Omega-3 fatty acids in ADHD and related neurodevelopmental disorders

ALEXANDRA J. RICHARDSON

Department of Physiology, Human Anatomy and Genetics, University of Oxford, UK

Summary

Omega-3 fatty acids are dietary essentials, and are critical to brain development and function. Increasing evidence suggests that a relative lack of omega-3 may contribute to many psychiatric and neurodevelopmental disorders. This review focuses on the possible role of omega-3 in attention-deficit/hyperactivity disorder (ADHD) and related childhood developmental disorders, evaluating the existing evidence from both research and clinical perspectives. Theory and experimental evidence support a role for omega-3 in ADHD, dyslexia, developmental coordination disorder (DCD) and autism. Results from controlled treatment trials are mixed, but the few studies in this area have involved different populations and treatment formulations. Dietary supplementation with fish oils (providing EPA and DHA) appears to alleviate ADHD-related symptoms in at least some children, and one study of DCD children also found benefits for academic achievement. Larger trials are now needed to confirm these findings, and to establish the specificity and durability of any treatment effects as well as optimal formulations and dosages. Omega-3 is not supported by current evidence as a primary treatment for ADHD or related conditions, but further research in this area is clearly warranted. Given their relative safety and general health benefits, omega-3 fatty acids offer a promising complementary approach to standard treatments.

Introduction

Attention-deficit/hyperactivity disorder and related disorders

Attention-deficit/hyperactivity disorder (ADHD) is the most common developmental disorder of childhood, with prevalence estimates varying between 4% and 15% for school-age children in the USA and elsewhere (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Wolraich, Hannah, Baumgaertel, & Feurer, 1998). Lower estimates are obtained when rigorous diagnostic criteria are used, but some of the variability reflects the actual dimensionality of ADHD-type symptoms; clear boundaries between normal and abnormal function are difficult to establish, because in many respects the core defining features of inattention and/or hyperactivity-impulsivity are simply extremes of normal individual differences in cognition and behaviour.

It is now clear that ADHD also persists into adulthood, although some of the symptoms change with age (Kooij et al., 2005). In both children and adults, the associated difficulties in health as well as social, educational and occupational functioning are not only damaging to those directly affected, but also represent a significant burden on society as a whole (Burd, Klug, Coumbe, & Kerbeshian, 2003; Secnik, Swensen, & Lage, 2005).

No objective biological markers for ADHD have been identified, and aetiology is obviously both complex and multi-factorial, involving both genetic and environmental factors that are likely to differ between affected individuals. The heterogeneity of ADHD is further exacerbated by its very high comorbidity with many other disorders of behaviour, learning or mood. In childhood, these most commonly include conduct and/or oppositional disorders as well as many forms of specific learning difficulties such as dyslexia (specific reading disabilities), developmental language disorders, dyspraxia (developmental coordination disorder or DCD) and the autistic spectrum of disorders (ASD) (Dery, Toupin, Pauze, & Verlaan, 2004; Doyle, Faraone, DuPre, & Biederman, 2001; Kadesjo & Gillberg, 2001; Willcutt & Pennington, 2000). In adulthood, ADHD has been linked with anxiety, depression and other mood disorders, antisocial personality, substance abuse and the schizophrenia spectrum of disorders (Biederman et al., 1996; Dilsaver, Henderson Fuller, & Akiskal, 2003; Hellgren, Gillberg, Bagenholm, & Gillberg, 1994; Rasmussen & Gillberg, 2000; Secnik et al., 2005).

As well as their frequent overlap within indivi-duals, these disorders also show considerable familial aggregation, suggesting some common elements at the level of biological predisposition. Increasing evidence, reviewed here, suggests that these may include functional deficiencies or imbalances of omega-3 fatty acids.

Omega-3 fatty acids

Both omega-3 and omega-6 fatty acids are essential to human health but must be provided by the diet. The longer-chain, highly unsaturated fatty acids (HUFA) of each series are the most important for brain development and function, notably the omega-6 arachidonic acid (AA) and the omega-3 eicosapentaenoic and docosahexaenoic acids (EPA and DHA). These and other HUFA can be synthesized within the body from their respective essential fatty acid (EFA) precursors, the omega-6 linoleic acid (LA) and the omega-3 alpha-linolenic acid (ALA), although this conversion process is not very efficient in humans (Pawlosky, Hibbeln, Novotny, & Salem, 2001; Salem, Pawlosky, Wegher, & Hibbeln, 1999) and males appear to be at a particular disadvantage in this respect (Burdge, Jones, & Wootton, 2002; Burdge & Wootton, 2002).

By historical standards, dietary intake of omega-3 is very low in many modern developed countries. The key omega-3 HUFA (EPA and DHA) are found in appreciable quantities only in fish and seafood, and ALA is found in green vegetables and some nuts and seeds. By contrast, omega-6 fats are usually abundant in Western-type diets, especially if these rely heavily on processed foods. Most vegetable and seed oils (as well as whole nuts, seeds and grains) are richer in LA than ALA, and the key omega-6 HUFA, AA, is provided directly by meat, eggs and dairy produce. The dietary ratio of omega-6 to omega-3 thus often far exceeds the ratios of between 1 : 1 and 4 : 1 that prevailed in the 'hunter-gatherer' type diets on which modern humans evolved (Simopoulos, 2002). Gene transfer studies have provided very powerful evidence that the earlier, lower ratios were much closer to the optimum for human health (Holman, 1998; Kang, 2003). Both epidemiological and clinical studies support this picture, and the relative disappearance of omega-3 from the diet in developed countries has been linked with increases in a wide range of both physical and mental disorders (Haag, 2003; Rudin, 1981; Simopoulos, 2002).

The critical importance of omega-3 fatty acids for normal brain development and function—and conversely, their potential relevance to a wide range of developmental, psychiatric and neurological disorders—has been amply reviewed elsewhere and cannot be considered in detail here (Bourre, 2004;

Carlson & Neuringer, 1999; Haag, 2003; Peet, Glen, & Horrobin, 2003). Instead, the following section will briefly outline how omega-3 fatty acid deficien-cies could help to explain both the high comorbidity of ADHD with other developmental and psychiatric disorders and many of their associated clinical features, as well as offering no conflict with current pharmacological approaches to ADHD and related disorders.

Theoretical plausibility of a role for omega-3 in ADHD and related conditions

Omega-3 in other psychiatric disorders

At the genetic level, associations have been docu-mented between ADHD and dyslexia, antisocial behaviour, mood disorders and schizophrenia (Faraone et al., 1995; Faraone, Biederman, Jetton, & Tsuang, 1997; Willcutt, Pennington, & DeFries, 2000), although there are obvious difficulties in relating genetic factors to any such behaviourally-defined phenotypes. Many of the genes involved in these conditions are likely to be widely distributed in the general population, (Fisher & DeFries, 2002) and environmental factors remain the obvious targets for management or prevention strategies. Dietary influences are firmly among these, as nutrition can influence gene expression, while genetic differences can affect the absorption and utilization of specific nutrients, contributing to individual variation in dietary requirements. It is more than plausible that some of the numerous genes already known to influence fatty acid metabolism may contribute to the risk for a wide range of inter-related developmental and psychiatric disorders, raising the possibility of a spectrum of vulnerability (Bennett & Horrobin, 2000; Peet et al., 2003).

There is now abundant experimental evidence of fatty acid abnormalities in a wide range of adult psychiatric disorders, but only properly controlled treatment trials can provide reliable evidence for HUFA deficiencies as a causal factor. Several such trials have shown benefits from treatment with omega-3 in schizophrenia, in both medicated and unmedicated patients, (Peet & Stokes, 2005) although the largest trial of this kind was negative (Fenton, Dickerson, Boronow, Hibbeln, & Knable, 2001). The evidence for a causal contribution for omega-3 currently appears strongest in relation to disorders of mood and/or impulsivity, most of which show high comorbidity with ADHD. Adjunctive treatment with omega-3, particularly EPA, has shown benefits in unipolar depression, (Nemets, Stahl, & Belmaker, 2002; Peet & Horrobin, 2002; Su, Huang, Chiu, & Shen, 2003) bipolar disorder (Stoll et al., 1999) and borderline personality

disorder, (Zanarini & Frankenburg, 2003) although one adjunctive study of DHA-rich fish oil for depression was negative, as was a trial of DHA as monotherapy (Marangell et al., 2003; Silvers, Woolley, Hamilton, Watts, & Watson, 2005).

Other evidence with relevance to ADHD includes research into possible links between omega-3 deficiency and various forms of antisocial behaviour. There is some epidemiological evidence that lower dietary omega-3 intakes may be associated with increased hostility in adolescents, (Iribarren et al., 2004) and preliminary evidence from small controlled trials suggests that omega-3 might protect against aggression in both women with borderline personality disorder and otherwise healthy young adults under mental stress (Hamazaki et al., 1996; Zanarini & Frankenburg, 2003). Omega-3 HUFA were also one component of the active supplement in a rigorous and much larger trial that showed significant reductions in offending by young prisoners, (Gesch, Hammond, Hampson, Eves, & Crowder, 2002) but the dose of omega-3 in this study was small, and the treatment also included a broad range of vitamins, minerals and omega-6 fatty acids.

Although the focus here is on omega-3 fatty acids, this is an appropriate point to emphasize that no nutrients work in isolation, and deficiencies in many other essential micronutrients have also been documented in ADHD and related disorders. Zinc has been the most consistently reported, and there is some preliminary controlled trial evidence of benefits from supplementation (Arnold & DiSilvestro, 2005). Like omega-3 fatty acids, this element plays innumerable roles in human physiology, but in addition to assisting in blood glucose regulation—which has obvious implications for mental function—zinc is also an essential co-factor in the synthesis of HUFA from EFA, hence these findings may be directly relevant to those reviewed here.

Clinical features associated with ADHD and related conditions

Many clinical features associated with ADHD and related conditions are consistent with relative deficiencies in omega-3 fatty acids, as discussed in more detail elsewhere (Richardson, 2004b; Richardson & Puri, 2000; Richardson & Ross, 2000). These include:

The excess of males affected. Reported sex ratios vary from around 2 : 1 in favour of males for dyslexia, dyspraxia and attentional disorders without hyperactivity to more than 5 : 1 for more disruptive forms of ADHD and autistic spectrum disorders.

While this male excess may partly reflect referral biases and/or sex differences in clinical presentation, the evidence points to at least some biological factors that put males at a greater risk for these and other neurodevelopmental disorders (Arnold, 1996; Rutter et al., 2004). Sex differences in fatty acid metabolism may be one such factor, because for hormonal reasons, males are more vulnerable than females to deficiencies in highly unsaturated fatty acids (Burdge et al., 2002; Burdge & Wootton, 2002; Giltay, Gooren, Toorians, Katan, & Zock, 2004).

Apparent links with allergies and other immune system disorders. Clinically, ADHD, dyslexia and autism are often associated with physical health conditions involving overt immune system dysfunction, such as increased proneness to infections, atopic conditions such as asthma, eczema and hayfever, and also with some less common autoimmune disorders (Ashwood & Van de Water, 2004; Comi, Zimmerman, Frye, Law, & Peeden, 1999; Jyonouchi, Sun, & Le, 2001). In early life, the availability and balance of dietary omega-3 and omega-6 HUFA can influence the programming of Th1 and Th2 responses and the establishment and maintenance of healthy gut flora, both of which have important consequences for autoimmune or allergic sensitivity (Das, 2002). The immune system has extensive and highly complex influences on brain development and function, and increasing evidence suggests that the neurobiological basis of ADHD and related developmental disorders may partly reflect inflammatory and/or autoimmune influences operating during early brain development, and possibly throughout life (Dalton et al., 2003; Taylor, Richardson, & Stein, 2001; Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005; Vincent et al., 2002). The omega-6 fatty acid AA has pro-inflammatory actions via several different mechanisms, while the omega-3 HUFA found in fish oils generally have opposing and complementary actions (Calder, 2003). The relatively high ratio of omega-6 to omega-3 in modern diets (and particularly the ratio of AA to EPA) may therefore contribute to risk for any disorders in which inflammation plays a part, although HUFA from both series play complex and complementary roles in both inflammatory and autoimmune responses (Harbige, 2003).

Abnormalities of mood and arousal. Children with ADHD and related conditions often have particular difficulties in the regulation of mood, arousal and sleep, (Hirshfeld-Becker et al., 2002; Owens, 2005) not all of which can be explained simply as consequences of their behavioural and

learning problems. The evidence for omega-3 as a factor in mood disorders has already been mentioned above, but along with omega-6, these fatty acids also play both direct and indirect roles in the initiation and maintenance of normal sleep (Chen & Bazan, 2005; Yehuda, 2003). Functional deficiencies or imbalances in highly unsaturated fatty acids may be one of the common underlying mechanisms in the association of these traits and features with ADHD and related conditions.

Sensory processing abnormalities. Subtle abnormalities of rapid visual and auditory processing are associated with dyslexia, dyspraxia, ADHD and other psychiatric disorders, and such sensory imprecision may underlie some of the cognitive features of these disorders, including impairments in attention and working memory (Javitt, Shelley, Silipo, & Lieberman, 2000; Stein & Richardson, 1999). The possible contribution of fatty acid abnormalities to sensory dysfunction in these disorders is discussed elsewhere, (Richardson, Cyhlarova, & Puri, 2003; Taylor & Richardson, 2000) but omega-3 fatty acids—particularly DHA—are critical for the development and functioning of the visual system (Litman, Niu, Polozova, & Mitchell, 2001; Uauy, Hoffman, Peirano, Birch, & Birch, 2001), and emerging evidence shows that the dietary intake of HUFA can also affect the development and maturation of low-level auditory processing systems (Haubner et al., 2002; Unay et al., 2004). Visual and auditory symptoms in dyslexia have been related to physical signs consistent with fatty acid deficiency, (Taylor et al., 2000) and experimental studies to follow up these observations are in progress.

*Neurotransmitter models of ADHD
and related disorders*

Standard pharmacological treatment for ADHD involves stimulant medications that increase the availability of dopamine, as reflected in all current etiological theories of this condition. It is therefore notable that in animal studies, chronic omega-3 deficiencies can reduce dopamine and its binding to D2 receptors both in frontal cortex and other brain regions, and are associated with attentional and behavioural dysfunctions comparable to those involved in ADHD (Takeuchi, Fukumoto, & Harada, 2002; Zimmer et al., 2002). Emerging evidence indicates that subsequent dietary supplementation may be able to remedy some of the dopaminergic abnormalities induced by omega-3 deficiencies during early development, but not others (Levant, Radel, & Carlson, 2004).

Fatty acids and their metabolism can also affect the functioning of other major neurotransmitter systems implicated in ADHD and related psychiatric disorders, as reviewed elsewhere (Yehuda, 2003). Effects of omega-3 on both serotonergic and noradrenergic function may help to account for the apparent links between omega-3 status and hostility-aggression, depression and other mood-related disorders as noted above. The effects of fatty acids on neural signalling can be mediated via a huge variety of different mechanisms, direct and indirect, as HUFA and their derivatives not only affect membrane structure and function, but help to regulate blood flow, endocrine and immune functions and can also modulate ion channels, neurotransmitter uptake, synaptic transmission, apoptosis and gene expression among other biological processes. Of particular relevance to many psychiatric disorders are their effects on cytokine and endocannabinoid metabolism, which are receiving serious attention in relation to schizophrenia, (Yao & van Kammen, 2004) and may be equally important in related childhood neurodevelopmental disorders including ADHD.

Experimental evidence for fatty acid abnormalities in ADHD and related disorders

Physical signs consistent with fatty acid deficiency

In animals, essential fatty acid deficiencies cause physical signs and symptoms including excessive thirst, frequent urination, rough, dry hair and skin, and follicular keratosis. An increased prevalence of these signs in hyperactive children was first reported 25 years ago by a UK support group, (Colquhoun & Bunday, 1981) who also pointed out that fatty acid deficiencies could help to explain other characteristics often associated with ADHD, such as zinc deficiency (zinc is a co-factor in HUFA synthesis); the apparent intolerance of some children to foods containing salicylates (these inhibit cyclo-oxygenase enzymes that convert AA and EPA into prostaglandins, and could thus exacerbate any problems stemming from low levels of these key HUFA derivatives); and the frequency of atopic conditions in these children. Noting that non-affected siblings consumed similar diets, these authors further suggested that the primary problem might lie in poor EFA-HUFA conversion.

Subsequent investigations confirmed that these physical signs of fatty acid deficiency were more common in ADHD children than controls, (Stevens et al., 1995; Stevens, Zentall, Abate, Kuczek, & Burgess, 1996) and also showed that high scores on a simple checklist rating scale devised to assess such signs were associated with low plasma concentrations

of AA, DHA and total omega-3 fatty acids. Both clinical signs and biochemical measures of fatty acid status were also correlated with measures of physical health and behaviour in these studies, as discussed further below.

In children and adults, the same physical signs suggestive of fatty acid deficiency have also been linked with both dyslexia (Richardson et al., 2000; Taylor et al., 2000) and autistic spectrum disorders (Bell, Sargent, Tocher, & Dick, 2000; 2004a). While these signs can obviously have other causes, their significance and their apparent association with ADHD and related neurodevelopmental disorders clearly merits further investigation.

Biochemical measures of fatty acid status or metabolism

Blood fatty acid deficiencies or imbalances. Reduced blood concentrations of HUFA in ADHD children relative to controls have been reported in several studies (Bekaroglu et al., 1996; Burgess, Stevens, Zhang, & Peck, 2000; Burgess & Stevens, 2003; Chen, Hsu, Hsu, Hwang, & Yang, 2004; Mitchell, Aman, Turbott, & Manku, 1987; Stevens et al., 1995). Although the specific pattern of results has varied, reductions of AA, DHA and total omega-3 have usually been found in ADHD subjects, and the most consistent findings appear to be from plasma rather than red blood cell (RBC) membranes. Thus in one study, membrane concentrations of key HUFA were actually elevated in ADHD children relative to controls, while the same fatty acids were unusually low in plasma (Burgess & Stevens, 2003). Reductions of omega-3 (in both RBC and plasma) were also reported in the only study to date investigating blood fatty acids in adults with ADHD (Young, Maharaj, & Conquer, 2004). In children and adults with autistic spectrum disorders, fatty acid abnormalities have been reported in both plasma (Vancassel et al., 2001) and RBC membranes (Bell et al., 2000; 2004a). Findings include particular reductions in omega-3 HUFA, an elevated ratio of AA : EPA (consistent with tendencies towards inflammation) and an apparent increased susceptibility to breakdown of membrane fatty acids, possibly reflecting increased oxidative stress. Few blood biochemical studies have yet focused on dyslexia, and none on dyspraxia/DCD, but one early case report noted fatty acid deficiencies in a dyslexic child whose learning difficulties were reduced following dietary intervention (Baker, 1985). Preliminary results from ongoing studies of dyslexic and non-dyslexic adults showed that higher RBC omega-3 concentrations were associated with better reading ability in both groups, although no significant group differences in fatty acid status were

found (Bell et al., 2004b). Poor working memory performance—a central feature of both ADHD and dyslexia—was also related to low omega-3 status, but only in dyslexic adults, not in controls (Ross et al., 2004). In addition to making case-control comparisons, other researchers have also explored correlations between blood biochemical indices of fatty acid status and various behavioural and/or health measures. In a combined sample of 96 boys with and without ADHD-type difficulties, HUFA deficiencies were associated with a range of behavioural and learning and health problems, irrespective of clinical diagnosis, (Stevens et al., 1996) supporting the idea that fatty acid abnormalities may relate in a dimensional rather than a categorical way to ADHD-type symptoms. It was also found that low omega-6 concentrations related only to some physical health measures (such as dry skin and hair, frequency of colds, and antibiotic use), not to parental ratings of either behaviour or learning. By contrast, low omega-3 fatty acid status was associated not only with clinical ratings of physical signs consistent with fatty acid deficiency, but also with both behavioural problems (including conduct disorder, hyperactivity-impulsivity, anxiety, temper tantrums and sleep problems) and learning difficulties in these children. This pattern of findings is consistent with other evidence that omega-3 rather than omega-6 status is likely to be more relevant to ADHD and related behavioural disorders.

Enzyme abnormalities. A few biochemical investigations have focused on particular enzymes involved in fatty acid metabolism. Abnormalities of phospholipase A2 (PLA2) enzymes that selectively remove HUFA from membrane phospholipids have already been extensively documented in schizophrenia, and an initial study also found elevations of a Type IV PLA2 enzyme in RBC membranes of dyslexic adults (MacDonell et al., 2000). Increases in the same PLA2 enzyme have also been reported in some subgroups of children and adults with autistic spectrum disorders, although preliminary observations suggested that this did not apply to those already taking omega-3 supplementation (Bell et al., 2004a).

Intepretation of the experimental evidence. Preliminary findings from experimental studies generally support the proposal that fatty acid abnormalities are associated with ADHD and related childhood developmental disorders, although the evidence remains limited. Some of the blood biochemical evidence suggests specific difficulties in the synthesis of HUFA from their EFA precursors, excessive susceptibility to

oxidative stress and/or an unusual distribution of fatty acids between RBC and plasma. While these findings may reflect metabolic abnormalities that have some constitutional basis, they could equally arise from dietary and other environmental factors that it is not always possible to monitor, let alone control (Hibbeln et al., 2003). Interpretation is also difficult because even with biochemical measures that have good reproducibility, too little is currently known about the functional significance of, for example, RBC versus plasma fatty acid concentrations, let alone the more detailed distribution and metabolism of these fatty acids in different tissues and intracellular compartments. Furthermore, because dietary intake of omega-3 in many countries is so low by historical standards, it cannot safely be assumed that reference values from control groups are necessarily optimal with respect to either physical or mental health. Investigations of the functional significance of these kinds of measures in general population samples are therefore needed, as well as further research into their potential relevance for ADHD and related disorders.

Clinical trials of omega-3 supplementation in ADHD and related developmental disorders of childhood

Anecdotal evidence, case reports and open studies have long suggested potential benefits from treatment with highly unsaturated fatty acids in ADHD and related childhood developmental disorders (Baker, 1985; Stordy, 1995; 2000) Unfortunately, the randomised controlled trials (RCT) needed to investigate this possibility properly still remain few, although additional studies are in progress.

Two early RCTs assessed the effects of evening primrose oil (providing the omega-6 fatty acid GLA) in hyperactive or ADHD children, (Aman, Mitchell, & Turbott, 1987; Arnold et al., 1989) but few if any benefits were apparent. With the recognition that omega-3 were far more likely than omega-6 to be lacking from modern diets, and increasing evidence for omega 3 deficiency in other psychiatric disorders in adults, the emphasis then shifted towards omega-3 fatty acids. Table I provides a summary of the RCTs published to date that have involved omega-3 treatment for ADHD and related childhood developmental disorders.

Basic reviews encompassing most of these studies can be found elsewhere, (Richardson, 2004a; 2004b) so after summarising the key findings from controlled trials, the aim here is to focus primarily on their broader interpretation, highlighting key issues for further research while also discussing the relevance of the existing evidence for clinicians dealing with ADHD and related disorders.

ADHD

The first RCT of omega-3 fatty acids for childhood behaviour and learning difficulties involved 63 USA children aged between 6 and 12 years with formal diagnoses of DSM-IV ADHD (Voigt et al., 2001). All were judged to be receiving effective and stable treatment with stimulant medication, and children with other psychiatric disorders (except conduct disorder or oppositional defiance) were excluded. Subjects were randomised to adjunctive treatment with 345 mg/day of pure DHA (from an algal source) or placebo for four months, and stimulant medication was withdrawn before study assessments. Analyses were presented on 54 subjects who completed the study.

No benefits of DHA treatment over placebo were found on a wide range of behavioural ratings or computerised measures of inattention and impulsivity, despite the fact that active treatment was associated with significantly increased blood concentrations of DHA. In fact, close inspection showed that active treatment was associated with a slightly worse outcome on almost all measures than placebo, although these group differences did not reach statistical significance.

Similarly negative findings came from a Japanese study of 40 ADHD-type children aged between 6 and 12 years attending a special summer camp (Hirayama, Hamazaki, & Terasawa, 2004). No formal diagnoses were available and only six children were receiving medication, apparently owing to parental preferences for non-pharmacological approaches. For two months, the children received foods fortified with DHA (providing approximately 500 mg/day) or indistinguishable control foods containing olive oil. Outcome measures included parent and teacher ratings of ADHD symptoms and aggression, measures of visual and auditory perception, working memory and visual-motor integration, and a continuous performance test.

The only group difference initially reported was a significant improvement between pre- and post-treatment measures of visual and auditory memory in the placebo group, which was not evident in the children receiving DHA. In subsequent analyses, however, slight modifications to scoring methods (combining parent and teacher ratings) indicated greater reductions in aggression for DHA supplementation over placebo (Hamazaki & Hirayama, 2004).

The only other RCT of children selected primarily for ADHD-type difficulties was carried out at Purdue University, USA, (Stevens et al., 2003) and showed

Table I.   Randomised controlled trials of treatment with omega-3 fatty acids in children with ADHD and related developmental disorders.

Investigators	Diagnosis (+ Ascertainment)	N (male, female)	Active treatment: Daily doses of Omega-3 + Other constituents	Trial design	Duration of treatment in parallel groups	Outcome
Voigt et al., 2001	DSM-IV ADHD with minimal or no comorbidity (Psychiatric clinic, USA)	54 (42,12)	DHA 345 mg (from algae)	RCT, double-blind, parallel groups; adjunctive to pharmacotherapy	4 months	No effect of treatment on a wide range of behavioural and computerized measures of ADHD-related symptoms
Richardson & Puri, 2002	Dyslexia + ADHD features (Special school, UK)	29 (25,4)	EPA 186 mg DHA 480 mg (from fish oil) Omega-6 (GLA 96 mg, AA 42 mg) Vitamin E 60 IU	RCT, double-blind, parallel groups (+ one-way placebo-active crossover); monotherapy	12 weeks (+12 weeks)	Active > placebo for changes in parent ratings of ADHD-related symptoms
Stevens et al., 2003	ADHD-type difficulties + physical signs consistent with EFA deficiency (Community-based sample, USA)	47 (41,6)	EPA 80 mg, DHA 480 mg (from fish oil) Omega-6 (GLA 96 mg, AA 40 mg) Vitamin E 56 IU	RCT, double-blind, parallel groups; adjunctive to pharmacotherapy	16 weeks	Active > placebo for changes in teacher-rated attention, parent-rated conduct, and % meeting clinical criteria for oppositional defiant disorder
Hamazaki et al., 2004	ADHD (Special summer camp, Japan)	40 (32,8)	EPA 100mg approx DHA 510mg approx (from fish oil & fermented soybean oil)	RCT, double-blind, parallel groups; adjunctive to pharmacotherapy	2 months?	No effect of treatment on a wide range of behavioural and psychometric measures
Richardson & Montgomery, 2005	DSM-IV DCD (mainstream schools in one UK geographical region)	117 (78,39)	EPA 558 mg DHA 174 mg (from fish oil) Omega-6 (GLA 60 mg) Vitamin E 15 IU	RCT, double-blind, parallel groups (+ one-way placebo-active crossover); monotherapy	12 weeks (+12 weeks)	Active = Placebo for changes in motor function Active > Placebo for changes in teacher-rated ADHD-related symptoms and age-standardised measures of reading and spelling achievement

some modest benefits from fatty acid treatment. Participants were recruited from the community by advertisement, and although full psychiatric evaluations were not available, participants had all been diagnosed with ADHD by a psychiatrist, clinical psychologist or paediatrician according to parental report, and around 80% were receiving pharmacological treatment, mainly stimulant medications. In an attempt to reduce heterogeneity and provide a valid test of the fatty acid hypothesis, volunteers were further selected for elevated scores on clinical ratings of physical signs consistent with fatty acid deficiency (such as excessive thirst and dry skin). Fifty children with a mean age of around 10 years were randomised to treatment for four months with either fish oil and evening primrose oil—supplying mainly omega-3 fatty acids (80 mg EPA and 480 mg DHA daily) with some omega-6 (96 mg GLA and 40 mg AA)—or an olive oil placebo. Three recruits dropped out at a very early stage, so intention-to-treat analyses were conducted on 47 children.

Significant benefits of active treatment over placebo were found for teacher-rated attention and parent rated conduct, as well as clinical ratings of oppositional defiant disorder, but no group differences were seen on a range of other measures. Interpretation was also complicated by the fact that biochemical measures showed significant increases for some omega-3 fatty acids in both treatment groups, as discussed further below.

Dyslexia

Only one peer-reviewed RCT to date has involved children with a primary diagnosis of dyslexia (Richardson & Puri, 2002). From children attending a special school in the UK, volunteers were further selected for scoring >1 SD above population normative values on age-standardized parent ratings of inattention, hyperactivity and combined-type ADHD symptoms (a criterion met by 41 of 74 children screened). No child had a formal ADHD diagnosis, however, or was receiving any treatment for this condition. Parent-rated ADHD-type symptoms were the primary outcome measure, and children were treated for 12 weeks with either an omega-3/omega-6 combination very similar to that used in the Purdue study, or an olive oil placebo. In this pilot study, analyses were conducted only on the 29 children who completed the 12 week study period.

Group comparisons showed an advantage of active treatment over placebo for changes in all components of the rating scales used (CPRS-L [Conners, 1997]) but these differences reached significance only for inattention, anxiety/withdrawal and one global measure of disruptive behaviour.

Following an additional 12 weeks in which there was a one-way treatment crossover (placebo to active treatment) similar improvements were seen in the crossover group, while children continuing with active treatment maintained or improved on their earlier symptom reductions (Richardson, 2003).

Developmental coordination disorder

The largest trial to date of fatty acids for child behavioural and learning difficulties involved 117 children aged 5–12 years with DSM-IV DCD, identified from mainstream schools in one UK geographical region (Richardson & Montgomery, 2005). Because of the high comorbidity of DCD with dyslexia and ADHD, primary outcomes were selected to reflect each of these domains, consisting of age-standardised measures of motor performance, reading and spelling, and teacher-rated ADHD-type symptoms (CTRS-L [Conners, 1997]). Active treatment was a high-EPA fish oil with some evening primrose oil (providing 558 mg EPA, 174 mg DHA and 60 mg GLA daily) and placebo was olive oil, administered for 12 weeks in parallel groups. None of the children were receiving any other treatment for their behavioural and learning difficulties, and all analyses were conducted on a strict intention-to-treat basis.

No effect of treatment was found for motor functioning, although a clear placebo effect was seen for these measures, in that both groups showed significant improvements after 12 weeks compared with their baseline scores. By contrast, highly significant group differences in favour of active treatment were found for the changes in reading and spelling, and also for a wide range of ADHD-related symptoms. With respect to literacy skills, average gains for children on active treatment were three times the normal expected rate of progress for reading and twice the normal rate for spelling, while children on placebo made only the age-expected progress in reading and fell further behind in spelling. On teacher ratings of ADHD, significant improvements for active treatment over placebo were seen on almost all the symptom scales, with reductions of 0.3 and just over 0.5 SD on the core ADHD dimensions of hyperactivity and inattention respectively.

In the follow-up period involving a one-way treatment crossover, children switching from placebo to active treatment made gains similar to those shown by children on active treatment during the main parallel group phase, while those continuing with active treatment maintained or improved on their earlier progress.

Interpretation of findings from controlled treatment trials

At this stage, controlled trials of omega-3 fatty acids as a treatment for ADHD and related conditions remain too few, and their findings too diverse, for any firm conclusions to be drawn. Most studies in this area have been small and researcher-led, using different populations, outcome measures, and treatment formulations. Although direct comparisons between these studies, or a clear synthesis of their collective findings, is therefore difficult, the balance of evidence to date does suggest that supplementation with highly unsaturated omega-3 fatty acids may improve behaviour and learning in at least some children with dyslexia, dyspraxia or ADHD.

The findings from these studies have also illuminated several key issues that now need further investigation, and provided useful pointers for the design of future research studies. An evaluation of the existing evidence is therefore offered here with particular reference to these issues, followed by discussion of their potential clinical implications.

Key issues for future research

Populations studied

Age and sex. Treatment trials of omega-3 fatty acids for ADHD and related disorders have primarily involved children aged from 5–13 years of age. These disorders are usually evident in infancy, however, and also persist into adulthood, so there is a clear need for studies of younger children as well as adolescents and adults. Possible sex differences in both behavioural correlates of omega-3 status and response to treatment also deserve specific investigation. Existing studies have included far more males than females, as is the case with research into ADHD in general, (Arnold, 1996) but this probably reflects ascertainment bias rather than the relative prevalence of these disorders by sex in the general population. As already noted, males have a higher risk of HUFA deficiencies than females owing to sex differences in fatty acid metabolism, but the potential significance of these differences for behaviour, learning and mood is currently unknown. Preliminary evidence from the studies reviewed here suggests that attentional difficulties (and perhaps impulsivity) may respond better to omega-3 treatment than hyperactivity per se, and the predominantly inattentive subtype of ADHD is relatively more common in girls. In addition, some successful trials of omega-3 in adults with mood-related disorders have involved predominantly or exclusively female samples, (Stoll et al., 1999; Zanarini & Frankenburg, 2003) so there is a good rationale for including more females in future studies of ADHD and related conditions.

Clinical diagnosis. Treatment trials to date have typically focused on one particular diagnostic category, be this ADHD, dyslexia or DCD/dyspraxia. Given the substantial heterogeneity and comorbidity associated with these conditions, however, and the fact that all these diagnoses are based on purely behavioural criteria, it seems a priori unlikely that omega-3 deficiency would play a major role in more than a subset of children within any particular diagnostic category. In the studies of ADHD-type children, differences in selection criteria might help to account for at least some of the inconsistency in findings. The negative USA study (Voigt et al., 2001) used a strict DSM-IV diagnosis of ADHD and deliberately ruled out most psychiatric comorbidities, while the only positive study focusing on ADHD (also from the USA) involved a community-based sample of children in whom high comorbidity would normally be expected, and who were also pre-selected for showing physical signs consistent with fatty acid deficiency (Stevens et al., 2003). The two other positive studies involved children with a primary diagnosis of either dyslexia (Richardson & Puri, 2002) or dyspraxia/DCD, (Richardson & Montgomery, 2005), and although ADHD symptoms were a primary outcome measure in both trials, none of the children studied had a formal ADHD diagnosis. On average, their pre-treatment scores on age-standardized parent or teacher rating scales were only around one standard deviation above the mean for the general population, although up to one third scored more than 2 SD above this level, placing them well inside the usual clinical range for ADHD. Improvements following fatty acid treatment appeared to apply to both lower and higher-scoring children, suggesting that a trait-based or symptom-based approach using dimensional measures may be more appropriate than a reliance on categorical diagnoses.

Other selection criteria. Biological markers (genetic or biochemical) that could reliably index fatty acid status and/or individual metabolic differences would seem a more promising way to identify individuals who may be particularly likely to benefit from fatty acid treatment. Unfortunately, however, the development of such markers still requires further research. Blood fatty acid profiles were monitored in two of the three treatment trials involving ADHD-type children, but only in the Purdue study were subjects pre-selected in any way according to presumed fatty acid status, (Stevens et al., 2003)

and this was done using checklist ratings of physical signs and symptoms previously found to correlate with blood biochemical measures of fatty acid deficiency. In fact, 75% of the initial respondents met this criterion, but blood biochemical measures taken at the pre-treatment baseline later revealed that these children in fact had unusually *high* membrane concentrations of key omega-3 (and omega-6 HUFA) relative to non-ADHD controls, although they did show relative deficiencies of the same fatty acids in plasma (Burgess & Stevens, 2003). Very little is yet known about the normal range of blood HUFA concentrations in the general population or their functional significance, but it is notable that the ADHD children in this study still appeared to benefit from supplementation despite their apparently high blood fatty acid status pre-treatment.

In summary, although existing studies have shown that at least some children with ADHD and related disorders can benefit from omega-3 treatment, several important issues still remain to be explored.

- Within ADHD, might omega-3 fatty acids be particularly (or only) beneficial for children with particular patterns of comorbidity—such as mood disorders, oppositional defiance and/or specific learning difficulties?
- Is omega-3 more helpful for children with milder ADHD-type difficulties than for those with more extreme symptoms?
- What proportion of children in the general population might benefit from an increased dietary intake of omega-3 fatty acids?

Most of these questions would be best addressed via large-scale studies, ideally drawing from samples representative of the general population.

Omega-3 treatment formulations and dosages

The optimal composition and dosage of fatty acid treatment for ADHD and related conditions also requires systematic investigation. Studies in this area so far have used supplements containing varying amounts of the highly unsaturated omega-3 EPA and/or DHA, mainly from fish oils. None have used flax oil or other sources of ALA, although a recent study explored the effects of high doses of flax oil versus fish oils on blood fatty acids in adults with ADHD, and again confirmed the poor in vivo conversion of ALA from the former into EPA and DHA (Young, Conquer, & Thomas, 2005).

Omega-3: EPA versus DHA.   In the three positive studies (Richardson & Montgomery, 2005; Richardson & Puri, 2002; Stevens et al., 2003), treatment consisted predominantly of fish oils,

containing both EPA and DHA in varying ratios. By contrast, the negative studies both involved treatment primarily or exclusively with DHA (Hirayama et al., 2004; Voigt et al., 2001). This pattern of findings is consistent with other evidence from studies of adult psychiatric patients, suggesting that EPA may be more effective than DHA in the treatment of functional disturbances of attention, cognition or mood. Thus DHA was ineffective in the few studies using primarily or exclusively this fatty acid in either major depression or schizophrenia, (Marangell et al., 2003; Peet, Brind, Ramchand, Shah, & Vankar, 2001; Silvers et al., 2005) while trials using primarily or exclusively EPA have usually shown some benefits in these conditions, (Nemets et al., 2002; Peet & Horrobin, 2002; Peet et al., 2002; Su et al., 2003) although not in all cases (Fenton et al., 2001). Pure ethyl EPA has also shown some benefits in other disorders such as Borderline Personality Disorder and Huntington's disease (Puri et al., 2005; Zanarini & Frankenburg, 2003). While it is DHA that matters most in the structure of neuronal membranes, EPA nonetheless plays many critical roles in brain function. Its eicosanoid derivatives are key regulators of immune, endocrine and cardiovascular functions, and direct actions of EPA on cyclo-oxygenases, lipoxygenases, phospholipases, acylating systems, ion channels, mitochondria and peroxisome proliferator-activated receptors (PPARs) are the focus of current investigations across many different fields of study. Existing evidence indicates that EPA is likely to be more effective than DHA for the conditions considered here, but further studies involving direct comparisons, and different ratios of EPA and DHA, are still needed to investigate this issue.

Omega-6 and antioxidant components.   In all three of the positive trials, but not in the two negative studies, the active treatments also contained both some omega-6 fatty acids in the form of evening primrose oil, and also some vitamin E. (The latter is often added to specialist fish oil supplements for its antioxidant properties in protecting membrane HUFA from peroxidation, although recent research indicates reciprocal effects, in that HUFA supplementation may also help to enhance Vitamin E status [Kaempf Rotzoll, Hellstern, & Linderkamp, 2003]). Despite the fact that two early trials of evening primrose oil alone for ADHD gave essentially negative results, (Aman et al., 1987; Arnold et al., 1989) the possibility that this may have made some contribution to the benefits observed cannot yet be ruled out. Studies using EPA-rich fish oils without any omega-6 component are now in progress, which may help to address this. The possible contribution

of Vitamin E (and other dietary antioxidants) also merits serious consideration. The evidence for oxidative stress as a factor in schizophrenia and related adult psychiatric disorders is now substantial, (Yao, Reddy, & van Kammen, 2001) and this may also be relevant to ADHD and related conditions. Of particular interest is that in the Purdue study of ADHD-type children, improvements in behaviour in both treatment groups were correlated with improvements in blood Vitamin E status.

Dosage issues

Evidence from epidemiological studies and clinical trials for the benefits of omega-3 for cardiovascular health have led to general population recommendations for a daily intake of around 500 mg of EPA and DHA. As Table I illustrates, most treatment trials of fatty acids for ADHD and related conditions have used doses of around 300–700 mg of EPA and DHA in varying ratios, which barely exceed these general recommendations for adults. Dose-ranging studies are now needed, and ideally large-scale investigations to determine whether optimal intakes may vary with age, body mass, sex or diagnosis. Currently there is no evidence base for any recommendations for optimal mental health and performance.

Comparison treatments

The choice of placebo is another potentially important factor. Olive oil has been most commonly used as placebo in studies of fatty acid treatment in ADHD and related disorders, as its acceptability and tolerability in these populations is excellent, and its properties also allow for good colour and flavour matching. In other respects olive oil is not an ideal placebo, however, because as well as containing small amounts of Vitamin E, it is a rich source of oleic acid. This can be converted within the body to oleamide, which has some psychoactive properties that might possibly be beneficial in ADHD and related disorders (Puri & Richardson, 2000).

Significant placebo effects were not evident in most trials, although there were some exceptions. In the Oxford-Durham study of children with DCD, (Richardson & Montgomery, 2005) both treatment groups did show significant improvements in one domain (motor skills), but no such placebo effects were seen for the measures of reading and spelling or ADHD-related symptoms, on which active treatment led to highly significant and clinically meaningful improvements. In the Purdue study of ADHD-type children, (Stevens et al., 2003) an unexpected pattern of improvements in the placebo group was found for some of both the biochemical and the behavioural measures, and the correlations

between the two were consistent. While the reasons for these apparent placebo effects remain unknown, they obviously served to reduce the apparent effect of the active treatment.

Outcome measures

ADHD-related symptoms. Different methods have been used to assess ADHD-related symptoms, but most studies have included age-standardized parent and/or teacher rating scales that have been well validated in trials of pharmacological treatments for ADHD. One exception was the negative Japanese study of DHA-fortified foods, (Hirayama et al., 2004) in which ratings were based on DSM-IV checklist criteria. Although these might arguably be less sensitive in detecting any changes in ADHD symptoms, no benefits of active treatment were found for a wide range of other measures used in this study. Similarly, in the only study of children with rigorous DSM-IV diagnoses of ADHD, (Voigt et al., 2001), treatment with omega-3 (in the form of pure algal-source DHA) was completely ineffective for symptoms assessed via both the Conners Parent Rating Scales and the Child Behaviour Checklist. In two of the more successful trials, very similar effect sizes were obtained for parent ratings of ADHD-related symptoms in children with a primary diagnosis of dyslexia (Richardson & Puri, 2002) and teacher ratings of the same kinds of symptoms in children with DCD/dyspraxia (Richardson & Montgomery, 2005). In each case, active treatment led to a reduction of around 0.5 SD in DSM-IV total ADHD symptom scores after three months, with slightly greater improvements for inattention than for hyperactivity-impulsivity symptoms. While the similar findings from these two studies are encouraging, concordance between parent and teacher ratings of ADHD symptoms is typically low, (Wolraich et al., 2004) and proper comparisons would require the use of both types of rating in the same study. In the one positive trial of omega-3 treatment in children selected primarily for ADHD-type difficulties, parent but not teacher ratings showed an effect of treatment on conduct problems, while the reverse was true for ratings of attentional difficulties. Further investigations are clearly needed to determine whether some ADHD symptoms may respond better than others to omega-3 supplementation.

Academic achievement. A major limitation of current pharmacological treatments for ADHD is that despite their proven ability to reduce the core behavioural symptoms of this disorder, there is still no convincing evidence that either these or behavioural interventions have any real benefits for the

associated difficulties in learning and academic achievement. On average, children with ADHD have a poor prognosis in terms of educational, social and occupational functioning, and this may obviously be exacerbated by comorbidities such as dyslexia and DCD (Rasmussen & Gillberg, 2000). Only one of the omega-3 treatment studies reviewed here included measures of academic achievement, and this was the Oxford-Durham study of children with DCD. Compared with placebo, active treatment led to highly significant improvements in reading and spelling progress in these children in addition to significant improvements in their ADHD symptoms. Larger trials are strongly indicated to replicate these findings, and to find out whether they might generalise to other populations.

Mechanisms of action?

As emphasized throughout this review, omega-3 fatty acids influence almost every aspect of brain function, offering numerous potential mechanisms by which they may affect behaviour in ADHD and related conditions. At this stage, further controlled trials first need to confirm the potential benefits of dietary supplementation that existing studies have indicated. In these, however, the inclusion of biochemical and physiological measures would be very helpful in order to refine and test the many plausible hypotheses concerning potential mechanisms.

Many less central features associated with dyslexia, dyspraxia and ADHD may themselves have clinical relevance, in that improvements in these domains alone could well help to improve some of the core behavioural and learning difficulties. Mood disturbances, sleep problems and abnormalities of sensory processing are obvious examples, and although these were not included as outcomes in any of the RCTs reviewed here, existing evidence for the importance of omega-3 in each of these domains suggests that assessing these kinds of associated features in future studies would be helpful.

Clinical implications

The effective management of ADHD and related disorders remains a major challenge in clinical practice. The evidence that omega-3 fatty acids may be of benefit is far from definitive at this stage, but given the limited range of treatment options currently available for such children, the use of supplements or other dietary strategies to increase omega-3 intake has already attracted the interest of parents and practitioners looking for complementary or alternative treatments.

Safety and tolerability

The safety and tolerability of any potential treatment are clearly of paramount importance, and in this respect omega-3 fatty acids have very few if any limitations. Omega-3 and omega-6 are both essential nutrients, but while dietary intake of omega-6 is usually adequate if not excessive in most modern western-type diets, the intake of omega-3, and particularly EPA and DHA, is often sub-optimal (Simopoulos, 2002).

No adverse side-effects have been reported in any of the treatment trials of fatty acids for ADHD and related disorders. The treatments used all appeared to be well tolerated and compliance was generally very high, although this would not necessarily be expected in most clinical settings.

Safety and tolerability will depend to some extent on the precise formulation and dosage of fatty acids used, but EPA and DHA from fish oils are generally regarded as safe at doses much higher than those used in these studies, (FDA, 2000) with medical supervision usually recommended only for intakes above 3 g daily. Negative side effects of high doses of fish oils can include digestive symptoms such as nausea, belching or loose stools. Caution should be exercised in their use with patients on anticoagulant medications, as EPA in particular can have similar actions at high doses.

Adjunctive treatment or monotherapy?

Without more substantial RCT evidence, omega-3 fatty acids cannot be regarded as an effective sole treatment for ADHD or related disorders, but remain at the level of a promising complementary therapy. In the two studies of children with a primary diagnosis of either dyslexia or DCD, fatty acid supplementation was used as monotherapy, as no other interventions were currently available to these children and effective pharmacological treatments for these conditions have not yet been identified.

In the three studies of ADHD-type children (Hirayama et al., 2004; Stevens et al., 2003; Voigt et al., 2001) many participants were already receiving stimulant and/or other medications, although the proportions varied between studies. No adverse side effects of fatty acid supplementation were reported in these adjunctive trials. More generally, there is no reason to believe that omega-3 HUFA cannot be safely used in addition to stimulant or other medications, and the daily doses of between 0.5 and 1.0 g used in treatment trials to date could be obtained from the diet in any case. Possible synergistic effects or other interactions between omega-3 and standard drug treatments for ADHD

and related disorders are nonetheless worth investigation in future research studies.

Which individuals are most likely to benefit from supplementation?

As discussed above, further research is still needed to find out whether some children may be particularly likely to benefit from omega-3 supplementation, and if so, how they might best be identified. For most children in developed countries, however, an increased dietary intake of omega-3 would carry no risk and offers potential health benefits. With respect to behaviour, no reliable predictions can be made at this stage, but possible features that might help to predict a positive response to this kind of treatment are briefly considered here.

Comorbidities of ADHD with specific learning difficulties are an obvious possibility, as two of the three positive trials reviewed above involved children with a primary diagnosis of DCD or dyslexia (Richardson & Montgomery, 2005; Richardson & Puri, 2002). Comorbid anxiety or mood disorders may also be relevant given the promising preliminary evidence for omega-3 supplementation in adults with mood-related symptoms, which affect a significant proportion of ADHD children. Responsiveness to stimulant medications appears to be particularly low in this subgroup (Buitelaar, Van-der-Gaag, Swaab-Barneveld, & Kuiper, 1995; Pliszka, 1989; Taylor et al., 1987), and negative side-effects more likely, (DuPaul, Barkley, & McMurray, 1994) so complementary or alternative therapies may be sought for these children in any case.

The slightly greater treatment effects for inattention than hyperactivity-impulsivity symptoms observed in two treatment trials (Richardson & Montgomery, 2005; Richardson & Puri, 2002) could very easily be a chance finding, but merits further investigation. Hyperactivity and impulsivity are separable features, albeit usually strongly intercorrelated, and omega-3 treatment might perhaps have more impact on impulsivity than on hyperactivity *per se*. Many of the adult psychiatric disorders in which omega-3 deficiencies are implicated are ones in which impulsivity is a component (Brunner, Parhofer, Schwandt, & Bronisch, 2002; Hallahan & Garland, 2004).

Other possible clinical indicators of a good response to omega-3 might include atopic tendencies or physical symptoms such as excessive thirst, frequent urination, or dry skin and hair. Although these kinds of 'soft signs' did not relate clearly to omega-3 status as assessed by blood biochemical measures in the Purdue treatment trial, some improvements over placebo were nonetheless evident (Stevens et al., 2003). Similarly, sleep problems or visual symptoms can sometimes reflect relative omega-3 deficiency, and although these features too may obviously have other causes, they might help to identify some children who could benefit from an increased dietary intake of omega-3 fatty acids.

Treatment regimes

A treatment period of at least three months is the minimum suitable for this kind of intervention owing to the slow turnover of highly unsaturated fatty acids in neuronal membranes (Bourre, Durand, Pascal, & Youyou, 1989). Observations from the two studies that included a one-way treatment crossover suggest that continuing treatment from three to six months may produce additional benefits, but issues of both durability and maintenance of treatment effects require attention in future studies.

Summary and conclusions

The proposal that omega-3 fatty acids may play a role in ADHD and related developmental disorders is supported both by theoretical considerations and by some promising, but inconclusive, experimental evidence. With respect to treatment, there is preliminary evidence from three randomized controlled trials that supplementing the diet with omega-3 HUFA can alleviate ADHD-related symptoms in children with a primary diagnosis of either dyslexia, ADHD, or dyspraxia/DCD, at least in the short-term. All of these positive trials involved supplementation primarily with fish oils (providing both EPA and DHA), but also included some omega-6 fatty acids and Vitamin E. In two other studies of ADHD children, however, no benefits were found from supplementation primarily or exclusively with DHA.

There is considerable scope for cost-offsets from better management of ADHD symptoms in both children and adults. In the USA, direct health care costs attributable to ADHD have been estimated at around 2% of total health expenditures for children (approximately 2.15 billion dollars in 2003; Burd et al., 2003), and these figures do not include the burden on other services, the costs to affected individuals and families, or the wider costs to society as a whole. ADHD in adults is similarly associated with significantly increased medical costs and work absences even when comorbid conditions are taken into account (Secnik et al., 2005).

Currently, the standard treatment for ADHD is pharmacological, as there is good evidence that stimulant medications can help to reduce overt behavioural problems, at least in the short-term, in more than 70% of children and adolescents.

However, their potential side effects include loss of appetite, growth restriction and sleep problems as well as other physical and mental health, and despite their apparent benefits for the core symptoms of ADHD, such medications do not appear to improve academic achievement or social functioning (National Institutes of Health, 1998).

Complementary and alternative therapies for ADHD are frequently used, and of these, dietary interventions are the most popular (Sinha & Efron, 2005). Most such therapies still await proper scientific evaluation, (Arnold, 2001) but the preliminary evidence from treatment trials reviewed here indicates that omega-3 HUFA may be a useful adjunctive treatment for ADHD and related childhood developmental conditions. Of particular note is that one study has also shown benefits for learning and academic achievement in addition to significant improvements in behaviour. Further work is now needed to confirm and extend these findings, and to establish the specificity and durability of the treatment effects observed.

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Potential conflicts of interest

References

Aman, M. G., Mitchell, E. A., & Turbott, S. H. (1987). The effects of essential fatty acid supplementation by Efamol in hyperactive children. *Journal of Abnormal Child Psychology*, *15*, 75–90.

Arnold, L. E. (1996). Sex differences in ADHD: Conference summary. *Journal of Abnormal Child Psychology*, *24*, 555–569.

Arnold, L. E. (2001). Alternative treatments for adults with attention-deficit hyperactivity disorder (ADHD). *Annals of the New York Academy of Sciences*, *931*, 310–341.

Arnold, L. E., & DiSilvestro, R. A. (2005). Zinc in attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, *15*, 619–627.

Arnold, L. E., Kleykamp, D., Votolato, N. A., Taylor, W. A., Kontras, S. B., & Tobin, K. (1989). Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biological Psychiatry*, *25*, 222–228.

Ashwood, P., & Van de Water, J. (2004). Is autism an autoimmune disease? *Autoimmunity Reviews*, *3*, 557–562.

Baker, S. M. (1985). A biochemical approach to the problem of dyslexia. *Journal of Learning Disabilities*, *18*(10), 581–584.

Bekaroglu, M., Aslan, Y., Gedik, Y., Deger, O., Mocan, H., Erduran, E., et al. (1996). Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: A research note. *Journal of Child Psychology and Psychiatry*, *37*, 225–227.

Bell, J. G., MacKinlay, E. E., Dick, J. R., MacDonald, D. J., Boyle, R. M., & Glen, A. C. (2004a). Essential fatty acids and phospholipase A2 in autistic spectrum disorders. *Prostaglandins Leukotrienes & Essential Fatty Acids*, *71*, 201–204.

Bell, J. G., Ross, M. A., Cyhlarova, E., Shrier, A., Dick, J. R., Henderson, R. J., et al. (2004b). Membrane fatty acids, reading and spelling in dyslexic and non-dyslexic adults. ISSFAL 6th International Congress, 2004. Brighton, UK.

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

Bennett, C. N., & Horrobin, D. F. (2000). Gene targets related to phospholipid and fatty acid metabolism in schizophrenia and other psychiatric disorders: An update. *Prostaglandins Leukotrienes & Essential Fatty Acids*, *63*, 47–59.

Biederman, J., Faraone, S., Mick, E., Wozniak, J., Chen, L., Ouellette, C., et al. (1996). Attention-deficit hyperactivity disorder and juvenile mania: An overlooked comorbidity? *Journal of the American Academy of Child and Adolescent Psychiatry*, *35*, 997–1008.

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

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

Brunner, J., Parhofer, K. G., Schwandt, P., & Bronisch, T. (2002). Cholesterol, essential fatty acids, and suicide. *Pharmacopsychiatry*, *35*, 1–5.

Buitelaar, J. K., Van-der-Gaag, R. J., Swaab-Barneveld, H., & Kuiper, M. (1995). Prediction of clinical response to methylphenidate in children with attention-deficit hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *34*(8), 1025–1032.

Burd, L., Klug, M. G., Coumbe, M. J., & Kerbeshian, J. (2003). Children and adolescents with attention deficit-hyperactivity disorder: 1. Prevalence and cost of care. *Journal of Child Neurology*, *18*, 555–561.

Burdge, G. C., & Wootton, S. A. (2002). Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *British Journal of Nutrition*, *88*, 411–420.

Burdge, G. C., Jones, A. E., & Wootton, S. A. (2002). Eicosapentaenoic and docosapentaenoic acids are the principal products of alpha-linolenic acid metabolism in young men. *British Journal of Nutrition*, *88*, 355–363.

Burgess, J. R., & Stevens, L. J. (2003). Essential fatty acids in relation to attention deficit hyperactivity disorder. In M. Peet, I. Glen & D. F. Horrobin (Eds.), *Phospholipid spectrum disorders in psychiatry and neurology* (pp. 511–519). Carnforth: Marius Press.

Burgess, J. R., Stevens, L., Zhang, W., & Peck, L. (2000). Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder. *American Journal of Clinical Nutrition*, *71*, 327S–330S.

Calder, P. C. (2003). N-3 polyunsaturated fatty acids and inflammation: From molecular biology to the clinic. *Lipids*, *38*, 343–352.

Carlson, S. E., & Neuringer, M. (1999). Polyunsaturated fatty acid status and neurodevelopment: A summary and critical analysis of the literature. *Lipids*, *34*, 171–178.

Chen, C., & Bazan, N. G. (2005). Lipid signaling: Sleep, synaptic plasticity, and neuroprotection. *Prostaglandins and other Lipid Mediators*, *77*, 65–76.

Chen, J. R., Hsu, S. F., Hsu, C. D., Hwang, L. H., & Yang, S. C. (2004). Dietary patterns and blood fatty acid composition in children with attention-deficit hyperactivity disorder in Taiwan. *Journal of Nutritional Biochemistry*, *15*, 467–472.

Colquhoun, I., & Bunday, S. (1981). A lack of essential fatty acids as a possible cause of hyperactivity in children. *Medical Hypotheses*, *7*, 673–679.

Comi, A. M., Zimmerman, A. W., Frye, V. H., Law, P. A., & Peeden, J. N. (1999). Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *Journal of Child Neurology*, *14*, 388–394.

Conners, C. K. (1997). Conners' Parent Rating Scales—Revised. New York: Multi-Health Systems Inc.

Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., & Angold, A. (2003). Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*, *60*, 837–844.

Dalton, P., Deacon, R., Blamire, A., Pike, M., McKinlay, I., Stein, J., et al. (2003). Maternal neuronal antibodies associated with autism and a language disorder. *Annals of Neurology*, *53*, 533–537.

Das, U. N. (2002). Essential fatty acids as possible enhancers of the beneficial actions of probiotics. *Nutrition*, *18*, 786.

Dery, M., Toupin, J., Pauze, R., & Verlaan, P. (2004). Frequency of mental health disorders in a sample of elementary school students receiving special educational services for behavioural difficulties. *Canadian Journal of Psychiatry*, *49*, 769–775.

Dilsaver, S. C., Henderson Fuller, S., & Akiskal, H. S. (2003). Occult mood disorders in 104 consecutively presenting children referred for the treatment of attention-deficit/hyperactivity disorder in a community mental health clinic. *Journal of Clinical Psychiatry*, *64*, 1170–1176.

Doyle, A. E., Faraone, S. V., DuPre, E. P., & Biederman, J. (2001). Separating attention deficit hyperactivity disorder and learning disabilities in girls: A familial risk analysis. *American Journal of Psychiatry*, *158*, 1666–1672.

DuPaul, G. J., Barkley, R. A., & McMurray, M. B. (1994). Response of children with ADHD to methylphenidate: Interaction with internalizing symptoms. *Journal of the American Academy of Child and Adolescent Psychiatry*, *33*, 894–903.

Faraone, S. V., Biederman, J., Chen, W. J., Milberger, S., Warburton, R., & Tsuang, M. T. (1995). Genetic heterogeneity in attention-deficit hyperactivity disorder (ADHD): Gender, psychiatric comorbidity, and maternal ADHD. *Journal of Abnormal Psychology*, *104*, 334–345.

Faraone, S. V., Biederman, J., Jetton, J. G., & Tsuang, M. T. (1997). Attention deficit disorder and conduct disorder: Longitudinal evidence for a familial subtype. *Psychological Medicine*, *27*, 291–300.

FDA, U. (2000). Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements, October 31, 2000.

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

Fisher, S. E., & DeFries, J. C. (2002). Developmental dyslexia: Genetic dissection of a complex cognitive trait. *Nature Reviews Neuroscience*, *3*, 767–780.

Gesch, C. B., Hammond, S. M., Hampson, S. E., Eves, A., & Crowder, M. J. (2002). Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. *British Journal of Psychiatry*, *181*, 22–28.

Giltay, E. J., Gooren, L. J., Toorians, A. W., Katan, M. B., & Zock, P. L. (2004). Docosahexaenoic acid concentrations are higher in women than in men because of estrogenic effects. *American Journal of Clinical Nutrition*, *80*, 1167–1174.

Haag, M. (2003). Essential fatty acids and the brain. *Canadian Journal of Psychiatry*, *48*, 195–203.

Hallahan, B., & Garland, M. R. (2004). Essential fatty acids and their role in the treatment of impulsivity disorders. *Prostaglandins Leukotrienes and Essential Fatty Acids*, *71*, 211–216.

Hamazaki, T., & Hirayama, S. (2004). The effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder-a placebo-controlled double-blind study. *European Journal of Clinical Nutrition*, *58*, 838.

Hamazaki, T., Sawazaki, S., Itomura, M., Asaoka, E., Nagao, Y., Nishimura, N., et al. (1996). The effect of docosahexaenoic acid on aggression in young adults. A placebo-controlled double-blind study. *Journal of Clinical Investigations*, *97*, 1129–1133.

Harbige, L. S. (2003). Fatty acids, the immune response, and autoimmunity: A question of n-6 essentiality and the balance between n-6 and n-3. *Lipids*, *38*, 323–341.

Haubner, L. Y., Stockard, J. E., Saste, M. D., Benford, V. J., Phelps, C. P., Chen, L. T., et al. (2002). Maternal dietary docosahexanoic acid content affects the rat pup auditory system. *Brain Research Bulletin*, *58*, 1–5.

Hellgren, L., Gillberg, I. C., Bagenholm, A., & Gillberg, C. (1994). Children with deficits in attention, motor control and perception (DAMP) almost grown up: Psychiatric and personality disorders at age 16 years. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, *35*(7), 1255–1271.

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

Hirayama, S., Hamazaki, T., & Terasawa, K. (2004). Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder—a placebo-controlled double-blind study. *European Journal of Clinical Nutrition*, *58*, 467–473.

Hirshfeld-Becker, D. R., Biederman, J., Faraone, S. V., Violette, H., Wrightsman, J., & Rosenbaum, J. F. (2002). Temperamental correlates of disruptive behavior disorders in young children: Preliminary findings. *Biological Psychiatry*, *51*, 563–574.

Holman, R. T. (1998). The slow discovery of the importance of omega 3 essential fatty acids in human health. *Journal of Nutrition*, *128*(2 Suppl), 427S–433S.

Iribarren, C., Markovitz, J. H., Jacobs Jr, D. R., Schreiner, P. J., Daviglus, M., & Hibbeln, J. R. (2004). Dietary intake of n-3, n-6 fatty acids and fish: Relationship with hostility in young adults—the CARDIA study. *European Journal of Clinical Nutrition*, *58*, 24–31.

Javitt, D. C., Shelley, A. M., Silipo, G., & Lieberman, J. A. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. *Archives in General Psychiatry*, 57, 1131–1137.

Jyonouchi, H., Sun, S., & Le, H. (2001). Pro-inflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression. *Journal of Neuroimmunology*, 120, 170–179.

Kadesjo, B., & Gillberg, C. (2001). The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 42, 487–492.

Kaempf Rotzoll, D. E., Hellstern, G., & Linderkamp, O. (2003). Influence of long-chain polyunsaturated fatty acid formula feeds on vitamin E status in preterm infants. *International Journal for Vitamin and Nutrition Research*, 73, 377–387.

Kang, J. X. (2003). The importance of omega-6/omega-3 fatty acid ratio in cell function: The gene transfer of omega-3 fatty acid desaturase. *World Reviews of Nutrition & Diet*, 92, 23–36.

Kooij, J. J., Buitelaar, J. K., van den Oord, E. J., Furer, J. W., Rijnders, C. A., & Hodiamont, P. P. (2005). Internal and external validity of attention-deficit hyperactivity disorder in a population-based sample of adults. *Psychological Medicine*, 35, 817–827.

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

Litman, B. J., Niu, S. L., Polozova, A., & Mitchell, D. C. (2001). The role of docosahexaenoic acid containing phospholipids in modulating G protein-coupled signaling pathways: Visual transduction. *Journal of Molecular Neuroscience*, 16 (2–3), 237–242; discussion 279–284.

MacDonell, L. E., Skinner, F. K., Ward, P. E., Glen, A. I., Glen, A. C., Macdonald, D. J., et al. (2000). Increased levels of cytosolic phospholipase A2 in dyslexics. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 63(1–2), 37–39.

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

Mitchell, E. A., Aman, M. G., Turbott, S. H., & Manku, M. (1987). Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clinical Pediatrics Philadelphia*, 26, 406–411.

National Institutes of Health. (1998). *NIH Consensus Statement: Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD)*. Bethesda: National Institutes of Health.

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

Owens, J. A. (2005). The ADHD and sleep conundrum: A review. *Journal of Developmental and Behavioral Pediatrics*, 26, 312–322.

Pawlosky, R. J., Hibbeln, J. R., Novotny, J. A., & Salem Jr, N. (2001). Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. *Journal of Lipid Research*, 42(8), 1257–1265.

Peet, M., & 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. *Archives of General Psychiatry*, 59, 913–919.

Peet, M., & Stokes, C. (2005). Omega-3 fatty acids in the treatment of psychiatric disorders. *Drugs*, 65, 1051–1059.

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

Peet, M., Glen, I., & Horrobin, D. F. (2003). *Phospholipid spectrum disorders in psychiatry and neurology*. Carnforth: Marius Press.

Peet, M., Horrobin, D. F., & E-E-Multicentre-Study-Group, (2002). A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *Journal of Psychiatry Research*, 36 (1), 7–18.

Pliszka, S. R. (1989). Effect of anxiety on cognition, behavior, and stimulant response in ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry*, 28, 882–887.

Puri, B. K., & Richardson, A. J. (2000). The effects of olive oil on omega-3 fatty acids and mood disorders. *Archives of General Psychiatry*, 57, 715.

Puri, B. K., Leavitt, B. R., Hayden, M. R., Ross, C. A., Rosenblatt, A., Greenamyre, J. T., et al. (2005). Ethyl-EPA in Huntington disease: A double-blind, randomized, placebo-controlled trial. *Neurology*, 65, 286–292.

Rasmussen, P., & Gillberg, C. (2000). Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-based study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(11), 1424–1431.

Richardson, A. J. (2003). Clinical trials of fatty acid supplementation in dyslexia and dyspraxia. In M. Peet, I. Glen & D. F. Horrobin (Eds.), *Phospholipid spectrum disorders in psychiatry and neurology* (pp. 491–500). Carnforth: Marius Press.

Richardson, A. J. (2004a). Clinical trials of fatty acid treatment in ADHD, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 70, 383–390.

Richardson, A. J. (2004b). Long-chain polyunsaturated fatty acids in childhood developmental and psychiatric disorders. *Lipids*, 39, 1215–1222.

Richardson, A. J., & Montgomery, P. (2005). The Oxford-Durham study: A randomised controlled trial of fatty acid supplementation in children with developmental coordination disorder. *Pediatrics*, 115, 1360–1366.

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

Richardson, A. J., & Puri, B. K. (2002). A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 26, 233–239.

Richardson, A. J., & 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 Leukotrienes and Essential Fatty Acids*, 63, 1–9.

Richardson, A. J., Calvin, C. M., Clisby, C., Schoenheimer, D. R., Montgomery, P., Hall, J. A., et al. (2000). Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 63, 69–74.

Richardson, A. J., Cyhlarova, E., & Puri, B. K. (2003). Clinical and biochemical fatty acid abnormalities in dyslexia, dyspraxia, and schizotypy: An overview. In M. Peet, I. Glen & D. F. Horrobin (Eds.), *Phospholipid spectrum disorders in psychiatry and neurology* (pp. 477–490). Carnforth: Marius Press.

Ross, M. A., Cyhlarova, E., Shrier, A., Henderson, R. J., MacKinlay, E. E., Dick, J. R., et al. (2004). Working memory and schizotypal traits in relation to fatty acid status in dyslexia. ISSFAL 6th International Congress, 2004. Brighton, UK.

Rudin, D. O. (1981). The major psychoses and neuroses as omega-3 essential fatty acid deficiency syndrome: Substrate pellagra. *Biological Psychiatry*, 16, 837–850.

Rutter, M., Caspi, A., Fergusson, D., Horwood, L. J., Goodman, R., Maughan, B., et al. (2004). Sex differences in developmental reading disability: New findings from four epidemiological studies. *Journal of the American Medical Association*, 291, 2007–2012.

Salem Jr, N., Pawlosky, R., Wegher, B., & Hibbeln, J. (1999). *In vivo* conversion of linoleic acid to arachidonic acid in human adults. *Prostaglandins Leukotrienes & Essential Fatty Acids*, 60(5–6), 407–410.

Secnik, K., Swensen, A., & Lage, M. J. (2005). Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. *Pharmaco Economics*, 23, 93–102.

Silvers, K. M., Woolley, C. C., Hamilton, F. C., Watts, P. M., & Watson, R. A. (2005). Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukotrienes & Essential Fatty Acids*, 72, 211–218.

Simopoulos, A. P. (2002). The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomedical Pharmacotherapy*, 56, 365–379.

Sinha, D., & Efron, D. (2005). Complementary and alternative medicine use in children with attention deficit hyperactivity disorder. *Journal of Paediatrics and Child Health*, 41, 23–26.

Stein, J., & Richardson, A. (1999). Cognitive disorders: A question of misattribution. *Current Biology*, 9, R374–376.

Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstat, N., Mahon, A., et al. (2003). EFA supplementation in children with inattention, hyperactivity and other disruptive behaviours. *Lipids*, 38, 1007–1021.

Stevens, L. J., Zentall, S. S., Abate, M. L., Kuczek, T., & Burgess, J. R. (1996). Omega-3 fatty acids in boys with behavior, learning, and health problems. *Physiology and Behaviour*, 59, 915–920.

Stevens, L. J., Zentall, S. S., Deck, J. L., Abate, M. L., Watkins, B. A., Lipp, S. R., et al. (1995). Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *American Journal of Clinical Nutrition*, 62, 761–768.

Stoll, A. L., Freeman, M. P., Severus, W. E., Rueter, S., Zboyan, H. A., Diamond, E., et al. (1999). Omega 3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Archives of General Psychiatry*, 56, 407–412.

Stordy, B. J. (1995). Benefit of docosahexaenoic acid supplements to dark adaptation in dyslexics. *Lancet*, 346, 385.

Stordy, B. J. (2000). Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia. *American Journal of Clinical Nutrition*, 71, 323S–326S.

Su, K. P., Huang, S. Y., Chiu, C. C., & Shen, W. W. (2003). Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *European Neuropsychopharmacology*, 13(4), 267–271.

Takeuchi, T., Fukumoto, Y., & Harada, E. (2002). Influence of a dietary n-3 fatty acid deficiency on the cerebral catecholamine contents, EEG and learning ability in rat. *Behavioural Brain Research*, 131, 193–203.

Taylor, E., Schachar, R., Thorley, G., Wieselberg, H. M., Everitt, B., & Rutter, M. (1987). Which boys respond to stimulant medication? A controlled trial of methylphenidate in boys with disruptive behaviour. *Psychological Medicine*, 17, 121–143.

Taylor, K. E., & Richardson, A. J. (2000). Visual function, fatty acids and dyslexia. *Prostaglandins Leukotrienes & Essential Fatty Acids*, 63, 89–93.

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

Taylor, K. E., Richardson, A. J., & Stein, J. F. (2001). Could platelet activating factor play a role in developmental dyslexia? *Prostaglandins Leukotrienes and Essential Fatty Acids*, 64, 173–180.

Uauy, R., Hoffman, D. R., Peirano, P., Birch, D. G., & Birch, E. E. (2001). Essential fatty acids in visual and brain development. *Lipids*, 36(9), 885–895.

Unay, B., Sarici, S. U., Ulas, U. H., Akin, R., Alpay, F., & Gokcay, E. (2004). Nutritional effects on auditory brainstem maturation in healthy term infants. *Archives of disease in childhood. Fetal and neonatal edition*, 89, F177–F179.

Vancassel, S., Durand, G., Barthelemy, C., Lejeune, B., Martineau, J., Guilloteau, D., et al. (2001). Plasma fatty acid levels in autistic children. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 65(1), 1–7.

Vargas, D. L., Nascimbene, C., Krishnan, C., Zimmerman, A. W., & Pardo, C. A. (2005). Neuroglial activation and neuroinflammation in the brain of patients with autism. *Annals of Neurology*, 57, 67–81.

Vincent, A., Deacon, R., Dalton, P., Salmond, C., Blamire, A. M., Pendlebury, S., et al. (2002). Maternal antibody-mediated dyslexia? Evidence for a pathogenic serum factor in a mother of two dyslexic children shown by transfer to mice using behavioural studies and magnetic resonance spectroscopy. *Journal of Neuroimmunology*, 130, 243–247.

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

Willcutt, E. G., & Pennington, B. F. (2000). Psychiatric comorbidity in children and adolescents with reading disability. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 41(8), 1039–1048.

Willcutt, E. G., Pennington, B. F., & DeFries, J. C. (2000). Twin study of the etiology of comorbidity between reading disability and attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics*, 96(3), 293–301.

Wolraich, M. L., Hannah, J. N., Baumgaertel, A., & Feurer, I. D. (1998). Examination of DSM-IV criteria for attention deficit/hyperactivity disorder in a county-wide sample. *Journal of Developmental and Behavioural Pediatrics*, 19(3), 162–168.

Wolraich, M. L., Lambert, E. W., Bickman, L., Simmons, T., Doffing, M. A., & Worley, K. A. (2004). Assessing the impact of parent and teacher agreement on diagnosing attention-deficit hyperactivity disorder. *Journal of Developmental and Behavioral Pediatrics*, 25, 41–47.

Yao, J. K., & van Kammen, D. P. (2004). Membrane phospholipids and cytokine interaction in schizophrenia. *International Review of Neurobiology*, 59, 297–326.

Yao, J. K., Reddy, R. D., & van Kammen, D. P. (2001). Oxidative damage and schizophrenia: An overview of the evidence and its therapeutic implications. *Central Nervous System Drugs*, 15, 287–310.

Yehuda, S. (2003). Omega-6/omega-3 ratio and brain-related functions. *World Review of Nutrition and Dietetics*, 92, 37–56.

Young, G. S., Conquer, J. A., & Thomas, R. (2005). Effect of randomized supplementation with high dose olive, flax or fish oil on serum phospholipid fatty acid levels in adults with attention deficit hyperactivity disorder. *Reproduction Nutrition and Development*, *45*, 549–558.

Young, G. S., Maharaj, N. J., & Conquer, J. A. (2004). Blood phospholipid fatty acid analysis of adults with and without attention deficit/hyperactivity disorder. *Lipids*, *39*, 117–123.

Zanarini, M. C., & Frankenburg, F. R. (2003). Omega-3 Fatty acid treatment of women with borderline personality disorder: A double-blind, placebo-controlled pilot study. *American Journal of Psychiatry*, *160*, 167–169.

Zimmer, L., Vancassel, S., Cantagrel, S., Breton, P., Delamanche, S., Guilloteau, D., et al. (2002). The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *American Journal of Clinical Nutrition*, *75*, 662–667.