negative emotional states such as anxiety, anger and depression. The nutrients are considered to be factors that induce rather short term effects, so that they should be administrated on a continuing basis to maintain long term efficacy.

More studies, however, are needed, particularly with double-blind placebo controlled trials. Although functional effects on the CNS of dietary variations in essential fatty acids seem widely accepted as a fact, the underlying biochemical mechanisms are poorly understood and are not currently an area of intensive study. As noted, a great deal of studies on correlates between psychological outcomes and dietary compounds mainly involve pathological situations. Data concerning nutrients and affective/cognitive function of healthy people remain insufficient. One might have reservations about the dietary-intake-control methods typically used

– such as dietary questionnaires, ω 3 PUFA blood level (which does not say much about past nutrition habits), and about fish consumption recommendations and/or supplement capsules intake in intervention trials. Moreover, the most controlled trials published have been rather small and the duration rarely exceeded 90 days. It seems essential to provide randomised trials with functional food enriched in precisely determined specific nutrients composition.

There are still further unsolved issues related to the role of ω 3 fatty acids. First of all, there is not enough data on potential undesirable effects of long term ω 3 supplementation. Why does the 1- 2 g/d ω 3 PUFA dose seem more effective than higher amounts? What is the optimal ratio between EPA and DHA? And finally, what period of regular supplementation is necessary in order to reach maximal therapeutic response? [95, 96]

We believe that the significance of ω 3 PUFAs in diet is undeniable, as they have been a natural part of our diet since the onset of the brain across all living species, humans in particular. In fact, it is only in the last two centuries that consumption of ω 3 PUFAs has decreased in the western world, mainly because of food processing and commercial issues. Many authors see this dietary change as one of the main sources of continual increase in chronic degenerative diseases in modern societies. It appears that ω 3 polyunsaturated fatty acids may become useful in both prophylaxis and treatment of many human conditions including mental disorders. It seems vital to gradually fill the gaps in common knowledge in this area.

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