Nutritional Modulators of Neuropsychiatric Dysfunction

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Abstract: This review article gathers evidence on the potential relationship between dietary intake of ω3 polyunsaturated fatty acids (ω3 PUFAs) and mental function. Several pieces of evidence that ω3 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, ω3 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 ω3 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 ω3 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 ω3 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: 2ω6), saturated fat and transunsaturated 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, ω3 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
PUFA, mainly eicosapentaenoic acid (EPA, C20:5) present in wild meat and eggs, and fish (salmon, tuna, her-}

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

<table>
<thead>
<tr>
<th>Beneficial Effects</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omega 3 fatty acids</td>
<td>Excess of Total fat</td>
</tr>
<tr>
<td>Monounsaturated fatty acids</td>
<td>Excess of Saturated fat</td>
</tr>
<tr>
<td>Vegetable proteins</td>
<td>Trans fat</td>
</tr>
<tr>
<td>Soluble fiber</td>
<td>Excess of Linoleic acid</td>
</tr>
<tr>
<td>Vitamins: A.E.C, beta-carotines</td>
<td>Excess of Sodium</td>
</tr>
<tr>
<td>B vitamins and folic acid</td>
<td></td>
</tr>
<tr>
<td>Coenzyme Q10</td>
<td></td>
</tr>
<tr>
<td>Flavonoids</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
</tr>
<tr>
<td>Zinc</td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td></td>
</tr>
<tr>
<td>Selenium</td>
<td></td>
</tr>
<tr>
<td>Chromium</td>
<td></td>
</tr>
</tbody>
</table>

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, ω3 fatty acids and coenzyme Q10 in the neurons may influence the excitability of nerve centres. These vitamins, minerals, antioxidants, flavonoids and ω3 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 ω3 fatty acids (i.e. C18:3o3 or ALA or alpha-linolenic acid) and ω6 fatty acids (i.e. C18:2o6 or LA or linoleic acid) [10]. ω3 PUFAs have their first double bond at the third carbon, while ω6 PUFAs at the sixth carbon from the omega end. In the wild, ALA, often referred to as short chain ω3 PUFA, can be metabolized to longer chain ω3 PUFA, mainly eicosapentaenoic acid (EPA, C20:5o3) and docosahexaenoic acid (DHA, C22:6o3), whereas LA can be converted into arachidonic acid (AA, C20:4o6). 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 ω3 PUFAs play an important role in neural structure and function. The brain and CNS contain high concentrations of ω3 PUFAs and several studies suggest a role for ω3 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, C20:4o6) 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 ω3 PUFAs [3, 20], and the role of ω3 in visual and cognitive development has been described [21-24]. Any dietary deficiency in ω3 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 ω3 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-ω6/3). It is known that the relative amounts of ω6 and ω3 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 (ω3 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, ω3 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 ω3 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 ω3 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 ω3 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 antidepressive 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 ω3 PUFAs and depressed mood. There is epidemiologic evidence that ω3 PUFAs play a role in affective function. Numerous studies have shown a clear link between the drop in ω3 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 ω3 PUFAs levels, and higher ω6/ω3 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 ω3 PUFAs compared with placebo, and Nemets et al. [45] reported benefits of ω3 PUFAs compared with placebo for treating unipolar disorder.

The role of ω3 PUFAs in major depressive disorder has been studied by Su et al. [69]. They conducted an 8-week double-blind, placebo controlled trial comparing ω3 PUFAs (9.6g/d) with placebo, on top of the usual treatment. Interestingly, participants in the ω3 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 ω3 PUFAs effects on mood, cognitive and physiologic function have been reported by researchers from the University of Siena [49]. The study aimed to examine the effects of ω3 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 neuroelectric 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 glycemia. Over a period of 35 days they were supplemented with ω3 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 ω3 treatment. Supplementation with ω3 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 ω3. An EEG frequency distribution showed a shift towards low frequencies in all recordings after ω3 supplementation. In particular, after ω3 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 ω3 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 ω3 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 ω3 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 ω3 PUFAs could help to decipher the unsolved enigma of depression and connect the body and mind. The deficit of ω3 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 ω3 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 ω3 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 ω3 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 ω3 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 ω3 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 ω3 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 ω3 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 ω3 in varied groups of subjects. The evidence analyzed provides some support for the use of ω3 PUFAs in improving depressed mood. Larger trials with adequate precision to detect clinically important benefits are still required.

Indeed, the effects of ω3 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 ω3 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 ω3 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 then 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: 0.0; 2.0).
With the ratios of DHA/AA and in the total sample with erythrocyte in later adulthood. IQ at age 64 y was significantly correlated to higher cognitive function in late adulthood. IQ at age 64 y was significantly correlated to higher cognitive function in late adulthood. The blood samples of fish oil users and nonusers were examined; there were significant correlations between childhood IQ and erythrocyte ω3 PUFAs in 2000/01. This means that higher childhood IQ is probably related to higher 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 oil - compared with non-users. Cognitive advantages were found in the digit symbol subtest, which is highly sensitive to cognitive impairment, Alzheimer disease, dementia and stroke [i.e. 32, 84-89]. Relatively few studies have examined the beneficial role of ω3 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 ω3 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 oil - 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 ω3 PUFAs in 2000/01. This means that higher childhood IQ is probably related to higher cognitive function in late adulthood. IQ at age 64 y was significantly correlated in the total sample with erythrocyte ω3 PUFA content and with the ratios of DHA/AA and ω6/ω3 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 ≥10g/d had significantly better mean results in cognitive tests and a lower prevalence of poor cognitive performance than did those whose intake was <10g/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 ω3 PUFAs).

The association between plasma ω3 PUFA proportions and cognitive performance in older adults was also shown in another longitudinal study [93]. Researchers found that higher plasma proportions of ω3 PUFA predicted significantly less decline in such cognitive domains as sensory motor speed and complex speed over three years than did lower proportions of ω3 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 / ω3 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 ω3 PUFAs, remains uncertain. In example, participants with higher mental ability may be better informed about healthy nutritional habits, and eat a diet rich in ω3, 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 ω3 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 ω3 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 ω3 PUFA supplementation. These results indicate a beneficial influence of ω3 PUFAs on cognitive functions (attention) in healthy humans. It is possible that

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

<table>
<thead>
<tr>
<th>No.</th>
<th>Study</th>
<th>Year</th>
<th>Group</th>
<th>No. of subjects, total: treatment/placebo</th>
<th>Intervention</th>
<th>Daily dose</th>
<th>Duration (d)</th>
<th>Outcome measures</th>
<th>Statistical significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Behan et al.</td>
<td>1990</td>
<td>chronic fatigue syndrome</td>
<td>63:39/24</td>
<td>0.09g EPA</td>
<td>10</td>
<td>112</td>
<td>No</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>2</td>
<td>Warren et al.</td>
<td>1999</td>
<td>chronic fatigue syndrome</td>
<td>50:24/26</td>
<td>0.09g EPA</td>
<td>10</td>
<td>112</td>
<td>No</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>3</td>
<td>Stoll et al.</td>
<td>1999</td>
<td>bipolar disorder</td>
<td>30:14/16</td>
<td>0.14g EPA</td>
<td>120</td>
<td>112</td>
<td>Yes</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>4</td>
<td>Keck et al.</td>
<td>2002</td>
<td>bipolar disorder</td>
<td>116:59/57</td>
<td>0.14g EPA</td>
<td>84</td>
<td>112</td>
<td>No</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>5</td>
<td>Nemets et al.</td>
<td>2002</td>
<td>unipolar depressive disorder</td>
<td>20:10/10</td>
<td>2.0g EPA</td>
<td>28</td>
<td>112</td>
<td>Yes</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>6</td>
<td>Peet and Horrobin</td>
<td>2002</td>
<td>major depression</td>
<td>70:17_1gd 18_2gd 17_4gd</td>
<td>1.24g EPA</td>
<td>84</td>
<td>112</td>
<td>Yes</td>
<td>HDRS MADRS BDI</td>
</tr>
<tr>
<td>7</td>
<td>Llorente et al.</td>
<td>2003</td>
<td>postpartum depression</td>
<td>99:44/45</td>
<td>ok 0.2g DHA</td>
<td>120</td>
<td>112</td>
<td>No</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>8</td>
<td>Maranget al.</td>
<td>2003</td>
<td>major depression</td>
<td>36:18/18</td>
<td>2.0g DHA</td>
<td>42</td>
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<tr>
<td>9</td>
<td>Suet al.</td>
<td>2003</td>
<td>major depression</td>
<td>28:14/14</td>
<td>4.4g EPA</td>
<td>56</td>
<td>112</td>
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<td>HDRS YMR S CSI CGI GAS</td>
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<tr>
<td>10</td>
<td>Zanarini and Frankenburg</td>
<td>2003</td>
<td>bipolar disorder</td>
<td>30:20/10</td>
<td>1.0g EPA</td>
<td>56</td>
<td>112</td>
<td>Yes</td>
<td>HDRS MADRS MOAS</td>
</tr>
<tr>
<td>11</td>
<td>Post et al.</td>
<td>2003</td>
<td>bipolar disorder</td>
<td>121</td>
<td>6g EPA</td>
<td>112</td>
<td>-</td>
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<tr>
<td>12</td>
<td>Fux et al.</td>
<td>2004</td>
<td>obsessive compulsive disorder</td>
<td>11</td>
<td>2.0g EPA</td>
<td>42</td>
<td>112</td>
<td>No</td>
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<tr>
<td>13</td>
<td>Hirashima et al.</td>
<td>2004</td>
<td>bipolar disorder</td>
<td>21:12/9</td>
<td>5.02g EPA</td>
<td>28</td>
<td>112</td>
<td>Yes</td>
<td>HDRS YMR S CSI CGI GAS</td>
</tr>
<tr>
<td>14</td>
<td>Silvers et al.</td>
<td>2005</td>
<td>major depression</td>
<td>77:40/37</td>
<td>0.6g EPA</td>
<td>84</td>
<td>112</td>
<td>No</td>
<td>HDRS MADRS YBOC S</td>
</tr>
<tr>
<td>15</td>
<td>Fontniet al.</td>
<td>2005</td>
<td>healthy subjects</td>
<td>49:33/16</td>
<td>1.0g EPA</td>
<td>35</td>
<td>112</td>
<td>Yes</td>
<td>HDRS YMR S CSI CGI GAS</td>
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<tr>
<td>16</td>
<td>Osher et al.</td>
<td>2005</td>
<td>bipolar disorder</td>
<td>12</td>
<td>1.52g EPA</td>
<td>up to 168</td>
<td>112</td>
<td>Yes</td>
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<tr>
<td>17</td>
<td>Freeman et al.</td>
<td>2005</td>
<td>postpartum depression</td>
<td>16:6_0.5g EPA-DHA 3_1.4g EPA-DHA 7_2.5g EPA-DHA</td>
<td>0.5g EPA+DHA 1.4g EPA+DHA 2.8g EPA+DHA</td>
<td>56</td>
<td>HDRS YMR S CSI CGI GAS</td>
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<tr>
<td>18</td>
<td>Frangou et al.</td>
<td>2006</td>
<td>bipolar disorder</td>
<td>75:24_1gd 25_2gd 26_placbebo</td>
<td>1.2gd EPA</td>
<td>84</td>
<td>HDRS YMR S CSI CGI GAS</td>
<td></td>
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<tr>
<td>19</td>
<td>Nemets et al.</td>
<td>2006</td>
<td>children[6-12y][major depression]</td>
<td>28:13/15</td>
<td>0.38-0.4g EPA</td>
<td>112</td>
<td>HDRS YMR S CSI CGI GAS</td>
<td></td>
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<tr>
<td>20</td>
<td>Hallahan et al.</td>
<td>2007</td>
<td>patients with current self harm</td>
<td>49:22/27</td>
<td>1.2g EPA</td>
<td>84</td>
<td>HDRS BDI YBOC S MOAS INT RT MT PSS</td>
<td></td>
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<tr>
<td>21</td>
<td>Rogers et al.</td>
<td>2008</td>
<td>mild to moderate depressive disorder</td>
<td>190:96/94</td>
<td>0.63g EPA</td>
<td>84</td>
<td>HDRS BDI YBOC S MOAS INT RT MT PSS</td>
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<tr>
<td>22</td>
<td>van de Restetal.</td>
<td>2008</td>
<td>older subjects(~65 y) independently living</td>
<td>302</td>
<td>1.8g EPA+DHA or 0.4g EPA+DHA</td>
<td>182</td>
<td>HDRS MADRS GDS 15 HADS A</td>
<td></td>
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<tr>
<td>23</td>
<td>Buydens-Branchey et al.</td>
<td>2008</td>
<td>substance abusers</td>
<td>22:11/11</td>
<td>2.25g EPA+0.5g DHA+0.25 otherPUFAs</td>
<td>84</td>
<td>HDRS POMS</td>
<td></td>
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<tr>
<td>24</td>
<td>Lucas et al.</td>
<td>2009</td>
<td>middle aged women with moderate to severe psychological disorders (with and without MDE diagnosis)</td>
<td>120:59/61</td>
<td>1.05g EPA 0.15g EDHA</td>
<td>56</td>
<td>HDRS POMS</td>
<td></td>
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</table>

Note: HDRS YMR S CSI CGI GAS, HDRS MADRS BDI, HDRS YMR S CSI CGI GAS, HDRS MADRS MOAS INT RT MT PSS, HDRS BDI YBOC S MOAS INT RT MT PSS, HDRS MADRS GDS 15 HADS A, HDRS POMS.
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 w3 on the central nervous system. These results are in line with the above mentioned effects of w3 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 w3 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 w3 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 w3 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 w3 PUFAs might play a similarly beneficial role also in healthy humans’ mental function. Data indicate that high w3 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, w3 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 w3 fatty acids. First of all, there is not enough data on potential undesirable effects of long term w3 supplementation. Why does the 1-2 g/d w3 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 w3 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 w3 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 w3 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.

REFERENCES

Nutritional Modulators of Neuropsychiatric Dysfunction


