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## **Omega-3 Fatty Acids and Cognitive Functioning**

The impact of long-chain polyunsaturated acids on mental function is a topic of great interest due to the high levels of these fats found in the brain. Neural membrane phospholipids are largely composed of n-3 polyunsaturated fatty acids (PUFA) (1). Of particular interests are docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) because of low intake in Western diet (2) and the high levels of the latter in the cerebral cortex, synaptosome, and synaptic vesicles of mammals (1). The association between n-3 fatty acids and cardiovascular health is supported by the epidemiological reports of low incidence rates of ischemic heart disease in Greenland Eskimos whose high fat and high cholesterol diets, presumed to put great stress on the heart, are predominated by fatty fish: the primary source for dietary EPA and DHA (3). Direct parallels have been reported between a decline in cardiovascular health and a decline in cognitive function of humans.

At various points during the human life, researchers have found correlations between these fatty acids and mental functioning. It is believed that DHA and arachidonic acid (AA) are crucial for neural development of the mammalian fetus due to the increase in cerebral content of these fatty acids during the late pregnancy growth spurt of the brain (4). Following birth, the growing brain continues to require DHA for proper development (5). The only other major source of DHA is breast milk, but the amount varies based on the mother's diet. Maternal supplementation with DHA increases DHA levels in both breast milk and in the infant's plasma lipids (5). It is hypothesized that increasing the child's intake of DHA will result in improved mental functioning. Two randomized, double-blind, placebo-controlled trials were conducted in attempt to follow up on this hypothesis. It was found that beginning supplementation, of 200 mg/day of DHA for four months 5 days after delivery resulted in around 50% more DHA in the

mother's blood plasma, around 75% more DHA in the breast milk, and around 35% more DHA in the infant's blood plasma as opposed to that of the control group. This provides biological evidence of the successful delivery of DHA to the infant through maternal supplementation. Mental development was assessed at thirty months because assessments of younger infants tend to be less indicative of later abilities (5). At thirty months, the children of mothers whom had received supplementation did not receive different scores than the control group for the Clinical Adaptive Test, Clinical Linguistic and Auditory Milestone Scale, and Mental Environment Scale; however, the supplemented children did place higher on the scale measuring psychomotor development (5). It is reasonable to suspect that the superior psychomotor skills may be predictive of delayed neuropsychological effects of supplementation. It is not uncommon for chemical effects on infants' minds to become evident until later in life. Infants suffering from iron deficiency, for example, may not show any impairment of cognitive function until twelve years of age (5). In support of this concept, it has been found that the children of women receiving supplementation did perform better than the control group on intelligence tests at four years of age (4). In another trial, women between the ages of 19 and 35 received either 10 mL/day cod liver oil (1183 mg DHA, 803 mg EPA) or 10 mL/day of corn oil (4747 mg linoleic acid, 92 mg alpha-linolenic acid) beginning at eighteen weeks of pregnancy. Based on results from the mothers' food frequency questionnaires, there were no differences between the two groups in regards to dietary fatty acid intake. Blood and milk samples revealed a substantial increase in the ratio of n-3 to n-6 fatty acids in the supplemented mothers and likewise for the infants' umbilical and plasma phospholipids. As a potential confounder however, samples from the placebo group revealed greater concentrations of AA and Osbond acid (22:5n-6) in both the mother and child. This fact is not mentioned in the study, yet the action of even greater levels of AA are worthy of inquiry. At the four year assessment of mental processing, the children of supplemented mothers scored significantly higher on the Mental Processing Composite test, and displayed "a clear tendency to higher scores" on the remainder of the tests (4). There is a known

correlation between the Mental Processing Composite scores and head circumference at birth, but a regression model of the same study shows that this does not significantly factor into the statistics. N-3 fatty acid concentration in umbilical plasma phospholipids did not correlate with intelligence scores. In contrast, umbilical plasma concentration of Osbond acid did correlate negatively with intelligence scores; providing evidence of a neglected confounder (4). Much like the relationship between EPA and AA, Osbond acid is almost identical to DHA minus the double bond at the omega-3 position.

Between the two studies regarding DHA or cod liver oil supplementation for nursing mothers, it becomes increasingly apparent that such behavior has a positive impact on the child's cognitive function. The participants of one trial began receiving DHA and EPA at eighteen weeks into the pregnancy, whereas the other began receiving exclusive DHA supplementation at 5 days after birth, yet the results were both in favor of supplementation. In addition, a substantial percentage of the control group in the cod liver oil trial began receiving 3 mL/day of cod liver oil due to Norwegian health standards (4). Neither study was definitive but the biological evidence of nutrient delivery, the apparent superior cognitive skills, and the physiological activity of the unique nutrients in question do provide a high level of confidence in the hypothesis that supplementing nursing mothers with DHA or fish oil improves the cognitive functioning of their infants.

Measuring mental function is a challenging task considering the biological uncertainties of the mind. A number of studies have investigated the impacts of DHA and EPA supplementation on different mental disorders. A meta-analysis conducted by Ross et al. investigated the treatment of psychiatric disorders with EPA, DHA, or both. Each trial was analyzed and rated for quality based on the Jadad scoring system, in which a higher score indicated a higher quality (2).

Approximately 2-7% of school-age children in the U.S. are diagnosed with ADHD, and about 80% are medicated, usually with a stimulant such as methylphenidate (2). Research has

found a lack of PUFA abundance in plasma and erythrocyte membranes of children with ADHD. Previous studies have reported no correlation between n-6 supplementation and ADHD, but it wasn't until more recently that researchers began investigating an association with n-3 fatty acids. A non-placebo controlled trial reported decreased hyperactivity in children with ADHD who were receiving flax oil. Another trial that was mentioned, but not analyzed by Ross et al., reported enhanced attention in healthy adults receiving n-3 supplementation. Regardless of such promising facts, of five different placebo-controlled, double-blind clinical trial, none found a significant difference in symptoms of children with ADHD receiving various amounts of DHA (2).

Slightly more positive results came from a double-blind, placebo-controlled trial of high quality (Jadad = 5) supplementing children with Developmental Coordination Disorder (DCD). DCD involves specific impairment of motor functions but has some overlap with ADHD in relation to difficulties learning. Though there is some overlap, the participants of this trial would likely not meet the DSM-IV (Diagnostic and Statistical Manual for Mental Disorders Version IV) criteria for ADHD. Children with DCD were given 558mgEPA, 174mgDHA, 60mgGLA (n-6: gamma-linoleic acid) or placebo for five weeks. No improvement was noted regarding improved motor skills, but supplementation did lead to improvements in nearly all other symptoms of the condition.

The five trials investigating ADHD and DHA used similar formulas for supplementation where the ratio of DHA to EPA was around 2:1. The supplement ratios in the DCD trial were essentially reversed except they included an omega-6 fatty acid without explanation (2). This is puzzling because GLA is a precursor to AA, the twenty carbon counterpart of EPA, and thus competes for absorption in the brain (6).

Limited research has been conducted regarding anxiety disorders and DHA and EPA supplementation. Anxiety disorders are a category of psychological disorders characterized by any number of fears and phobias as well as generalized anxiety. The symptoms of anxiety are

biologically associated with the hypothalamic-pituitary-adrenal axis and the hormones therein. Research has shown that supplementation with 443mg EPA and 319 mg DHA per day reduces plasma levels of these hormones relative to a control group. A twelve week, placebo-controlled, double-blind clinical trial researching treatment of Obsessive Compulsive Disorder (OCD) with EPA supplementation ended without a solid conclusion. All of the participants suffered from mild symptoms, and due to the study's design, the placebo group received supplementation for the first half of the trial's duration (2). Anxiety resulting from substance abuse is similar in nature to anxiety suffered as result of an anxiety disorder, but not a clinically defined disorder. A double-blind, placebo-controlled randomized clinical trial was orchestrated to determine supplementing with 2.2g EPA and 0.5g DHA per day would suppress anxiety symptoms of 24 men recovering from substance abuse. A remarkable improvement was reported as compared to the placebo group (vegetable oil). In addition to the small size of the study, the results were acquired by way of self-assessment causing for unweighted results. Decreased anxiety was also reported by participating students preparing for exams who were provided with a mixture of n-3 and n-6 PUFAs in an open-label trial (2).

Major depressive disorder (MDD) affects at least 5% of the population and approximately 15% of sufferers commit suicide, making it the seventh most frequent cause of death in the nation (2). MDD is characterized by depressed mood, fluctuating weight, inconsistent sleep patterns, and reduced cognitive abilities. Selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants are commonly prescribed for sufferers of MDD but about 10-20% of patients do not respond positively to this treatment, and those that do respond at varying degrees. It has been speculated that the increase in dietary n-6 fatty acids and the decrease in n-3 fatty acids has contributed to the increased prevalence of the disorder. Studies have consistently found that while patients with MDD have normal n-6 levels, they lack an abundance of n-3 HUFAs. Three double-blind, placebo-controlled trials revealed a positive correlation between high-EPA supplementation and decreased symptoms of MDD. In one trial,

seventy patients whom had not responded well to medication received 1, 2, or 4g/day of EPA for twelve weeks. Only the 1 g/day dose provided clinically significant benefit, but showed marked improvement as quickly as four weeks into the trial. This may suggest that too much EPA without co-supplementation with DHA may be ineffective or even detrimental to treatment success. In contrast to these results, another trial provided 2 g/day of EPA to twenty medicated patients for four weeks, resulting in equally beneficial effects. A third study in which twenty-two patients (two were not medicated) received a fish oil capsule (2.2g EPA, 1.1g DHA) for eight weeks and the positive results were again replicated. The ratio of EPA to DHA was reversed in a separate double-blind, placebo-controlled trial, in which seventy-seven participants received 2.4g DHA and 0.6g EPA per day. The higher DHA supplementation did not result in greater improvement as compared to the control group (olive oil placebo).

Childhood depression affects approximately 2-4% of children (2). Two small, placebo-controlled trials of differing designs provide more support for the use of high EPA supplementation in the treatment of depression. A positive correlation between supplementation and decreased symptoms occurred in children receiving 380-400 mg/day EPA and 180-200 mg/day DHA (dosage varying dependent on weight) as opposed to children receiving a safflower oil placebo. Symptoms did not improve in the other trial in which children received 2g/day DHA in undisclosed form (speculated by Ross et al to be fish oil because several children complained of “fish” aftertaste) as compared to placebo. The absence of formula specifications further depletes the trial’s usefulness in determining efficacy of supplementation, but in viewing with the other trials, it does not provide dismissal to the positive correlations found in the other studies regarding depression.

The symptoms of depression were impacted, but to varying degrees, by supplementation in trials involving patients with bipolar disorder (BD). Depression is only half of the problem with regards to bipolar disorder though. The mania associated with bipolar disorder was unaffected and even postulated to be potentially worsened by n-3 supplementation (2). The

research displaying the frequency of n-3 PUFAs deficits with bipolar disorder have been recurrent yet with less consistent results than that of the association between n-3 deficits and MDD. In two placebo-controlled, double-blind clinical trials, high EPA supplementation has proven successful at treating the depressive symptoms of BD, while not affecting the manic symptoms. One trial conducted by Stoll et al included patients receiving 6.2g/day EPA and 3.4g/day DHA or olive oil placebo. It is noted that those receiving supplementation were significantly less likely to require changes in treatment (which would result in exclusion from the trial) for at least thirty days. The significance of this factor is unclear, but the authors also reported the positive correlation with symptoms of depression. Seventy-five medicated outpatients with BD received either 1g or 2g/day of ethyl-EPA or placebo for twelve weeks in a high quality trial (Jadad score = 5). Statistical analysis of the two supplemented groups independently of one another did not reveal a significant improvement in depressive symptoms. The report does express a statistically significant decline in depressive symptoms when data from both supplemented groups were combined. The need to manipulate the data for a positive correlation is indicative of less significant results, but it should not be overlooked that 2 g/day of ethyl-EPA was ineffective in the dose-ranging trial for MDD. Evidence is building in support of EPA as an effective treatment for symptoms of depression, but by offsetting some unspecified ratio of EPA to DHA, the treatment appears to become less effective. It is clear that supplementation with EPA is not an effective treatment for the symptoms of mania associated with bipolar disorder; however, it is unlikely, based on the results of these trials, that such supplementation will intensify manic episodes (2).

Another psychiatric disorder associated with limited successes in treating with pharmaceuticals is schizophrenia. Schizophrenia is an episodic condition with both positive and negative classes of symptoms. Positive symptoms include disorganized thoughts and behaviors, hallucinations, and delusions. Negative symptoms include limited verbal abilities and lack of emotion. Anti-psychotic drugs have limited efficacy, particularly with the negative class of

symptoms, and the side effects tend to be especially undesirable. It has been suggested that schizophrenia is associated with membrane phospholipids and numerous studies have explored this hypothesis, and have shown evidence of a lack of PUFA abundance in multiple body tissues. Inconsistencies in the studies' results have led to the consensus that PUFA alterations in the body are secondary to diet changes occurring as result of the mental illness (2). Small trials utilizing n-6 supplementation (predominantly gamma linoleic acid) had mostly negative results. Mixed results were obtained in more recent double-blind studies utilizing n-3 PUFAs. Determination of efficacy was heavily reliant on the Positive and Negative Syndrome Scale (PANSS) (2). A placebo-controlled, double-blind clinical trial conducted by Peet et al compared treatments of 2 g/day of EPA, 2 g/day DHA, or 2 g/day of corn oil placebo for three months for forty-five medicated patients. Based on PANSS scores, Peet et al reported a 25% decrease in symptoms of the EPA-treated patients as compared to the DHA-treated or control group. Following this trial, the same researchers conducted another double-blind trial in which they administered 2 g/day of EPA or placebo to twenty-six unmedicated patients for three months. The results were again positive for the EPA-treated group. The unmedicated patients of the second trial were provided with anti-psychotics in the event that they were required during the trial which limits the conclusions drawn from their results. However, four of the fifteen EPA-treated patients had not received any medication during the trial, whereas all of the patients receiving placebo did require medication during the trial. It was also noted by the authors that the EPA-treated patients that did receive medication required it for notably fewer days compared to that of patients receiving placebo. Peet and Horrobin conducted a later dose-ranging trial of a placebo-controlled, double-blind design in which one hundred fifteen medicated patients received 1, 2, or 4 g/day of ethyl-EPA or liquid paraffin placebo for twelve weeks. Patients receiving the anti-psychotic, clozapine, showed a marked improvement from supplementation with 2 g/day of EPA, but not 1 or 4 g/day. The same results were not recorded in patients receiving other anti-psychotics, yet all EPA-treated patients receiving neuroleptics, rather than anti-psychotics, showed improvement from

baseline PANSS scores as compared to the placebo-treated patients. Without clear explanation of physiological interactions of the drugs and the HUFA, the data is inconclusive. In addition, the statistical data was found by Ross et al to be flawed in that the intervals all contain zero, showing no statistical difference between any of the EPA-treated groups and the control group. As a result the trial conducted by Peet and Horrobin does not provide useful evidence in support or rejection of the findings reported by the earlier studies by Peet et al (2).

The meta-analysis discusses two more double-blind, placebo-controlled trials intended to measure effects of EPA supplementation on the symptoms of schizophrenia. Fenton et al provided supplementation or placebo for eighty-seven medicated patients in the form of 3 g/day of ethyl-EPA or a mineral oil placebo for sixteen weeks. No significant difference in PANSS scores were reported between the EPA-treated and placebo groups. Fenton et al comment on increases of erythrocyte EPA levels among participants receiving placebo suggesting that these participants altered their dietary intake of n-3 PUFAs either through increased consumption of fatty fish or fish oil supplements because of knowledge obtained by informed consent forms. Nonetheless, the change from baseline scores did not improve significantly in either group as compared to results from trials conducted by Peet and colleagues (2). In another trial in which forty medicated patients are administered 3 g/day of ethyl-EPA or liquid paraffin placebo for twelve weeks, the authors reported substantial improvements in PANSS scores of EPA-treated participants as opposed to placebo-treated participants. However, contrary to the findings of Peet and Horrobin, EPA-treated participants in this trial whom were receiving typical antipsychotics showed slightly better results than those medicated with the atypical antipsychotic clozapine. This contrast offers additional rationale for excluding the data from these trials when analyzing any overall effect of EPA-supplementation on schizophrenia. Other trials do offer suggestive evidence of interaction between HUFA supplementation and schizophrenia, but inconsistencies in results cause Ross et al to conclude that any relationship, if one exists, is likely to not be clinically relevant (2). Ross et al fail to acknowledge that every one of the trials mentioned in the meta-

analysis use supplementation of EPA exclusively without the co-supplementation with DHA; yet results from trials researching other disorders suggest this to be an important factor.

The advantages of EPA supplementation for treatment of depression are very promising, while the lack of improvement in symptoms of other disorders may raise questions of overall efficacy. From the perspective of whether or not supplementation improves cognitive functioning, it is helpful to look at the biology of the symptoms and accepted pharmaceutical treatments. Pharmaceuticals used in treatment of mood and anxiety disorders are believed to be effective as result of enhanced serotonergic or dopaminergic neurotransmission. In contrast, anti-psychotics used to treat schizophrenia are believed to provide relief from positive-class symptoms as a result of depressed dopaminergic neurotransmissions. In fact, chemicals that enhance dopaminergic neurotransmission can actually exacerbate symptoms of schizophrenia. Clearly, it would not be easily explained if the same treatment would be found to be effective in schizophrenia and mood disorders. Furthermore, if enhanced dopaminergic neurotransmission is found to be directly correlated to n-3 PUFA supplementation, it would be completely irrational to treat schizophrenia with such supplementation (2). This very relationship has been found to occur in the frontal cortex of rats in multiple studies reviewed by Horrocks and Farooqui (3). Rats synthesize DHA more efficiently than humans but comparable supplementation based on a number of different variables has shown the biological similarities between the importance of dietary n-3 PUFAs with regards to DHA levels in the brains of rats and humans (6). Considering this, rat models do hold a limited, yet valid, position in the explanation of n-3 HUFA supplementation effects on the brain.

A deficiency in dietary n-3 PUFAs directly effects dopamine metabolism as well as dopamine receptors and transporters of the nucleus accumbens in rats. As a result, dopaminergic neurotransmission within the mesolimbic system becomes altered by n-3 deficiencies (3). Interestingly, antipsychotics used for treatment of schizophrenia, are believed to depress D2 dopamine receptors of the portion of mesolimbic system which originates in the nucleus

accumbens (2). In the rat models, n-3 supplementation increases the levels of dopamine binding to the D2 receptors. In a study using students, aggression resulting from stress was reduced following DHA supplementation, further supporting the concept that while EPA supplementation does not offer relief from a number of symptoms of psychological disorders, the dual interactions of DHA and EPA may be crucial for successful psychotropic effect (3).

Alzheimer's disease (AD) and dementia are diseases associated mostly with the elderly and associated with age-related decline of cognitive functioning. Epidemiological studies have suggested that dietary n-3 HUFAs may play a role in delaying this decline, whereas the Chicago Health and Aging Project provided evidence that dietary n-3 HUFAs help reduce cognitive decline but are ineffective with regards to the rate at which it occurs (7). Autopsies have shown notably low levels of DHA in the hippocampus of patients with AD as compared to that of patients without AD of similar age (3). Due to the research that has shown cell membrane composition can be improved by n-3 HUFAs, it is speculated that they may be responsible for regeneration of nerve cells (7). In rat models, DHA supplementation reverses the effects of age-related increases of arachidonic acid in neural membranes that result in diminished synaptic plasticity and the associated learning and memory processes (3).

A prospective cohort study which obtained complete information for 210 men born from 1900 to 1920 examined the possibility of association between dietary PUFAs and cognitive decline (7). Dietary assessments were obtained in 1990 and 1995 by interview by dietician regarding diet over a course of two to four weeks. During this time, assessment of cognitive functioning was recorded based on the Mini-Mental State Examination (MMSE). In 1990, no difference in cognitive functioning was reported between men who did consume fish and those who did not. By 1995, a second examination revealed that the men who did not consume fish had a cognitive decline four times that of those who did consume fish based on MMSE scores. Inaccuracies in data could have resulted from interviewing men with cognitive impairment unintentionally providing false data, but results were not affected with the exclusion of men with

preexisting impairment of cognitive functioning (7). The design of the Zutphen Elderly Study causes it to provide limited support of its findings. Accuracy with dietary assessments are limited as a result of uncontrollable factors such as dishonesty or inaccurate recall of frequency, quantity, and food type provided by interviewees regardless of their mental states. It is also extremely difficult to accurately assess precise nutritional content retrospectively. Eggs, for example, may provide varying amounts of EPA and DHA potentially leading to significant differences between actual versus calculated intake of these nutrients. However, evidence from the Chicago Health and Aging Project suggests protective properties of consuming fish but not of consuming n-3 PUFAs from other sources, such as eggs, or plant products (7).

The Chicago Health and Aging Project was another prospective cohort study which included information on 815 subjects at the end of the trial period of approximately four years. The population consisted of adults at least 65 years of age, with a mean educational level of 11.8 years. Cognitive functioning was assessed by four different tests and a 90 minute interview. Dietary assessment was limited to a self-administered food frequency questionnaire (FFQ) with 154 questions. A multivariable model was used for analysis of data which accounted for age, sex, race, education, apolipoprotein 4 (the allele commonly associated with genetic predisposition for AD), and interaction between race and the allele. History of health and disease was self-reported. 131 participants were diagnosed with AD at follow up. Subjects who had the highest levels of n-3 HUFAs were more frequently male, with more education, a history of hypertension, and history of consuming higher levels of all types of fat. Those who consumed fish at least once a week were 60% less likely to develop AD than those who rarely or never ate fish. When data was reanalyzed with exclusion of weekly fish consumers whom had increased fish intake over past ten years, the data became more conclusive in same direction (1). Protective properties of dietary alpha linolenic acid against AD were reported in women with the apolipoprotein 4 allele but not in men or subjects without the allele (1). In addition to the confounding effect of the self-reporting design of the study, more than 90% of fish consumed was very low in fat. Fish low in

fat have low levels of DHA and insignificant amounts of EPA. A counter-balancing effect of the possible exaggeration of quantity of fish consumed, due to dishonesty in FFQ, and the low levels of EPA and DHA in the majority of fish reportedly consumed supports the claim made by Morris et al that consumption of fish decreases the risk of AD (1).

5,395 subjects were evaluated in a prospective cohort study designed to determine a relationship between dietary fat and dementia. Engelhart et al hypothesized that risk of dementia was increased with higher cholesterol and decreased with greater amounts of dietary n-3 PUFAs. At baseline, dietary assessment was obtained by FFQ, an extensive checklist of items, including supplements, consumed at least biweekly for the past year, and an interview by dietician. Assessment of nutritional values in diet were obtained with use of the Dutch Food Composition Table. Data was collected on subjects until death, onset of dementia, or end of trial period (mean: 6 years). During the trial, 3.7% developed dementia. The results show no relationship between intake of PUFAs and AD or dementia. The authors do not discuss the facts that the data reveals a ratio of 12:1 between n-6 and n-3 PUFAs, respectively, and a ratio of almost 2:1 saturated fat to PUFA, respectively (8). The twenty carbon PUFAs, EPA and the n-6 fatty acid, arachidonic acid (AA), compete with one another for absorption in the brain (6). Epidemiological support is provided by a case-control study which found that levels of n-3 PUFAs in plasma phospholipids were 60% to 70% lower in patients with AD as compared to control subjects of matched age (1). However, it cannot be determined by this data that the lower levels are a result of diet prior to onset of disease. DHA supplementation in aged rats reflected cortical lipid content similar to that of young rats. The typical cortical lipid content of the same species of aged rats consists of an increase in AA and a decrease in DHA levels. These changes are directly correlated with age-related decline in behavior and physiological state. Due to the large number of influences Little et al found DHA supplementation to have in the nervous system of the rat model, the authors conclusively express that the increase of PUFA in cortical phospholipids improves membrane fluidity and, consequently, synaptic transmission (9). Without further explanation, the authors

postulate that subjects with diets high in saturated fat that do not die from cardiovascular disease may be at less risk of developing dementia due to a decreased sensitivity to saturated fat unique to the individuals (8). Regardless of the size of the study and the thorough dietary assessment, the singular evaluation and neglect of other covariates dramatically lessens the validity of the findings in The Rotterdam Study.

The Doetinchem Cohort Study attained information for 1,209 subjects, with mean age of 56.3 years, over a course of six years to investigate a relationship between dietary PUFAs and cognitive performance at middle age. Dietary assessment was obtained by a self-administered FFQ, followed by nutritional assessment derived from the Dutch Food Composition Table. Multiple cognitive tests were carried out at time of dietary assessment by trained investigators. The data showed correlations between cholesterol and saturated fat with increased risk of decline in cognitive functioning, whereas fatty fish, EPA, and DHA were inversely related to cognitive decline. These relationships became slightly stronger when subjects who scored in the lowest 5% of memory score were excluded (10). Plasma samples were not taken so lipid concentrations and apolipoprotein allele were never included in the data. In comparison to The Rotterdam Study, the less reliable dietary assessment, resulting from lacking a dietician interview, is counter-balanced by the fact that the younger mean age of subjects in the second study causes Kalmijn et al to be less suspicious of false data resulting from cognitive impairment of the self-reporting subjects. And although measurement error associated with dietary assessment is unavoidable, it is also random, which, with a large enough sample population, could potentially nullify many of the inaccurate recordings in the final assessment of the collective data (10). The extensive array of cognitive tests also creates for a greater level of confidence in the results.

Limited data is available with regard to the cognitive effects of n-3 HUFA supplementation on healthy individuals. In a small, but well designed placebo-controlled study of forty-nine healthy volunteers, with a mean age of 33 +/- 7 years, subjects received either 4g/day of fish oil (1.60 g EPA, 0.80 g DHA, 0.40 g other types of n-3 PUFAs) or an olive oil

placebo for thirty-five days. Subjects were required to be free of drugs or medication, exercise for three to six hours per week, have no history of psychiatric or endocrine disorders, and habitual consumption of alcohol, tobacco, and caffeine was limited. Throughout the duration of the trial, the subjects were assigned a personalized diet by dietician to avoid excesses that would confound in the results. Each day, participants filled out a diary card to record psychological state and any deviations from diet or other constraints. An eight hour medical examination including blood samples was conducted on the first and last days of the trial. Also on days one and thirty-five, physiological status of the individuals was examined through electroencephalogram (EEG), electromyography (EMG), and electrocardiogram (ECG), while concurrently filling out the Profile of Mood States questionnaire (POMS). Four attention tests were administered in a controlled, homogenous environment testing reaction times to different stimuli. An eight minute relaxation period followed the attention tests. EEG and EMG recordings were obtained during the attention tests and the relaxation period (11).

At day one, no differences were recorded between fish oil and placebo groups with regards to blood lipid concentrations. The only variation in blood lipid concentrations was that the fish oil group showed a significant decrease in the ratio of AA to EPA at the end of the trial: whereas the placebo group did not. Analysis of POMS data showed a significant improvement in the fish oil group in vigor, the single positive category being measured, and significant decreases in anger, anxiety, fatigue, depression, and confusion. No significant change was reported for the placebo group. Among the results from the attention tests, reaction time only decreased for the fish oil group and only in Go/No Go (GO) and Sustained Attention (SA) tests. Both of these tests measured reaction time and accuracy when subject were required to react or not react in response to particular stimuli. The results of the POMS and attention tests are supportive of the theory that performance is influenced by emotional state (11). Changes in brain wave activity determined by EEG recordings were only attained from the subjects who had been receiving supplementation, most notably during GO, SA, and relaxation periods. The EEG fluctuated in

that there was a reduction of the higher frequency band and an increase in the low frequency bands. These concurrent fluctuations are significant because lower frequency bands are associated positively with memory and cognitive function; whereas attentional deficits and anger are associated with increases in higher frequency alpha bands. Furthermore, increases in lower frequency bands are positively associated with greater time spent performing a skilled task. EMG recordings revealed that improved reaction times were not the result of supplementation on peripheral muscles. Comparative analysis of the EEG and EMG recordings of the fish oil group suggests that changes were occurring in the tissue of the brain more so than in the muscle tissue (11). Fontani et al found no association between age or gender and the impacts of n-3 HUFA supplementation on cognitive functioning of healthy individuals, thus offering very convincing evidence in support of their hypothesis.

Overall, supplementation with EPA and DHA has a positive effect on cognitive functioning in humans. The specific mechanisms need to be better understood before supplementation is clinically accepted for treatment of psychological disorders, but supplementation with crude fish oil in coordination with medication appears to be safe and beneficial. Supplementation with synthetic EPA appears to be universally most beneficial when accompanied by at least 50% as much DHA. The most destructive confounder in the research of n-3 PUFAs and cognitive functioning is the use of other fatty acids as placebo. Future studies would be better conducted if placebo were a neutral agent until exact mechanisms of action are completely understood. The results from the study conducted by Fontani et al are very convincing and future clinical trials should be designed in a similar fashion. If all trials utilized EEG and EMG a collective analysis would become exponentially valid.

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