39 Fatty Acids, Cognition, Behavior, Brain Development, and Mood Diseases

Jean-Marie Edouard Bourre

CONTENTS

I. INTRODUCTION

Fatty acids control the structure and function of biological membranes, including membranes in the nervous system. The brain has higher lipid content than any other of the body's organs, except adipose tissue itself. All its lipids, which are mostly phospholipids, are found in cell membranes, and they are almost never sources of energy. Position 2 of the glycerol molecules in phospholipids generally bears a polyunsaturated fatty acid such as docosahexanoic acid (DHA; 22:6(n-3), 22:6ω3, cervonic acid), or arachidonic acid (ARA; 20:4(n-6), 20:4ω6). There may well be smaller amounts of adrenic acid (22:4ω6) and eicosapentanoic acid (EPA; 20:5(n-3), 20:5ω3) or docosapentaenoic acid (22:5ω3). The brain contains very little alpha-linolenic acid (ALA; 18:3(n-3), 18:3ω3) although this fatty acid is the precursor of all the other omega-3 fatty acids. The families of fatty acids are shown in Figure 39.1. A major component of brain membrane phospholipids is the omega-3 fatty acid DHA, and high concentrations of this fatty acid are found in the more metabolically active area of the brain, including the frontal cerebral cortex, which is involved in cognition, mitochondria, nerve endings, and synaptic vesicles. Most studies on cognition have focused on omega-3 fatty acids, or the

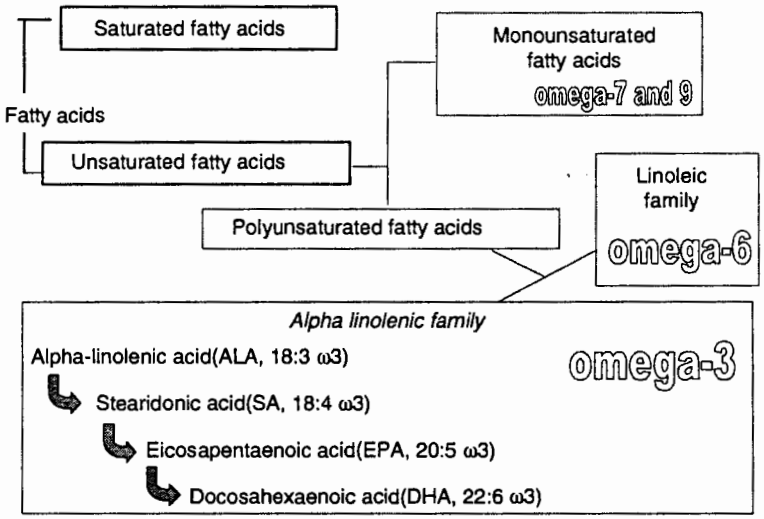

FIGURE 39.1 Omega-3 and other fatty acids.

balance between these fatty acids and omega-6 fatty acids. However, one review has examined the role of the ARA cascade in affective disorders (Sublette and Trappler, 2000).

The importance of the omega-3 fatty acids (ω3) for brain development is based on three findings. First, the brain is exceptionally rich in polyunsaturated fatty acids, including omega-3 fatty acids. They account for 15%–20% of cerebral fatty acids, and for as much as 40% in the neurons and nerve terminals (Bourre et al., 1984). Second, a lack of dietary ALA results in a reduced cerebral DHA content, which is offset by increase in 22:6 omega-6 (Bourre et al., 1984; Galli et al., 1972). Finally, human mother's milk is particularly rich in ALA, but the cow's milk used to prepare baby formula in the early 1980s is not. This was because many formula producers used sunflower oil (without any omega-3 fatty acids) in the 1980s rather than rapeseed oil (9% ALA). The effect of such a deficiency on brain structure and functions, including cognition was first examined in animal studies and later in human newborns. Human fetuses and newborns accumulate considerable quantities of omega-3 fatty acids, mainly DHA (Cunnane et al., 2000).

Experimental studies showed that the differentiation (Bourre et al., 1983) of brain cells in culture requires omega-3 fatty acids as well as omega-6 fatty acids. A lack of dietary ALA disturbs the composition of brain cell membranes (Bourre et al., 1984). Chemical, physicochemical, biochemical, and enzymological analyses, plus toxicological, physiological, electrophysiological, and behavioral studies on ALA-deficient animals provided the first experimental evidence that a dietary component could influence the structure and function of the brain (Bourre et al., 1989b). There is a dose–effect relationship between the amount of ALA in a nursing rat's diet and its accumulation in the pup's brain, a minimum must be added to the diet: 0.4% of the dietary calories in a rat, thus 0.8% in humans, taking into account the brain/body weight ratio and the energy need per unit of surface area (Bourre et al., 1989b). It was subsequently shown that the omega-3 fatty acids in modified baby formula influence the visual and cerebral (including intellectual) capacities of the child, as measured by its neurological development, intellectual quotient, and motor index (Uauy et al., 2003). Hence, all baby formulas now contain at least ALA, in quantities equivalent to those in mother's milk.

Omega-3 fatty acids have both long-term and short-term actions in the brain. Long-term, they influence the production and maintenance of brain structures, and hence their function. Many studies have shown their effects on the development of the brain. Their short-term effects are on the physiology of signal transduction. These are biochemical pathways that have no direct link with the diet, except that the molecules involved are of dietary origin. Several reports have claimed that

these reactions underlie such disorders as autism, dyslexia, or even schizophrenia. And of course, both long-term and short-term influences can be present at the same time, such as when membrane alterations are accompanied by neuroinflammation (Bourre, 2005a).

Several studies have examined the effects of omega-3 fatty acid on brain biochemistry, membrane physical chemistry, enzyme activities and carrier function, neuromediators, electrophysiological parameters, behavior, and cognition. Others have looked at how these and other fatty acids are implicated in the nervous systems of animals and humans during life, particularly during development and aging. They have been covered in recent reviews (Bourre, 2004a,b); there have even been popular books written about them (Bourre, 1990, 2004c), including a recent one on omega-3 fatty acids (Bourre, 2004c).

Psychiatrists are interested in omega-3 fatty acids for several reasons. The high content of these fatty acids in the brain is one reason. Another reason is the experimental demonstration that a lack of dietary ALA results in behavioral and cognitive defects, particularly problems of learning, memory and habits, and reactions to toxins such as morphine. A lack of ALA also results in the abnormal metabolism of neuromediators.

The main feature of the omega-3 and omega-6 fatty acids is that they are both essential and strictly complementary, but they compete for the desaturase enzymes. The human diet usually contains enough omega-6 fatty acid, but the diets of people in occidental countries may contain insufficient ALA and DHA for pregnant women, mainly because of an insufficient intake of rapeseed oil (canola oil), walnut oil, and oily fish.

II. BRAIN DEVELOPMENT: EVIDENCE FROM ANIMAL MODELS AND STUDIES ON HUMANS

A. Experimental Evidence

Animal studies have provided convincing and consistent evidence linking a decrease in brain concentrations of DHA to altered performance in cognitive and behavioral tests. ALA deficiency affects the cognition/behavior of animals. For example, a lack of dietary ALA does not severely alter the neuromuscular function of rats (Frances et al., 1995), but it does affect learning (Bourre et al., 1989b) and behavior in humans (Frances et al., 1996a; Wainwright et al., 1994). Those activities that are associated with memory and habituation are particularly affected (Frances et al., 1996b; Frances et al., 2000), as has been confirmed in studies (Carlson, 2000; Coscina et al., 1986; Heird and Lapillonne, 2005; McCann and Ames, 2005; Salem et al., 2001; Wainwright, 2002; Yamamoto et al., 1988) using other tests. The effects on rodent cognition were shown in tests that involved sensory pathways other than the visual pathway.

The suggested relationship between the changes in learning performance and the composition of the microsomal membrane (Yoshida et al., 1997) seems to correlate well with the cognitive and behavioral deficits seen in rats fed a low-ALA diet and the defects in their monoaminergic nerve transmission, particularly in the frontal cortex (Chalon et al., 2001; Levant et al., 2004). A lack of dietary omega-3 influences specific neurotransmitter systems, particularly the dopamine systems of the frontal cortex, which is involved in cognition, but restoring dietary ALA does not completely restore dopaminergic neurotransmission in the frontal cortex and other areas (Kodas et al., 2002). Thus, the slow incorporation of fatty acids into the brain (Bourre et al., 1989a) is correlated with a slow improvement in learning (Lim and Suzuki, 2001). There is a clear relationship between polyunsaturated fatty acids and neurotransmission, and so between them and behavior (Chalon et al., 2001). Cholinergic and serotoninergic neurotransmission (Aid et al., 2003; Kodas et al., 2004) are also influenced by a lack of dietary ALA.

The most commonly used developmental outcomes examined in human infants are visual function and general neurodevelopment. Neurodevelopment is assessed by the Bayley Scale of Infant Development (BSID), first or second edition. It includes both the mental developmental index (MID)

TABLE 39.1
Effect of ALA Concentration on Blood Parameters and the Mental Performance of Newborn Infants

ALA in milk	0.40	0.95	1.70	3.20
Plasma phospholipid ALA	0.10	0.16	0.23	0.46
Erythrocyte phospholipid ALA	0.05	0.09	0.12	0.23
Erythrocyte phospholipid DHA	0.83	1.55	1.72	2.52
Bayley PDI	88.80	95.50	93.70	96.40
Bayley MDI	94.80	96.30	101.00	100.50

MDI = mental developmental index; PI = psychomotor developmental index.

Source: From Voigt, R. G., et al. (2002). *J. Hum. Nutr. Diet.* 15: 111–120.

and psychomotor developmental index (PID). Other developmental assessments include the clinical Adaptative test (CAT); clinical Linguistic and Auditory Mileston Scale (CLAMS) and Gross Motor Scale (GMS) of the revised Gesell Developmental Inventory. Developmental quotients (DQ) are determined for language development (CLAMS DQ), visual problem solving ability (CAT DQ) in overall cognition (the mean of CLAMS and CAT DQ). A meta-analysis showed that infants fed ALA-supplemented formula had significantly higher concentrations of DHA in plasma and erythrocyte phospholipids, but further studies are needed to provide convincing evidence of the effect of ALA itself on growth and development (Udell et al., 2005).

ALA alone does not seem to be sufficient to ensure that the brain has an optimal concentration of DHA (Bowen and Clandinin, 2000), although an adequate equilibrium between linoleic acid (LA, 18:2(n-6), 18:2ω6) and ALA could ensure the optimal synthesis of DHA (Cheon et al., 2000). The brain seems to use preformed very long-chain omega-3 polyunsaturated (and omega-6) fatty acids most effectively under normal circumstances (Cunnane et al., 2001), which implies that they are synthesized in the liver from ALA (and LA, respectively) or are not obtained directly from the diet. DHA injected into the blood stream is taken up by the brain (Bazan and Scott, 1990). Supplementing the diet of animals with DHA (and EPA) improves certain aspects of their cognitive performance (Carlson, 2000). This has led to a comparison of diets without ALA and those containing either ALA (rapeseed and linseed oils), or DHA (seaweed extracts, fish oils, and purified products), or ALA plus DHA (algae, brain or egg extracts, and mixtures of vegetable and fish oils). There is a clear relationship between omega long-chain polyunsaturated fatty acid status during infancy and the neurodevelopmental status of babies at 1 year of age (Table 39.1) (Voigt et al., 2002).

Diets containing only very long-chain omega-3 fatty acids (EPA and DHA) are not satisfactory: a diet very rich in fish oil alters the composition of brain membranes by increasing the DHA content and considerably reducing the ARA content (Bourre et al., 1990). This favors arousal and learning in young mice, but reduces motor activity and learning in older mice (Carrie et al., 2000). The omega-6 fatty acids must therefore be in balance and accompanied by omega-3 fatty acids. Consequently, a diet supplemented with DHA and ARA prevents the decrease in dopaminergic and serotoninergic neurotransmitters in the frontal cortex of piglets caused by a lack of ALA (de la Presa and Innis, 1999).

Nearly all studies on cognition have concentrated on mammals; we have found no studies on birds and fish.

B. EPA and DHA in Human Baby Formulas

DHA is clearly required by babies, including full-term infants (Gibson et al., 1996). Analyses of the frontal cortex of dead infants have shown that babies fed formula lacking DHA have a lower-than-normal DHA content (Byard et al., 1995). The brain of a child takes up 48% of the 10 mg of DHA

incorporated each day. The brains of breast-fed babies (mother's milk provides about 60 mg/day) contain about 1 g DHA, while the brains of bottle-fed babies contain only 0.6 g DHA (Cunnane et al., 2000). Fetal accretion of omega-3 fatty acids was estimated at 67 mg/day during the third trimester (Clandinin et al., 1980a,b). In practice, formulas for premature babies should contain both ALA and DHA (Rodriguez et al., 2003), although there is yet to be a clear demonstration of the absolute need of DHA for cognition (Simmer and Patole, 2004). The negative effect of a lack of omega-3 fatty acids on the development of the nervous system (and vision) initially led to the addition of omega-3 fatty acids alone (both EPA and DHA, no omega-6 fatty acids), generally as fish oil. This improved visual acuity, but it does not favor the overall development of the infant, in terms of body weight, height, and head circumference. Finally, almost all experiments have provided evidence of causal links between altered brain concentrations of DHA during the perinatal period and subsequent cognitive or behavioral performance (McCann and Ames, 2005).

C. Importance of the Balance between Omega-6 and Omega-3 Fatty Acids

Consequently, baby formula must contain both DHA and ARA to maintain the omega-3/omega-6 fatty acid ratio. Although the biochemical and physicochemical results are quite conclusive, the behavioral results are somewhat less clear. Most studies on the cognitive/behavioral development of infants fed formula containing long-chain (omega-6 and omega-3) fatty acids have used the BSID, which is considered to be the best standard for assessing the overall ability of infants from birth to 42 months of age. They provide standardized indices of both psychomotor development (PDI) and mental development (MDI). The Fagan Test of Infant Intelligence (FTII) has also been used. An analysis of eight trials carried out in 2001 (Simmer, 2001) was inconclusive, but a second analysis, 3 years later, of 14 published studies comparing baby formulas with and without long-chain polyunsaturated fatty acids was positive. The 14 studies included 7 on the effects on cognitive development; the results take into account the fact that brain DHA is derived from both ALA (with a 10% conversion rate) and preformed dietary DHA (Uauy et al., 2003).

One study (Agostoni et al., 1995) showed a benefit at 4 months, as assessed by the DQ (Brunet–Lezine test), but there was no longer any difference when these children were examined later, at age 2–4 years (Agostoni et al., 1997) (Table 39.2). Another study found that adding ALA and DHA to the formula improved cognitive performance at 4 months and that the improvement persisted (Willatts et al., 1998; Willats, 2002). Thus, an effect at 4 months does not predict an effect at 24 months. However, there is still a close correlation between the long-chain fatty acids in erythrocytes and neurological development (Agostoni et al., 1997). A review of the literature showed a benefit for preterm infants somewhat more convincingly than for term infants (Heird and Lapillone, 2005).

TABLE 39.2
DHA in Milk, and Phospholipids in the Blood Plasma and Erythrocytes and the Neurodevelopment Quotient

	Formula 1	Formula 2	Mother's milk
DHA in milk (g/100 g fat)	0.3	0	01–0.6
DHA in plasma phospholipids (%)	2.7	0.9	2.8
DHA in erythrocyte phospholipids (%)	4.1	1.8	4.1
Neurodevelopment quotient	105	96	102

Formula 1 = milk enriched in long-chain fatty acids; Formula 2 = standard cow's milk. The ALA content of the 3 milks was equivalent to 0.7 g/100g fat.

Source: From Agostoni, C., et al. (1994). *J. Am. Coll. Nutr.* 13: 658–664; Agostoni, C., et al. (1997). *Arch. Dis. Child.* 76: 421–424.

The feeding habits of families undoubtedly vary considerably, so that the DHA status of an infant will be more influenced by the dietary pattern than by the nature of the baby formula/breast milk consumed during its initial months of life. This is probably why no difference was found in infants aged 39 months (Auestad et al., 2003), or any association between the status at birth and performance at age 7 years (Bakker et al., 2003). Another study found a statistically insignificant improvement in children fed formula containing DHA and ARA (Wezel-Meijler et al., 2002). In a more detailed study, a restricted number of children were monitored from before birth, showed that very long-chain polyunsaturated fatty acids are closely associated with an increased IQ at age 6.5 years (Gustafsson et al., 2004). The children of women who take cod liver oil during pregnancy and lactation have improved mental performance measured at 4 years old (Helland et al., 2003). Other authors (Birch et al., 2002) suggest that babies should be given supplemented formula for at least 6 weeks to ensure maturation of the cerebral cortex and optimal visual performance in later years. A quantitative analysis of the influence of the prenatal intake of omega-3 fatty acids on cognitive development estimated that increasing maternal DHA intake by 100 mg/day increased child's IQ by 0.13 points (Cohen et al., 2005).

These studies used multiple tests, and it is quite possible that only some of them are influenced by dietary omega-3 fatty acids, as has been shown in animal studies (Frances et al., 1996b). They do demonstrate the advantage of breast-feeding over feeding formula containing DHA or ARA.

Several studies have shown the importance of breast-feeding and some have justified it by the amount of polyunsaturated fatty acids, particularly omega-3 fatty acids, in mother's milk. It improves the neurological development of newborns, especially if continued for over 6 weeks, as evaluated by motor activity (Bouwstra et al., 2003), and this effect can be measured in infants up to 1 year old. Some believe that this is due to the presence of omega-3 fatty acids, especially DHA (Agostoni et al., 2001). Others have found that babies thus fed have an IQ 8.3 points higher at 18 months (Lucas et al., 1992). One study using the Bailey test showed that breast-feeding had a positive effect, measured at 1 year old, on baby boys, but not on girls (Paine et al., 1999). The effect on neurological development is measurable in children up to the age of 7 or 8 (Horwood et al., 2001) or even 9 years (Lanting et al., 1994). But others have found that the effect cannot be measured at 13 months or 5 years (Angelsen et al., 2001). These widely differing results may be due to the different tests used.

In fact, small differences in brain concentrations of DHA, such as might occur between infants fed unsupplemented or supplemented formulas, may result in small, subtle effects that are currently difficult to detect, but could be significant. This is sustained by animal studies linking a decrease in the brain concentration of DHA to altered performance in cognitive and behavioral tests. Thus, the published literature shows that long-chain polyunsaturated fatty acids are important for the growth and development (cognitive) of human infants (Fleith and Clandinin, 2005).

III. ADULT HUMANS, EPIDEMIOLOGICAL AND EXPERIMENTAL EVIDENCE

A. Mental Health, Cognition, and Mood

It has been reported that omega-3 fatty acids improve cognitive development and learning under certain conditions. Dietary omega-3 fatty acids may improve intentional and physiological functions involving complex cortical processing. Studies on the relationship between cognition alterations and mood and fatty acids (particularly omega-3 fatty acid) are scarce, but there has been a lot of speculation. These fatty acids are essential for normal general health and well-being, mainly because of their biochemical properties. An Australian study concluded that regular normal meals (including omega-3 fatty acid), including a good breakfast, improved mood and cognitive performance (Lombard, 2000). A New Zealand study found that the personal perception of good mental and physical health varied with the consumption of fish, thus of omega-3 fatty acids, so that they were considered to stabilize mood (Silvers and Scott, 2002). However, an English study found that

the consumption of fish did not improve the mood of people who were not depressed (Ness et al., 2003). The food consumption and nutrient intake of subjects with depressed mood was studied, using anxiety and insomnia as indices of compromised mental well-being. Those subjects reporting anxiety or depressed mood had higher intakes of omega-3 fatty acids and omega-6 fatty acids (Hakkarainen et al., 2004b). It is thus too early to say that omega-3 fatty acids modulate cognitive processes by altering mood.

B. Stress

As fish oil is known to influence behavior cognition, at least indirectly, its influence on aggressive behavior was assessed. Anxiety is an incapacitating syndrome. Subjects were given capsules of vegetable oils to determine the optimum dietary ratio between omega-3 and omega-6 fatty acids needed to counteract stress. The ratio was found to be 4 for LA and ALA. This protected against changes in the hippocampus in response to excess cortisol and corticosteroids, avoiding impaired learning (Yehuda et al., 2000). Aggression was found to vary inversely with the consumption of fish; daily doses of 1.5–1.8 g DHA (found in fish oil) helped to reduce stress and decreased the aggressive tendencies of young adults, perhaps by modulating stress. Fish oils reduced the aggressiveness of subjects aged 50–60 years, when given for 2 months, by 30%, but doses of 150 mg per day were insufficient (Hamazaki et al., 2002). An adequate DHA intake could prevent aggression from increasing at times of mental stress; this may indicate how fish oils prevent diseases such as coronary heart disease.

If increasing the intake of omega-3 fatty acids is favorable, what happens if the intake of linoleic (omega-6) acid is reduced? There is evidence for a correlation between the consumption of seed oils, the major dietary source of LA, and a greater incidence of homicide in western countries with similar socioeconomic and background seafood intakes. Thus, a diet poor in LA may prevent behavioral disorders that are now the concern of correctional institutions, social services, and mental health providers (Hibbeln et al., 2004).

C. Hyperactive and Dyslexic Children, Dyslexia in Adult

The cluster of age-inappropriate behavioral abnormalities including inattention, impulsiveness, and hyperactivity are the hyperkinetic disorders. Fatty acids seem to be important for attention deficit associated with hyperactivity (Richardson and Puri, 2000). A pilot study carried out on 50 children showed that supplementing their diet with essential fatty acids (daily doses of 480 mg DHA, 80 mg EPA, 40 mg ARA, 96 mg γ-linolenic acid, and 24 mg tocopherol acetate) improved their symptoms (Stevens et al., 2003). However, another study showed that dietary supplements improved the blood parameters of hyperactive children suffering from attention deficit, but not their clinical symptoms (Voigt et al., 2001). Polyunsaturated fatty acids, including omega-3 fatty acid, could be implicated not only in disorders of cerebral development, attention deficit, hyperactivity, but also in dyslexia and even in autism (Richardson and Ross, 2000). The severity of dyslexic signs was found to vary with the lack of polyunsaturated fatty acids in boys, but not in girls (Richardson et al., 2000). Dyslexia in adults is accompanied by indications of a lack of polyunsaturated fatty acids (Taylor et al., 2000).

D. Depression

The major mood disorders can be roughly divided into unipolar major depression and bipolar disorder. Bipolar disorder, also known as manic-depressive illness, causes shifts in a person's mood and ability to function. It is a complex and chronic condition associated with considerable morbidity and mortality, including a high suicide rate. The increased prevalence of depression over the past half century seems to parallel fundamental changes in dietary habits, with a reduced intake of foods containing omega-3 fatty acids (Colin et al., 2003). The frequency of depression in British Columbia

increased as the traditional dietary habit of fish eating was lost, and then fell as these dietary elements were reintroduced (Bates, 1988). There is a relationship between the drop in omega-3 fatty acid consumption (in fish) and the risk of depression, particularly as the incidence of the disorder varies from 1 to 50 per 1000 population, depending on the country, in parallel with fish consumption (Hibbeln and Salem, 1995; Tanskanen et al., 2001). This was not confirmed by another study (Hakkarainen et al., 2004b). Yet another study showed that, in Crete, there is an inverse relationship between the DHA concentration in adipose tissue and the risk of depression (Hibbeln, 2002). An overview of 41 published studies covering 23 countries shows that a fish-poor diet leads to a low-DHA concentration in mothers' milk (which is undesirable for newborns) and an increased risk that the mothers will suffer from postnatal depression (Hibbeln, 2002). However, there was no such relationship between dietary EPA and ARA.

There is still, however, little hard evidence showing a relationship between changes in dietary fatty acids and the risk of depression with aging, although plasma composition of fatty acids and depression are associated during aging (Tiemeier et al., 2003). Regular fish consumers in a community of elderly French people aged 65 years and above, had fewer depressive symptoms and scored higher on the Mini Mental Status Examination. The regular fish consumers (at least weekly) were better educated (OR 1.19–1.65) and had better incomes (1.37–1.89) than the controls (Barberger-Gateau et al., 2005).

Two clinical studies have used doses of 2 g per day of EPA ethyl ester to successfully treat cases of depression that responded only partially to classical psychiatric treatment (Peet and Horrobin, 2002; Puri et al., 2000). One patient was given EPA together with conventional treatment; this not only improved the clinical signs (suicidal tendencies, social phobias), but also resulted in morphological changes (reduced volume of the lateral ventricles) (Puri et al., 2001). DHA is also a successful treatment for minor depression (Mischoulon and Fava, 2000). A patient suffering from postnatal depression was successfully treated with omega-3 fatty acids (Chiu et al., 2003), while another study using fish oil (2.69 g per day, EPA/DHA = 1.4) starting at the 34–36 week of pregnancy and continuing until 12 weeks after birth obtained negative results (Marengell et al., 2004). Yet another study found that a dietary supplement of 200 mg DHA per day for 4 months after childbirth prevented the drop in plasma DHA but did not alter the patients' self-evaluated state of depression (Lombard, 2000). This could be because they measured mood changes rather than real depression and/or because the doses of DHA were too low. Treatment with 9.6 g omega-3 fatty acid per day for 8 weeks gave positive results with cases of major depression (Su et al., 2003), but DHA alone (2 g per day for 6 weeks) did not seem to be effective (Marangel et al., 2003). In fact, EPA seems to increase the action of antidepressant drugs (Murck et al., 2004).

A study of bipolar disorder patients (manic depressives) in 14 countries showed a correlation between the prevalence of the disorder and low fish consumption, with the threshold of vulnerability being 65 g per day (Noaghiul and Hibbeln, 2003); treatment with omega-3 fatty acids could be useful under certain specific conditions (Stoll et al., 1999).

Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes, thus dietary, genetic and hormonal factors may all play a role in both depression and coronary heart disease (Frasure-Smith et al., 2004).

Depressive symptoms are among the most prevalent psychiatric symptoms and are strongly associated with the development of depressive disorders; individuals with depressive symptoms are at four times greater risk of developing major depression within 1 year. Depression is a major source of functional disability. This has been consistently demonstrated in epidemiological, primary care, and out-patient studies, at least in Western Europe and North America.

E. Drug Addiction

Drug addiction alters cognition. Omega-3 fatty acids, and perhaps omega-6 fatty acids, may also be involved in drug addiction. Ex-cocaine addicts more rapidly return to addiction if they lack

polyunsaturated fatty acids (Buydens-Branchey et al., 2003a,b). It is possible that a diet-related change in the membranes of certain cerebral neurons makes some people more unstable, so that they may be more predisposed to drug addiction in response to other impulses. Whatever the cause, drug addicts often have very poor diets, but how this can aggravate their condition, interfere with curing their addiction or make re-addiction more likely remains a major question. Animal experiments have shown that a lack of ALA alters the response to morphine (Frances et al.,,1996a).

F. Autism

Autism remains one of the very few conditions classified as a syndrome, defined only in terms of observable symptoms. This is largely due to the lack of accepted biochemical diagnostic markers. Sufferers from autism often have a range of physiological problems, and alterations in their fatty acid metabolism, particularly those related to eicosanoid production. An autistic boy aged 11 years was successfully treated with fish oil (540 mg EPA per day) for 4 weeks (Johnson and Hollander, 2003). The plasma phospholipids of autistic children contain 23% less DHA than do those of normal children, while the total omega-3 fatty acid concentration is 20% lower and their omega-6 fatty acids are unchanged (Vancassel et al., 2001). Another study found that the phospholipids in erythrocytes were 70% below normal (Bell et al., 2000).

G. Dementias

Alzheimer's disease is a neurological disorder that is characterized by progressive memory loss, intellectual decline, and eventually global cognitive impairment. Major symptoms include short-term and long-term memory loss, impaired speech and language, visual-spatial changes, impaired abstract reasoning, and poor judgment. Several epidemiological studies have shown that omega-3 fatty acids play a role in the prevention of dementia, as expanding knowledge in the area of lipid biochemistry suggests that Alzheimer's disease is associated with brain lipid defects. For example, the Rotterdam study found that the risk of dementia with vascular features is positively correlated with the consumption of saturated fatty acids, but negatively correlated with the consumption of omega-3 fatty acid-rich fish (Kalminjn et al., 1997a); these results are discussed in (Engelhart et al., 2002). A diet rich in unsaturated fatty acids and unhydrogenated fat was found to protect against Alzheimer's disease, in contrast to a diet rich in saturated fatty acids and *trans* fatty acids (Morris et al., 2003b). Some epidemiological studies have shown that the consumption of finfish also seems to protect against dementia, including Alzheimer's disease. In France, the consumption of meat, because of its saturated fatty acid content, is only poorly correlated with an increased risk of dementia, while the consumption of fish has a protective effect. Those subjects who ate fish at least once a week were 34% less likely to develop any form of dementia, and 31% less likely to suffer from Alzheimer's disease. The effect was still present when socioeconomic factors were taken into account, as these factors are linked to both the reduced risk of Alzheimer's disease and the fish consumption (Barberger-Gateau et al., 2002). A study carried out in the United States found that Alzheimer's disease was 60% less common in people that consumed about 60 mg DHA per day (at least one fish meal a week) than in people that ate very little fish (Morris et al., 2003a). The overall findings in Japan are the same (Otsuka et al., 2002).

A low plasma concentration of omega-3 fatty acids (including DHA) is an indication of risk of cognitive deficiencies and other types of dementia, besides Alzheimer's disease (Conquer et al., 2000).

Cardiovascular risk often clusters into a metabolic syndrome that may increase the risk of dementia. Epidemiological studies have implicated cerebrovascular disease and its antecedent as risk factors for Alzheimer's disease. Vascular dementias and Alzheimer's disease have nutritional factors in common: an excess of omega-6 fatty acids and a lack of omega-3 fatty acids; this leads to changes in the microvasculature, chronic inflammation, platelet aggregation, and endothelial dysfunction (Otsuka et al., 2002). This provides at least a partial explanation of why the cognitive

disorders in very elderly people are positively correlated with the consumption of LA, and negatively correlated with the consumption of fish (Engelhart et al., 2002). The cardiovascular risk increases the risk of dementia, particularly vascular dementia (Kalmijn et al., 2000). Inflammatory processes may well be implicated in all these disorders (Simopoulos, 2002). It also seems clear that insufficient fish consumption is a significant risk factor, there has not yet been any published report on the use of omega-3 fatty acids in the preventive treatment of dementia of any type. One-fourth mixture of ALA and LA, given as a capsule, was shown to improve the quality of life for those suffering from Alzheimer's disease, as measured by tests of spatial orientation, cooperation, mood, appetite, short-term and long-term memory, sleep, and hallucinations (Yehuda et al., 1996). There have been no studies to date on the implication of omega-3 fatty acids in cognitive alterations due to alcoholism and in alcoholic dementia, although studies on experimental animals have shown that dietary ALA modulates the effects of alcohol on such things as the nerve terminals (Zerouga et al., 1991).

H. Schizophrenia

Antipsychotic drugs are the most effective treatment of schizophrenia, particularly the most disturbing symptoms such as agitation and psychosis. Treatment with new antipsychotics seems to have improved the negative symptoms and cognitive deficits that are considered difficult to treat. However, their side effects significantly reduce the patient's quality of life, so that it is important to develop adjunctive treatment strategies. Adjuncts of essential fatty acids, and their metabolites, such as eicosanoids, have been considered to improve the outcome of this disease. For instance, schizophrenics whose diet includes plenty of fish have less severe clinical signs (Peet et al., 1996).

Patients who ate 10 g of fish per day for 6 weeks seemed to have improved symptoms (Laugharne et al., 1996), as did patients given a combination of 120 mg EPA, 150 mg DHA, 500 mg vitamin C, and 400 IU vitamin E twice a day for 4 months, but the improvement was relatively modest (Arvindakshan et al., 2003). A single patient given EPA alone showed improved symptoms; the turnover of brain phospholipids (as measured by ^{31}P NMR) returned to normal and brain atrophy had receded after treatment for 6 months (Puri et al., 2000). This clearly needs to be confirmed. Some patients who had been treated and stabilized were then given EPA for 3 months (Peet et al., 2001). EPA has also been used to supplement a 6-month course of antipsychotic drugs, but it left residual symptoms (Emsley et al., 2002). One author reported that treatment with 3 g EPA per day produced no results (Fenton et al., 2001), perhaps because the dose was too low or because the patients were nonresponders (Horrobin, 2003). There have been several proposals as to how omega-3 fatty acids are involved in schizophrenia (Peet, 2003), including the modulation of neurotransmission, particularly dopaminergic transmission, but there is as yet no hard evidence (Peet et al., 2001).

Fatty acids differentially affect serotonin receptors and the binding of its transporters in the rat brain; this may be important for understanding neuropsychiatric diseases such as schizophrenia, where there seems to be an association between altered fatty acids levels and the serotoninergic system (Du Bois et al., 2006).

The erythrocyte membranes of schizophrenic patients contain subnormal concentrations of DHA and EPA, and a link has been found between the change in fatty acid profile and the severity of the clinical disease (Assies et al., 2001). Another study did not find these results (Hibbeln et al., 2003). However, there could well be subgroups of patients for whom the omega-3 fatty acids are particularly important, which would explain why clinicians find divergent results in which the DHA content is either elevated, depressed, or normal, depending on the publication. In fact, there is a relationship between membrane phospholipids composition, alterations in neurotransmitter systems and schizophrenia (Du Bois et al., 2005), and hence cognitive alterations.

I. Cognition and Aging

Dietary factors might modify the cognitive decline that results from aging. Several studies have shown that cognitive deterioration in the elderly is associated with deficiencies of macronutrients

and micronutrients. Fatty acids are the prime candidates, as they are quantitatively and qualitatively extremely important in the brain. The biochemical and physiological roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during aging have been reviewed (Bourre, 2004b). The changes that occur with advancing age are complex, in both animals and humans. Omega-3 fatty acids may be involved either directly or indirectly, depending on the part of the body, the structure, cells, and organelles, or lipids concerned. A recent French study showed that age-related cognitive deficit is linked to a reduction in the omega-3/omega-6 fatty acid ratio in erythrocytes (Heude et al., 2003); an excess of nutritional LA was also coupled to a decline in cognitive performance, while the reverse is true for fish oils (Kalmijn et al., 1997a,b). Studies on an aging population in southern Italy found that an elevated unsaturated fatty acid intake (monosaturated, unsaturated, and polyunsaturated), high intakes of antioxidant compounds, and a diet very low in saturated fatty acids could act synergistically to improve cognitive performance (Solfrizzi et al., 2005). Fish consumption may be associated with a slower cognitive decline with age: the rate was 10% slower among persons who consumed one fish meal per week, and 13% slower in persons who consumed two or more fish meals per week (Morris et al., 2005). Phosphotidyl-choline improves the memory, learning, concentration, vocabulary recall, and mood of elderly people suffering from cognitive loss. Phosphatidyl-choline, together with vitamin B_{12}, improves learning in aging mice (Hung et al., 2001). There appears to be no question but that an adequate intake of omega-3 fatty acids could ensure the turnover of membranes, so helping to protect against brain aging. However, a dietary supplement of high concentrations of omega-3 fatty acids produces behavioral changes that vary with the age of the individual, improving learning in young animals, but reducing learning and motor activity in older ones (Carrie et al., 2000). This should be borne in mind when considering dietary supplements.

There are well-established benefits of omega-3 fatty acids (from fish or fish oils) for vascular health, and theses advantages may explain better cognitive performances in those with high omega-3 fatty acids concentrations in their erythrocytes. (The evidence obtained from self-reported consumption of fish or fish-oil supplements is generally a less informative indicator than are measurements of erythrocyte omega-3 fatty acid contents.) Some vascular risk factors and cardiovascular diseases have been linked to cognitive decline (and dementia). Hence, fatty acid intake, mainly omega-3 fatty acids, might affect the development of cognitive impairment by influencing the development of thrombosis and atherosclerosis. Cerebrovascular disease is associated with a cognitive decline and progression of dementia, and this association could be weakened by a high intake of omega-3 fatty acids (from finfish or fish oils) to slow or prevent the development of age-related cerebrovascular disease. The vascular risk factors that predict stroke are associated with a wide range of cognitive alterations that occur around the age of 60 years; moreover, a lower childhood IQ is associated with an increased incidence of cardiovascular diseases.

These observations could be expanded to other stages of life. For instance, the consumption of oily fish and marine omega-3 fatty acids is associated with a reduced risk of impaired cognitive function, while a diet rich in cholesterol and saturated fat has been linked to an increased risk in a middle-aged population (Kalmijn et al., 2004). The spatial memory of rats fed sub-normal amounts of omega-3 fatty acids in the Morris maze is compromised. These animals seem to have fewer endothelial mitochondria, and a lower ratio of micro-vessels to degenerative pericytes (de Wilde et al., 2002).

Aging is associated with an increased production of free radicals and a decrease in antioxidant defences, both of which lead to increased oxidative stress that is implicated in altered cognition and the development of dementia. On the contrary, a diet rich in antioxidants such as vitamins E, A, and C, β-carotenoids, and flavonoids could protect against such changes. But only α-tocopherol is effective, at least in animals (Clement et al., 1995). It has been speculated that the loss of DHA in Alzheimer's disease may reflect its propensity for free radical-mediated lipid peroxidation. Thus, either a decreased intake or increased oxidative stress (or both) could contribute to brain DHA depletion and hence to altered cognitive function.

Food supplements (and erythrocyte content) are associated with better cognitive aging. If associations with omega-3 fatty acid are causal, optimizing the omega-3 and omega-6 fatty acid intakes could help preserve cognitive function in old age (Whalley et al., 2004). Greater fish oil intake is associated with better cognitive function in late adulthood. Supplementation is associated with improved attention and physiological functions, particularly those functions involving complex cortical processing, even in healthy subjects (Fontani et al., 2005).

IV. DISCUSSION

Omega-3 fatty acids have two broad actions, one long-term and the other short-term. Their long-term actions are on membrane composition and function. This is supported by studies on brain development and probably the role of dietary omega-3 fatty acids in the prevention of dementia, including Alzheimer's disease. Their short-term actions could involve phospholipid metabolism, and hence the modulation of signal transduction. The evidence for this includes the effect of EPA on depression, schizophrenia, and autism. But the two types of action can occur simultaneously, as in inflammation during Alzheimer's disease. It is too soon to state that omega-3 fatty acids prevent depression by treating inflammation, even though there are good indications that inflammation occurs during depression. Although there is clear evidence that omega-3 fatty acids do prevent and reduce these symptoms, to some extent, these relationships are not necessarily causal. Epidemiological studies showing that dietary fish, or fish oil capsules alleviate some psychiatric diseases, have flaws inherent in this type of epidemiological survey (e.g., association does not imply causation).

The timetable of cerebral development means that any short-term perturbation can result in long-term changes in the biochemistry, physiology, and function of the brain, and the possibilities of recovery are relatively restricted, because of the genetically programmed brain development, although a dietary lack of omega-3 fatty acids results in their replacement by other fatty acids. Dietary omega-3 fatty acids contribute to the construction and maintenance of the brain (Bourre, 2004a,b,c).

Dietary omega-3 fatty acids, especially DHA, have probably had a major influence of the evolution of the human brain. It is found in a few special vegetables, oily fish, all seafood (fish and shellfish), and certain eggs (Broadhurst et al., 2002). The lack of dietary ALA can readily be overcome by using rapeseed oil (canola oil) and walnut oil ("noix de Grenoble" oil) (soybean oil has too much omega-6 fatty acids) and a special variety of eggs (omega-3 eggs, Columbus® or Benefic®)—all other eggs, including organic ones, are unsuitable. Walnuts, mixtures of oils containing at least 50% rapeseed oil, or 10% linseed oil, and other plant-based foods rich in ALA are also useful (Bourre, 2005b). Thus, it is not difficult to find food rich in omega-3 fatty acids (Bourre, 2003, 2005b).

An adequate intake of the precursor ALA enables the body to regulate interconversion, as dietary DHA results in a regulatory systems being short-circuited, requiring precise definitions of nutritional requirements for all physiological and pathological situations, which is not presently possible. Dietary intake of DHA varies enormously and depends on where people live. Children are at particular risk of such deficiencies. Thus, those with low-dietary intakes need to be identified and counseled. Wild oily fish are generally very rich in DHA and EPA, as are farmed fish, provided they are fed correctly. The human nutritional value of meat and eggs, in terms of lipid (amounts of omega-3 fatty acids), may vary considerably depending on the fats fed to the animals/hens (Bourre, 2003, 2005b).

Although a good dietary intake of omega-3 fatty acids is fundamental, it is not enough. The presence of omega-6 fatty acids must also be taken into account, to ensure that the omega-6/omega-3 ratio is not above 5. And this ratio is far too high in the diet of most people in the Western world. It should only be reduced by increasing the intake of omega-3 fatty acids, and most certainly not by decreasing the intake of omega-6 fatty acids, as our intake of omega-6 fatty acids is only slightly above the recommended value.

V. SUMMARY AND CONCLUSIONS

The effects of fatty acids, essentially omega-3 fatty acids, on cognition and behavior have been examined mainly during perinatal brain development and, to a lesser extent, during aging and in terms of some psychiatric diseases. Fatty acids control the structure and function of biological membranes, including membranes in the nervous system. The high omega-3 polyunsaturated fatty acid content of the brain clearly indicates that these lipids are involved in brain biochemistry, physiology, and functioning, and thus in cognitive performances during development and in some cognitive changes due to neuropsychiatric diseases and aging. Animal studies have provided convincing and consistent evidence linking a decrease in brain concentrations of DHA to altered performances in cognitive and behavioral tests. Some studies on perinatal cerebral development and omega-3 fatty acids have focused on ALA, while others have examined long-chain derivatives such as DHA and EPA. Other studies have examined the influence of ALA plus DHA, sometimes with the omega-6 fatty acid, ARA.

Studies on ALA first showed the effect of a dietary component on the structure and function of the brain. These include (1) cultures of dissociated brain cells, analyses of the fatty acids and lipids in whole organ, regions, cell types in the brain, and classes of phospholipids; (2) physicochemical studies on brain membrane fluidity, and biochemical and enzymological studies on enzymes such as ATPase; (3) physiological studies on dopaminergic, serotoninergic, and cholinergic neurotransmission; (4) toxicology of heavy metals and trans fatty acids; (5) studies on vision, hearing, and taste; and (6) electrophysiological studies (ERG, EEG) and cognitive and behavioral studies, memory, and habituation being specifically affected. For instance, dietary omega-3 deficiency influences specific neurotransmitters systems, particularly the dopamine systems of the frontal cortex, which is related to cognition.

The accumulation of considerable conclusive experimental evidence led to the inclusion of ALA in baby formulas. This decision was due to many studies on newborns, including those on cognition. The nature of the polyunsaturated fatty acids (particularly the omega-3 fatty acids) in baby formulas for both full-term and premature infants influences the infant's visual, neurological, cerebral, intellectual capacities and cognition. Infants fed vegetable oil-based formulas (poor in ALA) may have poorer visual functions, lower cognitive scores, and acquiring learning tasks are slower in comparison with those breast fed or those fed formulas supplemented with DHA. Despite a lack of exhaustive experiments, DHA and EPA were also added to baby formula, which may have a limited or even negative effect because of competition with omega-6 fatty acids. A combination of DHA, EPA, and ARA was later shown to improve membrane composition and cognition.

Dietary omega-3 fatty acids may also help prevent psychiatric disorders such as depression and dementia, particularly Alzheimer's disease. They probably directly influence major depression, bipolar disorder (manic-depressive illness), and schizophrenia. Omega-3 fatty acids may be important in diseases such as dyslexia and autism. Dietary omega-3 fatty acids deficiency can alter membrane turnover, and thus accelerate cerebral aging and cognitive decline. The lack of omega-3 fatty acids in today's occidental diet suggests that consumer must be persuaded to select foods that are rich in omega-3 fatty acids, such as rapeseed and walnut oils and oily fish.

Quite possibly, at least part of the body's oleic acid requirement must come from the diet (Bourre et al., 1997), including that for the peripheral nerves (but not the brain) (Bourre and Dumont, 2003). Saturated fatty acids are synthesized in the cell cytosol and endoplasmic reticulum and in the process of myelinization (Bourre et al., 1976). Most lignoceric and nervonic acids are synthesized in the brain, but some may come from the diet (Bourre et al., 1977).

REFERENCES

Agostoni, C., Marangoni, F., Giovannini, M., Galli, C., and Riva, E. (2001). Prolonged breast-feeding (six months or more) and milk fat content at six months are associated with higher developmental scores at one year of age within a breast-fed population. *Adv. Exp. Med. Biol.* 501: 137–141.

Agostoni, C., Riva, E., Bellu, R., Trojan, S., Luotti, D., and Giovannini, M. (1994). Effects of diet on the lipid and fatty acid status of full-term infants at 4 months. *J. Am. Coll. Nutr.* 13: 658–664.

Agostoni, C., Trojan, S., Bellu, R., Riva, E., Bruzzese, M. G., and Giovannini, M. (1997). Developmental quotient at 24 months and fatty acid composition of diet in early infancy: a follow up study. *Arch. Dis. Child.* 76: 421–424.

Agostoni, C., Trojan, S., Bellu, R., Riva, E., and Giovannini, M. (1995). Neurodevelopmental quotient of healthy term infants at 4 months and feeding practice: the role of long-chain polyunsaturated fatty acids. *Pediatr. Res.* 38: 262–266.

Aid, S., Vancassel, S., Poumes-Ballihaut, C., Chalon, S., Guesnet, P., and Lavialle, M. (2003). Effect of a diet-induced n-3 PUFA depletion on cholinergic parameters in the rat hippocampus. *J. Lipid Res.* 44: 1545–1551.

Angelsen, N. K., Vik, T., Jacobsen, G., and Bakketeig, L. S. (2001). Breast feeding and cognitive development at age 1 and 5 years. *Arch. Dis. Child.* 85: 183–188.

Arvindakshan, M., Ghate, M., Ranjekar, P. K., Evans, D. R., and Mahadik, S. P. (2003). Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. *Schizophr. Res.* 62: 195–204.

Assies, J., Lieverse, R., Vreken, P., Wanders, R. J., Dingemans, P. M., and Linszen, D. H. (2001). Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. *Biol. Psychiatry* 49: 510–522.

Auestad, N., Scott, D. T., Janowsky, J. S., et al. (2003). Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. *Pediatrics* 112: e177–e183.

Bakker, E. C., Ghys, A. J., Kester, A. D., Vles, J. S., Dubas, J. S., Blanco, C. E., and Hornstra, G. (2003). Long-chain polyunsaturated fatty acids at birth and cognitive function at 7 y of age. *Eur. J. Clin. Nutr.* 57: 89–95.

Barberger-Gateau, P., Jutand, M. A., Letenneur, L., Larrieu, S., Tavernier, B., and Berr, C. (2005). Correlates of regular fish consumption in French elderly community dwellers: data from the Three-City study. *Eur. J. Clin. Nutr.* 59: 817–825.

Barberger-Gateau, P., Letenneur, L., Deschamps, V., Peres, K., Dartigues, J. F., and Renaud, S. (2002). Fish, meat, and risk of dementia: cohort study. *BMJ* 325: 932–933.

Bates, C. E. (1988). Racially determined abnormal essential fatty acid and prostaglandin metabolism and food allergies linked to autoimmune, inflammatory, and psychiatric disorders among Coastal British Columbia Indians. *Med. Hypotheses* 25: 103–109.

Bazan, N. G. and Scott, B. L. (1990). Dietary omega-3 fatty acids and accumulation of docosahexaenoic acid in rod photoreceptor cells of the retina and at synapses. *Ups. J. Med. Sci. Suppl.* 48: 97–107.

Bell, J. G., Sargent, J. R., Tocher, D. R., and Dick, J. R. (2000). Red blood cell fatty acid compositions in a patient with autistic spectrum disorder: a characteristic abnormality in neurodevelopmental disorders? *Prostaglandins Leukot. Essent. Fatty Acids* 63: 21–25.

Birch, E. E., Hoffman, D. R., Castaneda, Y. S., Fawcett, S. L., Birch, D. G., and Uauy, R. D. (2002). A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. *Am. J. Clin. Nutr.* 75: 570–580.

Bourre, J. M. (1990). La diététique du cerveau. Editions Odile Jacob, Paris, France. (1991) De la inteligencia y el placer, la dietetica del cerebro, Biblioteca Mondatori. (1992) Intelligenz und Ernährung, Econ Verlag, Germany. (1992) La dietetica del cervello, Sperling Kupfer, Italy. (1993) Comida inteligente, a dietética do cérebro, Gradiva. (1993) Brainfood, Little Brown, U.S.A.

Bourre, J. M. (2003). *Diététique du cerveau: la nouvelle donne*. Paris: Edition Odile Jacob.

Bourre, J. M. (2004a). The role of nutritional factors on the structure and function of the brain: an update on dietary requirements. *Rev. Neurol. (Paris)* 160: 767–792.

Bourre, J. M. (2004b). Roles of unsaturated fatty acids (especially omega-3 fatty acids) in the brain at various ages and during ageing. *J. Nutr. Health Aging* 8: 163–174.

Bourre, J. M. (2004c). *La vérité sur les oméga-3*. Paris: Edition Odile Jacob.

Bourre, J. M. (2005a). Dietary omega-3 Fatty acids and psychiatry: mood, behavior, stress, depression, dementia and aging. *J. Nutr. Health Aging* 9: 31–38.

Bourre, J. M. (2005b). Where to find omega-3 fatty acids and how feeding animals with diet enriched in omega-3 fatty acids to increase nutritional value of derived products for human: what is actually useful? *J. Nutr. Health Aging* 9: 232–242.

Bourre, J. M., Bonneil, M., Dumont, O., Piciotti, M., Calaf, R., Portugal, H., Nalbone, G., and Lafont, H. (1990). Effect of increasing amounts of dietary fish oil on brain and liver fatty composition. *Biochim. Biophys. Acta* 1043: 149–152.

Bourre, J. M., Daudu, O., and Baumann, N. (1976). Ontogenesis of three fatty acid synthesizing systems in cerebral microsomes: relation to myelinization. *Biochimie* 58: 1277–1279.

Bourre, J. M. and Dumont, O. (2003). Dietary oleic acid not used during brain development and in adult in rat, in contrast with sciatic nerve. *Neurosci. Lett.* 336: 180–184.

Bourre, J. M., Dumont, O. L., Clement, M. E., and Durand, G. A. (1997). Endogenous synthesis cannot compensate for absence of dietary oleic acid in rats. *J. Nutr.* 127: 488–493.

Bourre, J. M., Durand, G., Pascal, G., and Youyou, A. (1989a). Brain cell and tissue recovery in rats made deficient in n-3 fatty acids by alteration of dietary fat. *J. Nutr.* 119: 15–22.

Bourre, J. M., Francois, M., Youyou, A., Dumont, O., Piciotti, M., Pascal, G., and Durand, G. (1989b). The effects of dietary alpha-linolenic acid on the composition of nerve membranes, enzymatic activity, amplitude of electrophysiological parameters, resistance to poisons and performance of learning tasks in rats. *J. Nutr.* 119: 1880–1892.

Bourre, J. M., Faivre, A., Dumont, O., Nouvelot, A., Loudes, C., Puymirat, J., and Tixier-Vidal, A. (1983). Effect of polyunsaturated fatty acids on fetal mouse brain cells in culture in a chemically defined medium. *J. Neurochem.* 41: 1234–1242.

Bourre, J. M., Pascal, G., Durand, G., Masson, M., Dumont, O., and Piciotti, M. (1984). Alterations in the fatty acid composition of rat brain cells (neurons, astrocytes, and oligodendrocytes) and of subcellular fractions (myelin and synaptosomes) induced by a diet devoid of n-3 fatty acids. *J. Neurochem.* 43: 342–348.

Bourre, J. M., Paturneau-Jouas, M. Y., Daudu, O. L., and Baumann, N. A. (1977). Lignoceric acid biosynthesis in the developing brain. Activities of mitochondrial acetyl-CoA-dependent synthesis and microsomal malonyl-CoA chain-elongating system in relation to myelination. Comparison between normal mouse and dysmyelinating mutants (quaking and jimpy). *Eur. J. Biochem.* 72: 41–47.

Bouwstra, H., Boersma, E. R., Boehm, G., Dijck-Brouwer, D. A., Muskiet, F. A., and Hadders-Algra, M. (2003). Exclusive breastfeeding of healthy term infants for at least 6 weeks improves neurological condition. *J. Nutr.* 133: 4243–4245.

Bowen, R. A. and Clandinin, M. T. (2000). High dietary 18:3n-3 increases the 18:3n-3 but not the 22:6n-3 content in the whole body, brain, skin, epididymal fat pads, and muscles of suckling rat pups. *Lipids* 35: 389–394.

Broadhurst, C. L., Wang, Y., Crawford, M. A., Cunnane, S. C., Parkington, J. E., and Schmidt, W. F. (2002). Brain-specific lipids from marine, lacustrine, or terrestrial food resources: potential impact on early African Homo sapiens. *Comp Biochem. Physiol B Biochem. Mol. Biol.* 131: 653–673.

Buydens-Branchey, L., Branchey, M., McMakin, D. L., and Hibbeln, J. R. (2003a). Polyunsaturated fatty acid status and relapse vulnerability in cocaine addicts. *Psychiatry Res.* 120: 29–35.

Buydens-Branchey, L., Branchey, M., McMakin, D. L., and Hibbeln, J. R. (2003b). Polyunsaturated fatty acid status and aggression in cocaine addicts. *Drug Alcohol Depend.* 71: 319–323.

Byard, R. W., Makrides, M., Need, M., Neumann, M. A., and Gibson, R. A. (1995). Sudden infant death syndrome: effect of breast and formula feeding on frontal cortex and brainstem lipid composition. *J. Paediatr. Child Health* 31: 14–16.

Carlson, S. E. (2000). Behavioral methods used in the study of long-chain polyunsaturated fatty acid nutrition in primate infants. *Am. J. Clin. Nutr.* 71: 268S–274S.

Carrie, I., Guesnet, P., Bourre, J. M., and Frances, H. (2000). Diets containing long-chain n-3 polyunsaturated fatty acids affect behavior differently during development than ageing in mice. *Br. J. Nutr.* 83: 439–447.

Chalon, S., Vancassel, S., Zimmer, L., Guilloteau, D., and Durand, G. (2001). Polyunsaturated fatty acids and cerebral function: focus on monoaminergic neurotransmission. *Lipids* 36: 937–944.

Cheon, S. H., Huh, M. H., Lee, Y. B., Park, J. S., Sohn, H. S., and Chung, C. W. (2000). Effect of dietary linoleate/alpha-linolenate balance on the brain lipid composition, reproductive outcome and behavior of rats during their prenatal and postnatal development. *Biosci. Biotechnol. Biochem.* 64: 2290–2297.

Chiu, C. C., Huang, S. Y., Shen, W. W., and Su, K. P. (2003). Omega-3 fatty acids for depression in pregnancy. *Am. J. Psychiatry* 160: 385.

Clandinin, M. T., Chappell, J. E., Leong, S., Heim, T., Swyer, P. R., and Chance, G. W. (1980a). Extrauterine fatty acid accretion in infant brain: implications for fatty acid requirements. *Early Hum. Dev.* 4: 131–138.

Clandinin, M. T., Chappell, J. E., Leong, S., Heim, T., Swyer, P. R., and Chance, G. W. (1980b). Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. *Early Hum. Dev.* 4: 121–129.

Clement, M., Dinh, L., and Bourre, J. M. (1995). Uptake of dietary RRR-a. *Biochim. Biophys. Acta* 1256: 175–180.

Cohen, J. T., Bellinger, D. C., Connor, W. E., and Shaywitz, B. A. (2005). A quantitative analysis of prenatal intake of n-3 polyunsaturated fatty acids and cognitive development. *Am. J. Prev. Med.* 29: 366–374.

Colin, A., Reggers, J., Castronovo, V., and Ansseau, M. (2003). [Lipids, depression and suicide]. *Encephale* 29: 49–58.

Conquer, J. A., Tierney, M. C., Zecevic, J., Bettger, W. J., and Fisher, R. H. (2000). Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. *Lipids* 35: 1305–1312.

Coscina, D. V., Yehuda, S., Dixon, L. M., Kish, S. J., and Leprohon-Greenwood, C. E. (1986). Learning is improved by a soybean oil diet in rats. *Life Sci.* 38: 1789–1794.

Crawford, M. A., Bloom, M., Cunnane, S., et al. (2001). Docosahexaenoic acid and cerebral evolution. *World Rev. Nutr. Diet.* 88: 6–17.

Cunnane, S. C., Francescutti, V., Brenna, J. T., and Crawford, M. A. (2000). Breast-fed infants achieve a higher rate of brain and whole body docosahexaenoate accumulation than formula-fed infants not consuming dietary docosahexaenoate. *Lipids* 35: 105–111.

Cunnane, S. C., Nadeau, C. R., and Likhodii, S. S. (2001). NMR and isotope ratio mass spectrometry studies of *in vivo* uptake and metabolism of polyunsaturates by the developing rat brain. *J. Mol. Neurosci.* 16: 173–180.

de la Presa, O. S. and Innis, S. M. (1999). Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotoninergic neurotransmitters in frontal cortex caused by a linoleic and alpha-linolenic acid deficient diet in formula-fed piglets. *J. Nutr.* 129: 2088–2093.

de Wilde, M. C., Farkas, E., Gerrits, M., Kiliaan, A. J., and Luiten, P. G. (2002). The effect of n-3 polyunsaturated fatty acid-rich diets on cognitive and cerebrovascular parameters in chronic cerebral hypoperfusion. *Brain Res.* 947: 166–173.

du Bois, T. M., Deng, C., Bell, W., and Huang, X. F. (2006). Fatty acids differentially affect serotonin receptor and transporter binding in the rat brain. *Neuroscience* 139: 1397–1403.

du Bois, T. M., Deng, C., and Huang, X. F. (2005). Membrane phospholipid composition, alterations in neurotransmitter systems and schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 29: 878–888.

Emsley, R., Myburgh, C., Oosthuizen, P., and van Rensburg, S. J. (2002). Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am. J. Psychiatry* 159: 1596–1598.

Engelhart, M. J., Geerlings, M. I., Ruitenberg, A., et al. (2002). Diet and risk of dementia: Does fat matter?: The Rotterdam Study. *Neurology* 59: 1915–1921.

Fenton, W. S., Dickerson, F., Boronow, J., Hibbeln, J. R., and Knable, M. (2001). A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am. J. Psychiatry* 158: 2071–2074.

Fleith, M. and Clandinin, M. T. (2005). Dietary PUFA for preterm and term infants: review of clinical studies. *Crit Rev. Food Sci. Nutr.* 45: 205–229.

Fontani, G., Corradeschi, F., Felici, A., Alfatti, F., Migliorini, S., and Lodi, L. (2005). Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. *Eur. J. Clin. Invest.* 35: 691–699.

Frances, H., Coudereau, J. P., Sandouk, P., Clement, M., Monier, C., and Bourre, J. M. (1996a). Influence of a dietary alpha-linolenic acid deficiency on learning in the Morris water maze and on the effects of morphine. *Eur. J. Pharmacol.* 298: 217–225.

Frances, H., Monier, C., Clement, M., Lecorsier, A., Debray, M., and Bourre, J. M. (1996b). Effect of dietary alpha-linolenic acid deficiency on habituation. *Life Sci.* 58: 1805–1816.

Frances, H., Drai, P., Smirnova, M., Carrie, I., Debray, M., and Bourre, J. M. (2000). Nutritional (n-3) polyunsaturated fatty acids influence the behavioral responses to positive events in mice. *Neurosci. Lett.* 285: 223–227.

Frances, H., Monier, C., and Bourre, J. M. (1995). Effects of dietary alpha-linolenic acid deficiency on neuromuscular and cognitive functions in mice. *Life Sci.* 57: 1935–1947.

Frasure-Smith, N., Lesperance, F., and Julien, P. (2004). Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol. Psychiatry* 55: 891–896.

Galli, C., Trzeciak, H. I., and Paoletti, R. (1972). Effects of essential fatty acid deficiency on myelin and various subcellular structures in rat brain. *J. Neurochem.* 19: 1863–1867.

Gibson, R. A., Neumann, M. A., and Makrides, M. (1996). Effect of dietary docosahexaenoic acid on brain composition and neural function in term infants. *Lipids* 31(Suppl): S177–S181.

Gustafsson, P. A., Duchen, K., Birberg, U., and Karlsson, T. (2004). Breastfeeding, very long polyunsaturated fatty acids (PUFA) and IQ at 6 1/2 years of age. *Acta Paediatr.* 93: 1280–1287.

Hakkarainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D., and Lonnqvist, J. (2004a). Food and nutrient intake in relation to mental wellbeing. *Nutr. J.* 3: 14.

Hakkarainen, R., Partonen, T., Haukka, J., Virtamo, J., Albanes, D., and Lonnqvist, J. (2004b). Is low dietary intake of omega-3 fatty acids associated with depression? *Am. J. Psychiatry* 161: 567–569.

Hamazaki, T., Thienprasert, A., Kheovichai, K., Samuhaseneetoo, S., Nagasawa, T., and Watanabe, S. (2002). The effect of docosahexaenoic acid on aggression in elderly Thai subjects—a placebo-controlled double-blind study. *Nutr. Neurosci.* 5: 37–41.

Heird, W. C. and Lapillonne, A. (2005). The role of essential fatty acids in development. *Annu. Rev. Nutr.* 25: 549–571.

Helland, I. B., Smith, L., Saarem, K., Saugstad, O. D., and Drevon, C. A. (2003). Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* 111: e39–e44.

Heude, B., Ducimetiere, P., and Berr, C. (2003). Cognitive decline and fatty acid composition of erythrocyte membranes—the EVA study. *Am. J. Clin. Nutr.* 77: 803–808.

Hibbeln, J. R. (2002). Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J. Affect. Disord.* 69: 15–29.

Hibbeln, J. R., Makino, K. K., Martin, C. E., Dickerson, F., Boronow, J., and Fenton, W. S. (2003). Smoking, gender, and dietary influences on erythrocyte essential fatty acid composition among patients with schizophrenia or schizoaffective disorder. *Biol. Psychiatry* 53: 431–441.

Hibbeln, J. R., Nieminen, L. R., and Lands, W. E. (2004). Increasing homicide rates and linoleic acid consumption among five Western countries, 1961–2000. *Lipids* 39: 1207–1213.

Hibbeln, J. R. and Salem, N., Jr. (1995). Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am. J. Clin. Nutr.* 62: 1–9.

Horrobin, D. F. (2003). Omega-3 Fatty acid for schizophrenia. *Am. J. Psychiatry* 160: 188–189.

Horwood, L. J., Darlow, B. A., and Mogridge N. (2001). Breast milk feeding and cognitive ability at 7–8 years. *Arch. Dis. Child. Fetal Neonatal Ed.* 84: F23–F27.

Hung, M. C., Shibasaki, K., Yoshida, R., Sato, M., and Imaizumi, K. (2001). Learning behavior and cerebral protein kinase C, antioxidant status, lipid composition in senescence-accelerated mouse: influence of a phosphatidylcholine-vitamin B12 diet. *Br. J. Nutr.* 86: 163–171.

Johnson, S. M. and Hollander, E. (2003). Evidence that eicosapentaenoic acid is effective in treating autism. *J. Clin. Psychiatry* 64: 848–849.

Kalmijn, S., Launer, L. J., Ott, A., Witteman, J. C., Hofman, A., and Breteler, M. M. (1997a). Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Ann. Neurol.* 42: 776–782.

Kalmijn, S., Feskens, E. J., Launer, L. J., and Kromhout, D. (1997b). Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am. J. Epidemiol.* 145: 33–41.

Kalmijn, S., Foley, D., White, L., Burchfiel, C. M., Curb, J. D., Petrovitch, H., Ross, G. W., Havlik, R. J., and Launer, L. J. (2000). Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study. *Arterioscler. Thromb. Vasc. Biol.* 20: 2255–2260.

Kalmijn, S., van Boxtel, M. P., Ocke, M., Verschuren, W. M., Kromhout, D., and Launer, L. J. (2004). Dietary intake of fatty acids and fish in relation to cognitive performance at middle age. *Neurology* 62: 275–280.

Kodas, E., Galineau, L., Bodard, S., Vancassel, S., Guilloteau, D., Besnard, J. C., and Chalon, S. (2004). Serotoninergic neurotransmission is affected by n-3 polyunsaturated fatty acids in the rat. *J. Neurochem.* 89: 695–702.

Kodas, E., Vancassel, S., Lejeune, B., Guilloteau, D., and Chalon, S. (2002). Reversibility of n-3 fatty acid deficiency-induced changes in dopaminergic neurotransmission in rats: critical role of developmental stage. *J. Lipid Res.* 43: 1209–1219.

Lanting, C. I., Fidler, V., Huisman, M., Touwen, B. C., and Boersma, E. R. (1994). Neurological differences between 9-year-old children fed breast-milk or formula-milk as babies. *Lancet* 344: 1319–1322.

Laugharne, J. D., Mellor, J. E., and Peet, M. (1996). Fatty acids and schizophrenia. *Lipids* 31(Suppl): S163–S165.

Levant, B., Radel, J. D., and Carlson, S. E. (2004). Decreased brain docosahexaenoic acid during development alters dopamine-related behaviors in adult rats that are differentially affected by dietary remediation. *Behav. Brain Res.* 152: 49–57.

Lim, S. and Suzuki, H. (2001). Changes in maze behavior of mice occur after sufficient accumulation of docosahexaenoic acid in brain. *J. Nutr.* 131: 319–324.

Llorente, A. M., Jensen, C. L., Voigt, R. G., Fraley, J. K., Berretta, M. C., and Heird, W. C. (2003). Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am. J. Obstet. Gynecol.* 188: 1348–1353.

Lombard, C. B. (2000). What is the role of food in preventing depression and improving mood, performance and cognitive function? *Med. J. Aust.* 173(Suppl): S104–S105.

Lucas, A., Morley, R., Cole, T. J., Lister, G., and Leeson-Payne, C. (1992). Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 339: 261–264.

Mamalakis, G., Tornaritis, M., and Kafatos, A. (2002). Depression and adipose essential polyunsaturated fatty acids. *Prostaglandins Leukot. Essent. Fatty Acids* 67: 311–318.

Marangell, L. B., Martinez, J. M., Zboyan, H. A., Chong, H., and Puryear, L. J. (2004). Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depress. Anxiety* 19: 20–23.

Marangell, L. B., Martinez, J. M., Zboyan, H. A., Kertz, B., Kim, H. F., and Puryear, L. J. (2003). A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am. J. Psychiatry* 160: 996–998.

McCann, J. C. and Ames, B. N. (2005). Is docosahexaenoic acid, an n-3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. *Am. J. Clin. Nutr.* 82: 281–295.

Mischoulon, D. and Fava, M. (2000). Docosahexanoic acid and omega-3 fatty acids in depression. *Psychiatr. Clin. North Am.* 23: 785–794.

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Wilson, R. S., Aggarwal, N., and Schneider, J. (2003a). Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. *Arch. Neurol.* 60: 940–946.

Morris, M. C., Evans, D. A., Bienias, J. L., Tangney, C. C., Bennett, D. A., Aggarwal, N., Schneider, J., and Wilson, R. S. (2003b). Dietary fats and the risk of incident Alzheimer disease. *Arch. Neurol.* 60: 194–200.

Morris, M. C., Evans, D. A., Tangney, C. C., Bienias, J. L., and Wilson, R. S. (2005). Fish consumption and cognitive decline with age in a large community study. *Arch. Neurol.* 62: 1849–1853.

Murck, H., Song, C., Horrobin, D. F., and Uhr, M. (2004). Ethyl-eicosapentaenoate and dexamethasone resistance in therapy-refractory depression. *Int. J. Neuropsychopharmacol.* 7: 341–349.

Nemets, B., Stahl, Z., and Belmaker, R. H. (2002). Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* 159: 477–479.

Ness, A. R., Gallacher, J. E., Bennett, P. D., Gunnell, D. J., Rogers, P. J., Kessler, D., and Burr, M. L. (2003). Advice to eat fish and mood: a randomised controlled trial in men with angina. *Nutr. Neurosci.* 6: 63–65.

Noaghiul, S. and Hibbeln, J. R. (2003). Cross-national comparisons of seafood consumption and rates of bipolar disorders. *Am. J. Psychiatry* 160: 2222–2227.

Otsuka, M. (2000). [Analysis of dietary factors in Alzheimer's disease: clinical use of nutritional intervention for prevention and treatment of dementia]. *Nippon Ronen Igakkai Zasshi* 37: 970–973.

Otsuka, M., Yamaguchi, K., and Ueki, A. (2002). Similarities and differences between Alzheimer's disease and vascular dementia from the viewpoint of nutrition. *Ann. N. Y. Acad. Sci.* 977: 155–161.

Paine, B. J., Makrides, M., and Gibson, R. A. (1999). Duration of breast-feeding and Bayley's Mental Developmental Index at 1 year of age. *J. Paediatr. Child Health* 35: 82–85.

Peet, M. (2003). Eicosapentaenoic acid in the treatment of schizophrenia and depression: rationale and preliminary double-blind clinical trial results. *Prostaglandins Leukot. Essent. Fatty Acids* 69: 477–485.

Peet, M., Brind, J., Ramchand, C. N., Shah, S., and Vankar, G. K. (2001). Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr. Res.* 49: 243–251.

Peet, M. and Horrobin, D. F. (2002). A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch. Gen. Psychiatry* 59: 913–919.

Peet, M., Laugharne, J. D., Mellor, J., and Ramchand, C. N. (1996). Essential fatty acid deficiency in erythrocyte membranes from chronic schizophrenic patients, and the clinical effects of dietary supplementation. *Prostaglandins Leukot. Essent. Fatty Acids* 55: 71–75.

Puri, B. K., Counsell, S. J., Hamilton, G., Richardson, A. J., and Horrobin, D. F. (2001). Eicosapentaenoic acid in treatment-resistant depression associated with symptom remission, structural brain changes and reduced neuronal phospholipid turnover. *Int. J. Clin. Pract.* 55: 560–563.

Puri, B. K., Richardson, A. J., Horrobin, D. F., Easton, T., Saeed, N., Oatridge, A., Hajnal, J. V., and Bydder, G. M. (2000). Eicosapentaenoic acid treatment in schizophrenia associated with symptom remission, normalisation of blood fatty acids, reduced neuronal membrane phospholipid turnover and structural brain changes. *Int. J. Clin. Pract.* 54: 57–63.

Richardson, A. J., Calvin, C. M., Clisby, C., Schoenheimer, D. R., Montgomery, P., Hall, J. A., Hebb, G., Westwood, E., Talcott, J. B., and Stein, J. F. (2000). Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children. *Prostaglandins Leukot. Essent. Fatty Acids* 63: 69–74.

Richardson, A. J. and Puri, B. K. (2000). The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot. Essent. Fatty Acids* 63: 79–87.

Richardson, A. J. and Ross, M. A. (2000). Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between attention-deficit/hyperactivity disorder, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukot. Essent. Fatty Acids* 63: 1–9.

Rodriguez, A., Raederstorff, D., Sarda, P., Lauret, C., Mendy, F., and Descomps, B. (2003). Preterm infant formula supplementation with alpha linolenic acid and docosahexaenoic acid. *Eur. J. Clin. Nutr.* 57: 727–734.

Salem, N., Jr., Moriguchi, T., Greiner, R. S., et al. (2001). Alterations in brain function after loss of docosahexaenoate due to dietary restriction of n-3 fatty acids. *J. Mol. Neurosci.* 16: 299–307.

Silvers, K. M. and Scott, K. M. (2002). Fish consumption and self-reported physical and mental health status. *Public Health Nutr.* 5: 427–431.

Simmer, K. (2001). Longchain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane. Database. Syst. Rev.* CD000376.

Simmer, K. and Patole, S. (2004). Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane. Database. Syst. Rev.* CD000375.

Simopoulos, A. P. (2002). Omega-3 fatty acids in inflammation and autoimmune diseases. *J. Am. Coll. Nutr.* 21: 495–505.

Solfrizzi, V., D'Introno, A., Colacicco, A. M., Capurso, C., Del Parigi, A., Capurso, S., Gadaleta, A., Capurso, A., and Panza, F. (2005). Dietary fatty acids intake: possible role in cognitive decline and dementia. *Exp. Gerontol.* 40: 257–270.

Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstad, N., Mahon, A., Zentall, S. S., Arnold, L. E., and Burgess, J. R. (2003). EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. *Lipids* 38: 1007–1021.

Stoll, A. L., Severus, W. E., Freeman, M. P., Rueter, S., Zboyan, H. A., Diamond, E., Cress, K. K., and Marangell, L. B. (1999). Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch. Gen. Psychiatry* 56: 407–412.

Su, K. P., Huang, S. Y., Chiu, C. C., and Shen, W. W. (2003). Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur. Neuropsychopharmacol.* 13: 267–271.

Sublette, E. and Trappler, B. (2000). Cultural sensitivity training in mental health: treatment of Orthodox Jewish psychiatric inpatients. *Int. J. Soc. Psychiatry* 46: 122–134.

Tanskanen, A., Hibbeln, J. R., Tuomilehto, J., Uutela, A., Haukkala, A., Viinamaki, H., Lehtonen, J., and Vartiainen, E. (2001). Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr. Serv.* 52: 529–531.

Taylor, K. E., Higgins, C. J., Calvin, C. M., Hall, J. A., Easton, T., McDaid, A. M., and Richardson, A. J. (2000). Dyslexia in adults is associated with clinical signs of fatty acid deficiency. *Prostaglandins Leukot. Essent. Fatty Acids* 63: 75–78.

Tiemeier, H., van Tuijl, H. R., Hofman, A., Kiliaan, A. J., and Breteler, M. M. (2003). Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. *Am. J. Clin. Nutr.* 78: 40–46.

Uauy, R., Hoffman, D. R., Mena, P., Llanos, A., and Birch, E. E. (2003). Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. *J. Pediatr.* 143: S17–S25.

Udell, T., Gibson, R. A., and Makrides, M. (2005). The effect of alpha-linolenic acid and linoleic acid on the growth and development of formula-fed infants: a systematic review and meta-analysis of randomized controlled trials. *Lipids* 40: 1–11.

Vancassel, S., Durand, G., Barthelemy, C., Lejeune, B., Martineau, J., Guilloteau, D., Andres, C., and Chalon, S. (2001). Plasma fatty acid levels in autistic children. *Prostaglandins Leukot. Essent. Fatty Acids* 65: 1–7.

Voigt, R. G., Jensen, C. L., Fraley, J. K., Rozelle, J. C., Brown, F. R., III, and Heird, W. C. (2002). Relationship between omega3 long-chain polyunsaturated fatty acid status during early infancy and neurodevelopmental status at 1 year of age. *J. Hum. Nutr. Diet.* 15: 111–120.

Voigt, R. G., Llorente, A. M., Jensen, C. L., Fraley, J. K., Berretta, M. C., and Heird, W. C. (2001). A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *J. Pediatr.* 139: 189–196.

Wainwright, P. E. (2002). Dietary essential fatty acids and brain function: a developmental perspective on mechanisms. *Proc. Nutr. Soc.* 61: 61–69.

Wainwright, P. E., Huang, Y. S., Coscina, D. V., Levesque, S., and McCutcheon, D. (1994). Brain and behavioral effects of dietary n-3 deficiency in mice: a three generational study. *Dev. Psychobiol.* 27: 467–487.

Wezel-Meijler, G., van der Knaap, M. S., Huisman, J., Jonkman, E. J., Valk, J., and Lafeber, H. N. (2002). Dietary supplementation of long-chain polyunsaturated fatty acids in preterm infants: effects on cerebral maturation. *Acta Paediatr.* 91: 942–950.

Whalley, L. J., Fox, H. C., Wahle, K. W., Starr, J. M., and Deary, I. J. (2004). Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids. *Am. J. Clin. Nutr.* 80: 1650–1657.

Willatts, P. (2002). Long chain polyunsaturated fatty acids improve cognitive development. *J. Fam. Health Care* 12: 5.

Willatts, P., Forsyth, J. S., DiModugno, M. K., Varma, S., and Colvin, M. (1998). Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 352: 688–691.

Yamamoto, N., Hashimoto, A., Takemoto, Y., et al. (1988). Effect of the dietary alpha-linolenate/linoleate balance on lipid compositions and learning ability of rats. II. Discrimination process, extinction process, and glycolipid compositions. *J. Lipid Res.* 29: 1013–1021.

Yehuda, S., Rabinovtz, S., Carasso, R. L., and Mostofsky, D. I. (1996). Essential fatty acids preparation (SR-3) improves Alzheimer's patients quality of life. *Int. J. Neurosci.* 87: 141–149.

Yehuda, S., Rabinovitz, S., Carasso, R. L., and Mostofsky, D. I. (2000). Fatty acid mixture counters stress changes in cortisol, cholesterol, and impair learning. *Int. J. Neurosci.* 101: 73–87.

Yoshida, S., Miyazaki, M., Takeshita, M., Yuasa, S., Kobayashi, T., Watanabe, S., and Okuyama, H. (1997). Functional changes of rat brain microsomal membrane surface after learning task depending on dietary fatty acids. *J. Neurochem.* 68: 1269–1277.

Zerouga, M., Beauge, F., Niel, E., Durand, G., and Bourre, J. M. (1991). Interactive effects of dietary (n-3) polyunsaturated fatty acids and chronic ethanol intoxication on synaptic membrane lipid composition and fluidity in rats. *Biochim. Biophys. Acta* 1086: 295–304.