

# Omega-3 fatty acids for child behaviour, learning and mood: ADHD, dyslexia, dyspraxia, autism and related conditions

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## Introduction

*Increasing evidence shows that omega-3 highly unsaturated fatty acids (HUFA) are relevant to many different disorders of behaviour, learning or mood<sup>1,2,3,4</sup>. Some of these disorders are usually first evident in childhood – including specific behavioural and learning difficulties such as attention deficit / hyperactivity disorder (ADHD); dyslexia or other specific learning disabilities (LD); dyspraxia or developmental coordination disorder (DCD); and the autistic spectrum of disorders (ASD). Others are more often diagnosed in adolescence or adulthood – including mental health disorders such as depression, bipolar disorder, and the schizophrenia spectrum of disorders.*

The key omega-3 HUFAs – eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) – are found primarily in fish and seafood, and are often relatively lacking from diets in the UK and other developed countries. The importance of these omega-3 fatty acids (FAs) for physical health, and most notably for cardiovascular and immune function, has already been well established. Experts now recommend an average daily intake of at least 450-500mg of EPA and DHA for the general population, simply to maintain cardiovascular health.<sup>5</sup>

By contrast, the idea that 'fish oils' may help children (or adults) to behave, learn or feel better remains more controversial, and media interest in this area has far outpaced the progress of researchers in gathering scientific evidence. Recent years have seen a dramatic increase in the popularity of various omega-3 supplements for children's behaviour, learning and mood. This is perhaps not surprising given that ADHD, dyslexia, dyspraxia, autism and related conditions are now thought to affect up to 20% of UK primary school children; these are children who are informally listed by schools and Local Education Authorities as having Special Educational Needs (although official 'SEN Statements' are limited to only a fraction of this by the system). The vast majority of these children have difficulties consistent with dyslexia, dyspraxia, ADHD, ASD or related conditions, and this 20% figure also matches the combined estimates of population prevalences from the leading support groups and charities, allowing for the usual overlaps. These conditions have huge consequences not only for the individuals affected, but also for their families, and for society as a whole.

A lack of access to effective help within standard health, educational or social services often leads desperate parents to seek complementary or alternative treatments, and many

professionals dealing with such children are also increasingly interested in dietary approaches. The prevalence of mental health problems also appears to be rising dramatically in children and adolescents in the UK and other developed countries. While this situation obviously reflects a complex interplay of many different contributory factors, the role of diet has to be one of them. What's more, diet is one factor over which the individuals affected have at least some influence, provided they are given sufficient information and incentive.

For these reasons, nutrition practitioners are increasingly in demand to advise on behavioural, learning or mood disorders in children, and omega-3 FAs are already very familiar to most of them in this context. It is now five years since I first reviewed this area of research for *The Nutrition Practitioner*,<sup>6</sup> and the purpose of this article is to provide an update that takes account of the latest evidence in this rapidly expanding field. Much of the material in the original article has stood the test of time, but other aspects deserve revision in the light of new and/or accumulated evidence. As before, my aim is to summarise and evaluate the information in a way that may be most useful for the clinical practitioner.

### **Childhood developmental and psychiatric disorders – a spectrum of vulnerability?**

Despite their separate diagnostic labels, there are substantial overlaps in practice between dyslexia, dyspraxia, ADHD and autistic spectrum disorders, with most affected individuals showing features of more than one of these conditions. The mutual overlaps between ADHD, dyslexia and dyspraxia are around 30-50%, although attentional problems (and possibly impulsivity) are usually more closely linked with specific learning difficulties than hyperactivity *per se*. In addition, each frequently co-occurs with milder forms of autistic spectrum disorders, although few reliable figures are available for these overlaps. These conditions all show individual and familial associations with other psychological and psychiatric disorders – including depression and other mood disorders, anxiety and the schizophrenia spectrum.

This high 'co-morbidity' between so many common developmental and psychiatric disorders strongly suggests some common features at the level of biological predisposition.<sup>7</sup> Focusing as they do on behaviour, most of the 'diagnoses' used in psychology and psychiatry are actually descriptions, not explanations. In other words, these labels don't tell us anything about the actual *causes* of the behavioural symptoms, features and traits involved – which are many and various, and can differ between individuals. As I have argued for many years, a 'trait-based' or 'symptom-based' approach often makes more sense than a focus on current diagnostic categories, and this may be particularly helpful with respect to the role of omega-3 FAs.<sup>8</sup> To view these behaviourally-defined conditions as categorical 'disease entities' distinct from normal functioning is also rather misleading, because in milder form, the core characteristics of these 'disorders' all form part of normal individual variations in behaviour, learning abilities and mood.

At the genetic level, the predispositions to ADHD, dyslexia, dyspraxia and autism (as well as those for mental health conditions like depression and anxiety) are in fact widely distributed in the general population. In each case, several (if not many) different genes are thought to act in combination to increase risk, and those combinations can vary between affected individuals. Many of the same chromosomal regions show linkage to more than one of these disorders, and some of these regions contain genes known to code for enzymes involved in fatty acid and membrane phospholipid metabolism.<sup>9</sup> The genetic predispositions to these overlapping developmental and psychiatric disorders could therefore include some shared elements that act to increase vulnerability to HUFA deficiencies. If so, the dramatic changes

in dietary fat consumption in developed countries over recent years (and particularly the relative disappearance of omega-3) could provide just one reason why the prevalence of some of these conditions seems to have increased over the same period. This is because the expression of any such individual genetic differences will depend heavily on the dietary intake of fatty acids, both during development and throughout life. The term ‘phospholipid spectrum disorders’, first coined some years ago,<sup>10</sup> captures this idea of a whole spectrum of vulnerability, whilst also emphasising the potential role of fatty acid and phospholipid metabolism – and therefore diet – in all of these conditions. While yet another ‘diagnostic label’ is hardly needed, the accumulating research evidence certainly supports this idea.

### Omega 3 fatty acids and the brain

Both omega-3 and omega-6 highly unsaturated fatty acids (HUFAs) are simply crucial to brain structure and function. The two so-called essential fatty acids (EFAs), linoleic acid (LA, omega-6) and alpha-linolenic acid (ALA, omega-3) cannot be synthesised *de novo* by

**Table 1: Pathways for the synthesis of omega-6 and omega-3 fatty acids**

The truly essential fatty acids (EFA) that cannot be synthesised within the body are linoleic acid (omega-6 series) and alpha-linolenic acid (omega-3 series). The highly unsaturated fatty acids (HUFA) that the brain needs can in theory be synthesised from these EFA precursors via processes of desaturation (insertion of a double-bond) and elongation (adding two carbon atoms to the fatty acid chain). However: **the conversion of EFA to HUFA is relatively slow and inefficient in humans**, so pre-formed HUFA from dietary sources may be needed to ensure an adequate supply of these vital nutrients.

<u>OMEGA-6 series</u>	Enzymes involved in HUFA synthesis	<u>OMEGA-3 series</u>
Linoleic (LA) 18:2	<i>Delta 6-desaturase</i>	Alpha-linolenic (ALA) 18:3
┆		┆
Gamma-linolenic (GLA) 18:3	<i>Elongase</i>	Octadecatetraenoic 18:4
┆		┆
<b>Dihomogamma-linolenic (DGLA) 20:3</b>	<i>Delta 5-desaturase</i>	Eicosatetraenoic 20:4
┆		┆
<b>Arachidonic (AA) 20:4</b>	<i>Elongase</i>	<b>Eicosapentaenoic (EPA) 20:5</b>
┆		┆
Adrenic 22:4	<i>Elongase, Delta 6-desaturase, Beta-oxidation</i>	Docosapentaenoic (DPA) 22:5
┆		┆
Docosapentaenoic (DPA) 22:5		<b>Docosahexaenoic (DHA) 22:6</b>

**Four HUFA are particularly important for brain development and function: DGLA and AA from the omega-6 series, and EPA and DHA from the omega-3 series.**

- AA and DHA are major structural components of neuronal membranes (making up 20% of the dry mass of the brain and more than 30% of the retina).
- EPA and DGLA are also crucial, but they play functional rather than structural roles.
- EPA, DGLA and AA are needed to manufacture *eicosanoids* - hormone-like substances including prostaglandins, leukotrienes, and thromboxanes. These and other HUFA derivatives play critical roles in the moment-by-moment regulation of a very wide range of brain and body functions.

**Fatty acids from one series cannot be converted into the other within the body. Both are essential, but the balance of omega-3 and omega-6 fatty acids is very important**, as they play complementary roles in many biological functions, e.g. derivatives of AA include the ‘pro-inflammatory’ series 2 prostaglandins, while DGLA and EPA give rise to less inflammatory prostaglandins (series 1 and series 3 respectively). Similarly, thromboxanes derived from AA act to constrict blood vessels while those derived from EPA act to relax blood vessels and improve blood flow.

humans, so must be provided by the diet. In theory, these EFAs can then be converted into the more complex HUFAs needed for optimal brain function (primarily DGLA and AA from the omega-6 series, and EPA and DHA from the omega-3 series), as shown in Table 1. In practice, however, these conversion processes are usually very limited, as discussed further below.

Structurally, AA and DHA are key components of cell membranes in the brain and nervous system, making up 15-20% of the brain's dry mass. Adequate supplies of these HUFAs are so essential during prenatal development that the placenta acts to double the levels circulating in maternal plasma,<sup>11</sup> and severe deficits can have permanent effects if they occur during critical periods of neural development. AA is crucial to brain growth, with mild deficiencies being associated with low birth weight and reduced head circumference. DHA is particularly concentrated in highly active sites such as synapses and photoreceptors, and makes up more than 30% of the retina, hence adequate supplies are absolutely vital for normal visual and cognitive development. Throughout life, adequate supplies of HUFA are crucial for maintaining the fluidity of neuronal membranes (which saturated fats and cholesterol act to reduce). Such fluidity is essential for the optimal functioning of membrane-bound and membrane-associated proteins that include both neurotransmitter receptors and ion channels.

Certain HUFAs also play key roles as 'second messengers' in neurotransmitter systems as well as contributing to many other aspects of cell signalling. Functionally, three of the 20-carbon HUFAs deserve special mention: the omega-6 fatty acids DGLA and AA and the omega-3 fatty acid EPA. These are substrates for the **eicosanoids**, a highly bioactive group of hormone-like substances including prostaglandins, leukotrienes and thromboxanes. Through their regulatory influences on hormonal, cardiovascular and immune systems among many others, these key HUFA derivatives can exert profound influences on brain development and function. In particular, an excess of AA relative to EPA and DGLA (very common in modern western diets) is likely to promote inflammation, narrow blood vessels and reduce blood coagulation time, other things being equal – with potential effects on mental as well as physical health and performance. AA also gives rise to various endocannabinoids,<sup>12</sup> which can influence many aspects of mood, cognition and behaviour as well as perception and sensitivity to pain. Such substances have obvious significance for some psychiatric disorders.

More recently, other important substances derived from either EPA or DHA have been identified that can combat inflammation and/or help protect brain cells against other types of injury.<sup>13,14,15</sup> Between them, these omega-3 HUFAs are now recognised as regulating not only blood flow, endocrine and immune functions but also ion channels, neurotransmitter uptake, synaptic transmission, apoptosis and numerous other biological processes, including energy metabolism and gene expression. As noted already, DHA (along with AA) plays a key structural role in the brain, and even more so in the retina. By contrast, the crucial importance of EPA in the regulation of numerous processes relevant to brain function is sometimes overlooked, simply because this omega-3 HUFA contributes very little to the brain's physical structure – and yet it has become clear that EPA and DHA each play different and complementary roles in the functioning of the brain and nervous system.

A massive amount of evidence now demonstrates the essentiality 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. This evidence cannot be considered in any detail here, but has been amply reviewed elsewhere.<sup>1,16,17</sup>

## Possible reasons for functional Omega-3 HUFA deficiencies

Direct sources of omega-3 HUFA are relatively lacking from many modern diets, especially vegetarian or vegan diets, and/or those in which highly processed foods predominate. This is because EPA and DHA are found naturally in appreciable quantities only in fish and seafood – although food manufacturers are increasingly trying to find ways to add them to other products such as eggs, milk and even bread. Their precursor, alpha-linolenic acid, is found in green vegetables and some nuts and seeds, but its conversion to EPA and DHA is very limited, as discussed further below. By contrast, dietary omega-6 fats are usually plentiful, because vegetable oils, nuts, seeds and grains all tend to be rich in linoleic acid, while meat, eggs and dairy produce contain AA pre-formed. The last century has seen dramatic increases in the ratios of omega-6 to omega-3 in average Western-type diets, from approximately 3:1 to more than 20:1 in some cases, and this relative lack of omega-3 is now thought to contribute to a wide range of both physical and mental health disorders.<sup>18</sup> Gene transfer studies indicate that the earlier ratios were much closer to the optimum for healthy human cells.<sup>19</sup>

Poor EFA-HUFA conversion is another important issue, because the *in vivo* conversion of ALA to EPA or DHA is very inefficient in humans,<sup>20,21</sup> although for any given individual this will depend on both genetic and environmental factors - with diet at their interface. When it comes to genetics, individual variability in the FADS1 and FADS2 genes coding for the fatty acid desaturase enzymes involved was recently found to explain almost 30% of variance in plasma concentrations of key HUFAs in adults.<sup>22</sup> Although this was a general population sample, the study was partly initiated by earlier evidence suggesting that atopic conditions such as eczema may be associated with abnormalities in EFA-HUFA conversion. Similar suggestions have long been made with respect to some developmental and psychiatric disorders, and new evidence supports this idea, as discussed below. EFA-HUFA conversion is also known to be less efficient in males than females,<sup>23,24</sup> a fact that is of interest given the excess of males affected by many childhood developmental disorders; but this sex difference appears to be primarily for hormonal rather than genetic reasons.

Functional HUFA deficiencies could also reflect other inefficiencies in fatty acid metabolism that have a constitutional basis. During the normal turnover and remodelling of membrane phospholipids, HUFA are constantly replaced and recycled if they are not 'used up', and this also happens in the cascades triggered by numerous cell signalling processes. In relation to schizophrenia and related psychiatric disorders, some attention has been focused on various phospholipase A2 enzymes (PLA2) that remove HUFA from membrane phospholipids, as discussed further below, but there are many other avenues to explore at the biochemical level.

Numerous dietary and lifestyle factors can also affect HUFA status. Synthesis of HUFAs from EFA can be impaired by a dietary excess of saturated, hydrogenated or *trans* fats; lack of vitamin and mineral co-factors (particularly zinc, magnesium and vitamins A, B3, B6 and C); some viral infections, and high levels of stress among other things. Smoking and use of alcohol appear to deplete HUFA stores rather than impairing synthesis, as do any other factors that increase oxidative stress, which can include exposure to some environmental toxins and/or some common medications.

## Fatty acid abnormalities in dyslexia, dyspraxia, ADHD and autism

As discussed in detail elsewhere,<sup>25,26,27</sup> fatty acid abnormalities could help to explain many clinical features associated with childhood developmental and psychiatric disorders, including the excess of males affected, associations with prematurity (or other pregnancy and birth complications), minor physical anomalies, and the apparent links with atopic or other auto-immune disorders in affected individuals and their families. As a huge body of

experimental literature now shows, fatty acid deficiencies or imbalances could also contribute to the key cognitive and behavioural features of these conditions (such as anomalous sensory, motor, attentional or language processing) as well as associated difficulties with mood, appetite or digestion, temperature regulation and sleep.

Physical signs associated with essential fatty acid deficiencies in animals include excessive thirst, frequent urination and very dry, scaly skin as well as behavioural abnormalities, although all of these signs can of course have other causes. The UK Hyperactive Children's Support group (HACSG) first reported that such signs were unusually common in children with ADHD-type difficulties, and explicitly proposed that abnormalities of fatty acid metabolism (and specifically, difficulties in EFA-HUFA conversion) may contribute to hyperactivity and related attentional disorders.<sup>28</sup> Since then, similar physical signs have been noted not only in association with ADHD,<sup>29,30</sup> but also in children and adults with dyslexia<sup>31,32,33</sup> or autistic spectrum disorders.<sup>34,35</sup>

Blood biochemical studies followed, some of which showed low concentrations of both omega-3 and omega-6 HUFA in many ADHD children despite plenty of the precursor EFAs,<sup>28,29</sup> consistent with the proposal of inefficient EFA-HUFA conversion. Much more recently, a new study has just linked ADHD to a genetic marker within a region on chromosome 11 that is known to code for the delta-6 desaturase enzyme.<sup>36</sup> This finding still needs confirmation and clarification, but it could potentially validate the original proposal that constitutional differences in EFA-HUFA conversion can increase the risk of ADHD-type difficulties.

Reduced blood omega-3 HUFA concentrations have also been reported in several other studies of children and adults with behavioural and learning difficulties, mainly ADHD<sup>37,38,39,40,41</sup> or ASD.<sup>33,34,42,43</sup> Most such studies have been small, and details of their results have naturally varied, but deficiencies in DHA and/or total omega-3 FAs relative to matched controls is one of the most consistent findings, often with low ALA and/or EPA, which makes up a much smaller proportion of blood fatty acids. Elevations in AA relative to EPA have also been noted in some studies of autistic spectrum subjects,<sup>34</sup> although others have found no obvious blood fatty acid abnormalities.<sup>42</sup> On balance, although abnormally low concentrations of AA and other omega-6 FAs have been found in some individuals and study groups, omega-3 FA deficiencies have generally shown much stronger associations with behavioural and learning difficulties. In some cases, these correlations have extended into control groups, suggesting that they may apply for behaviour and learning (and omega-3 FA concentrations) across the general population range.<sup>29,44</sup>

An unusually rapid rate of HUFA breakdown and loss could be another reason for relative HUFA deficiencies. Studies of children and adults with autistic spectrum disorders suggest that their membrane HUFAs may be unusually vulnerable to breakdown, possibly owing to actions of a PLA2 enzyme that removes HUFAs from membrane phospholipids,<sup>34</sup> although there could be many mechanisms for such damage via oxidative stress. Unusually high levels of this PLA2 enzyme, along with other membrane abnormalities, have also been reported in both schizophrenia and dyslexia,<sup>45</sup> and research to extend these findings is ongoing.

Blood biochemical measures of various kinds are valuable research tools, but further study is needed to assess their real utility in clinical practice. While they are very appealing as objective indices of fatty acid 'status' or 'metabolism', current measures still have serious limitations in this respect. With fatty acids, much depends on methods of collection, storage and analysis – and not enough is yet known about the significance of different 'compartments' in which HUFAs can be measured, even in blood (which is at best only a very

approximate model if the real interest is the 'functional availability' of fatty acids in the brain). In one study, for example, ADHD children showed reduced HUFA in plasma phospholipids, but significantly *elevated* concentrations of the same fatty acids in red cell membranes compared with an appropriate group of children from the community.<sup>46</sup> These ADHD children did in fact go on to show modest benefits following supplementation in a controlled trial – but this would not necessarily have been predicted from their initial blood fatty acid profiles.

For either clinical or research use, lifestyle factors (notably smoking and use of alcohol or other substances) as well as diet should ideally be taken into account when interpreting the results of any fatty acid profiles, and many studies in this area have not yet controlled properly for these factors.<sup>47</sup> Most fundamentally, however, we still have no idea what blood omega-3 FA concentrations may be 'optimal' for mental functioning. Dietary omega-3 FA intake in countries with modern western-type diets is probably lower than at any point in human history, so it cannot be assumed that the reference ranges found in general population samples are optimal. In keeping with this, significant improvements in mood and energy, along with reductions in anger and anxiety and corresponding physiological changes were recently reported following omega-3 FA supplementation in normal healthy adults.<sup>48</sup>

### **Can fatty acid supplementation help?**

There is now abundant anecdotal evidence of benefits for child behaviour, learning and mood following omega-3 FA supplementation, and much of the media attention to this issue in recent years has involved either case reports of this kind, or 'open-label' trials, i.e. studies with no placebo comparison. Scientifically speaking, such reports are virtually worthless – and practitioners are urged to be particularly sceptical where such stories are linked (overtly or covertly) to advertisements for particular products. As I have explained in detail elsewhere,<sup>49</sup> commercial influences – and the disproportionate power companies have over the media – can hugely distort the facts available to both the public and health professionals, and definitive evidence of a causal role for any intervention ideally requires randomised, double-blind placebo-controlled trials. For dietary treatments, such randomised controlled trials (RCT) are not always easy to design or implement, and they also have many other limitations,<sup>50</sup> but they nonetheless remain the best if not the only way to reduce potential confounds in the evaluation of treatment effects.

Only five RCTs of omega-3 fatty acid supplementation for child behaviour and learning have so far been published in peer-reviewed journals, although multiple media reports of some of these have given the impression of many more, and others are still in progress. The evidence from existing trials has been reviewed in detail elsewhere,<sup>4</sup> so only the key findings are outlined here (and see Table 2).

Three of these five RCTs have found benefits for behaviour and learning in children with a primary diagnosis of either dyslexia,<sup>51</sup> ADHD,<sup>52</sup> or dyspraxia.<sup>53</sup> (No trials of autistic spectrum subjects have yet come to publication, nor of unselected children from the general school population). These three successful trials used supplements containing both EPA and DHA in varying proportions for 3-4 months. Each used an active treatment of mainly fish oil, providing around 600-700mg of omega-3 HUFA, but the supplements in each case also contained a little evening primrose oil, providing 60-100mg GLA, along with some Vitamin E; and the placebo in all cases was olive oil. In all of these studies, the benefits reported included improved attention and concentration and reduced disruptive behaviour, according to either parents' or teachers' reports. Importantly, the largest study to date, involving over 100 children selected for dyspraxia/DCD, also showed significant benefits for both reading

**Table 2. Randomised controlled trials of treatment with omega-3 fatty acids for child behaviour and learning**

Investi-gators	Diagnosis (and recruitment source, age range)	N (male, female)	Active Treatment: Daily doses of Omega-3 + Other constituents	Trial Design	Duration of treatment in parallel groups (+ crossover)	Outcome
Voigt et al, 2001,	DSM-IV ADHD with minimal or no co-morbidity (USA Psychiatric clinic, 6-12 years)	54 (42,12)	DHA 345mg (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 (UK Special school for children with specific reading difficulties, 8-12 years)	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 (USA Community-based sample, 6-13 years)	47 (41,6)	EPA 80mg, DHA 480mg (from fish oil) Omega-6 (GLA 96mg, AA 40mg) 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 (Japanese Special summer camp for children with behaviour problems, 6-12 years)	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, 5-12 years)	117 (78,39)	EPA 558mg 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

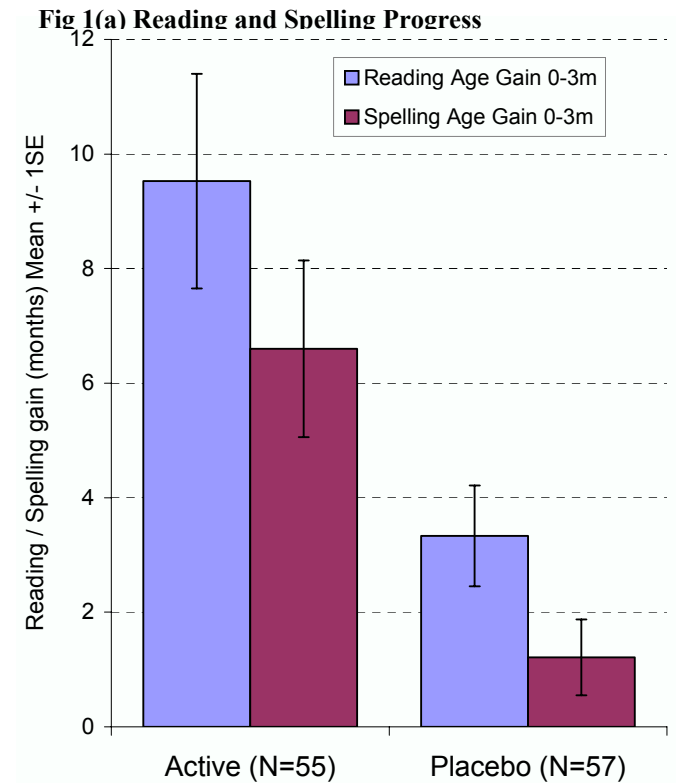
and spelling, as well as ADHD symptoms (see Figure 1), although no advantage could be shown for the core dyspraxia symptoms of poor motor skills.

A large placebo effect was seen for objective measures of motor skills, in that both groups improved significantly over the treatment period. Whilst this was obviously unfortunate, it illustrates the vital importance of having a placebo control group.

No such placebo effects were found for reading, spelling or behavioural measures – and the significant benefits of omega-3 for such ‘dyslexic’ and ‘ADHD’ features in these children (only some whom would have met formal criteria for these conditions too) once again shows the limitations of conventional diagnostic boundaries.

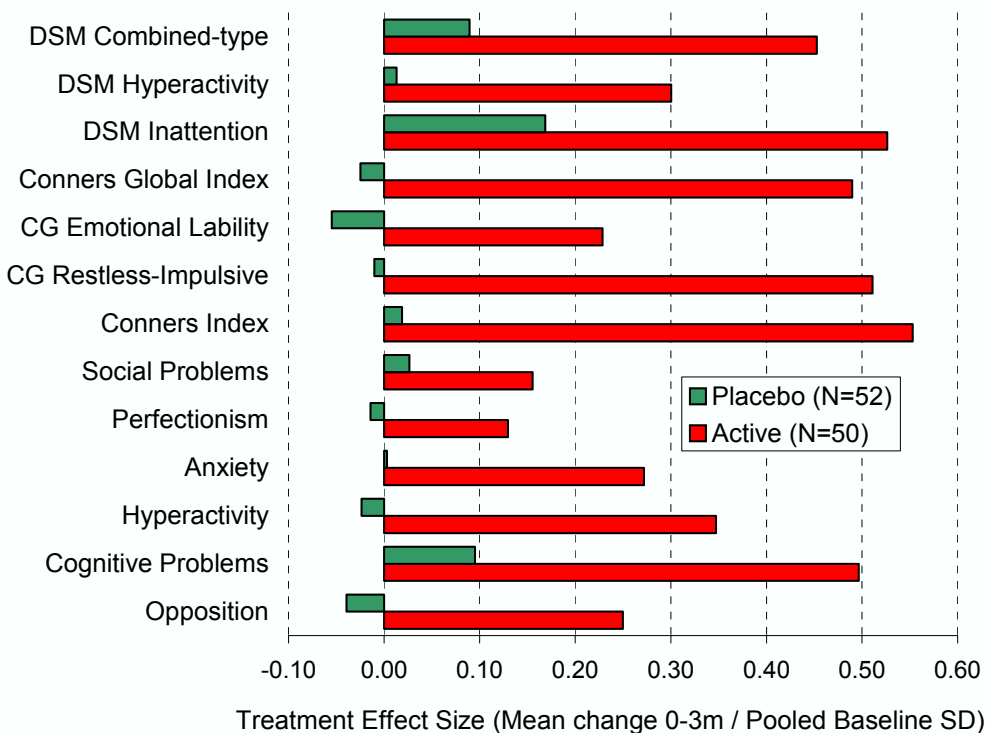
By contrast, there have been two negative studies – both involving children selected for ADHD, and both using supplementation primarily or exclusively with DHA.<sup>54,55</sup> While there were various other differences between these studies and the positive trials, as

**Figure 1. Changes in (a) reading, spelling and (b) teacher ratings of behavioural problems in children with DCD following 3 months of fatty acid supplementation in the Oxford-Durham study.<sup>52</sup>**



**Fig. 1 (b) Changes in ADHD-type symptoms**

**Reduction in ADHD-related Symptoms**



discussed elsewhere,<sup>4</sup> increasing evidence indicates that EPA may be more effective than DHA in the management of behaviour learning or mood, as discussed further below.

One additional trial well worth noting here is the first small RCT of omega-3 HUFAs for children with depression, which showed clear benefits over placebo.<sup>56</sup> This is obviously encouraging given the relative lack of safe and effective treatments for mood

disorders in children; and behavioural and/or learning problems can often reflect an underlying mood disorder. Stimulant medications are least successful when ADHD is accompanied by anxiety or depression, and could even exacerbate problems in children with tendencies towards bipolar disorder.<sup>57</sup> HUFA treatment may well be most effective in these subsets of 'ADHD' children, as substantial evidence now implicates omega-3 FAs in various mood disorders in adults.<sup>2,58</sup>

At present, firm evidence for omega-3 HUFAs as a useful treatment for any specific childhood developmental or psychiatric condition is limited, but this is hardly surprising given the significant heterogeneity and co-morbidity issues. The overall weight of evidence indicates that an increased intake of omega-3 may benefit behaviour, learning and mood in many children, but large-scale, properly controlled trials are now needed to confirm and elaborate on this, ideally involving unselected children from the general school population.

### Guidance for practitioners

As has already been emphasised, dietary supplementation with omega-3 HUFA cannot be expected to help all individuals with dyslexia, dyspraxia, ADHD, autism or related conditions. These kinds of diagnostic labels conceal huge individual variability, and all these syndromes are multi-factorial in nature. Nutritional interventions should always complement other management approaches, and should ideally be carried out in full consultation with other professionals involved, particularly if any medical treatment or supervision is ongoing.

Having said this, few 'normal' UK diets provide the minimum 450-500mg / day of omega-3 HUFA now recommended for heart health - and on balance, the general health benefits of an increased intake of EPA and DHA are likely to outweigh any possible risks for most people - although obviously some individuals may react badly to any particular food or substance. Mild nausea or other digestive symptoms are the only known negative side-effects of fish oil supplements, although should these occur, they can often be minimised with attention to other aspects of the diet. Otherwise, subject to the usual cautions (such as attention to possible interactions with anticoagulant or other medications), up to 3000mg/day of EPA and DHA is generally regarded as a safe dose.

I would usually advise no more than 1000mg/day without specialist advice or supervision, and always following an initial medical consultation. Like other nutrients, omega-3 FAs are always best obtained from food whenever practicable - but many children (and adults) are not willing or able to consume fish and seafood regularly. Official recommendations to limit consumption owing to possible (albeit remote) contaminant risks have not helped in this respect, so supplements can sometimes be the only realistic option.

### What factors might predict a good response to omega-3 HUFA supplementation?

Clearly, for benefits to follow from increasing omega-3 intake there must be some pre-existing functional deficiencies. As we have seen, however, even the best blood biochemical measures still give limited information in this respect, although progress is being made both in this area and in the search for reliable 'biomarkers' of vulnerability at the genetic level.

Meanwhile, clinical features that may help to identify those individuals most likely to benefit from an increased intake of omega-3 FAs appear to include the following, although all of these still need to be verified through further research.

- **Physical signs consistent with fatty acid deficiency** - such as excessive thirst, frequent urination, rough or dry skin and hair, dandruff, and soft or brittle nails, and/or

atopic tendencies. As noted above, these kinds of signs and symptoms appear to be unusually common in individuals with behavioural and learning difficulties (and were related to symptom severity in some studies). Their value in predicting response to treatment remains much less clear, however – and they may relate to omega-6 FA deficiencies at least as much as omega-3 FAs.

- **Visual symptoms** (such as poor night vision or sensitivity to bright light; and visual disturbances when reading - e.g. letters and words appearing to move, swim or blur on the page). The critical importance of omega-3 HUFAs (and particularly DHA) for the visual system is well established. Ongoing studies are now investigating effects of omega-3 FAs on specific 'fast' visual processing channels implicated in dyslexia and related conditions.
- **Attentional problems** (including distractibility, difficulties with sustained concentration, working memory problems and feelings often described as like 'brain fog') These are probably the most widely reported improvements following omega-3 FA supplementation, albeit somewhat non-specific. Symptoms of this kind are typical of not only dyslexia, dyspraxia and ADHD but also depression and some forms of dementia – all of which have now been linked with a lack of omega-3 FAs, albeit via many possible mechanisms including poor blood glucose regulation.<sup>59</sup>
- **Emotional sensitivity or instability** (especially undue anxiety/tension, excessive mood swings, irritability or temper tantrums arising from 'low frustration tolerance'. The latter can also contribute to impulsivity and some 'conduct disorders', particularly when this occurs without obvious hyperactivity. Like attentional problems, low or unstable mood is often linked with imbalances of blood sugar, but the overall evidence of a role for omega-3 FAs in mood is now substantial.
- **Sleep problems** (particularly if these involve difficulties in both falling asleep at night and waking up in the morning). There are numerous possible mechanisms by which omega-3 could affect general arousal and sleep-wake cycles,<sup>60</sup> but once again, further investigations are required.

### What Formulation is Optimal?

There can be no clear answer to this question – partly owing to individual differences and partly because the evidence base from properly controlled trials is still so small. For clinical recommendations, there are several key points to consider.

#### *Is omega-6 needed?*

Omega-3 fatty acids are much more likely to be lacking from modern diets than omega-6, and are also likely to be more important for these purposes. Adequate supplies of omega-6 FAs are also vital for health, but modern western diets usually provide a relative excess of linoleic acid, and anyone regularly consuming meat, eggs or dairy products will also usually get plenty of pre-formed AA, if not an excess. Under these circumstances, the only key omega-6 FA that might be lacking (if EFA-HUFA conversion is poor) is DGLA – and this is easily obtained from the GLA found in evening primrose or borage (starflower) oil. There is RCT evidence that evening primrose oil can benefit children with atopic tendencies (notably eczema), but with respect to behaviour, two small early trials of evening primrose oil in ADHD-type children showed no real benefits,<sup>61,62</sup> Although some contribution from the small amounts of GLA (and Vitamin E) in the supplements used in the few positive trials with children cannot yet be ruled out, many adult studies have used omega-3 HUFAs only (and notably EPA) to good effect, so there remains no good evidence that omega-6 FA supplementation is helpful for behaviour, learning and mood.

### ***Omega 3: EPA or DHA?***

This is an artificial question, because as emphasised earlier, EPA and DHA are both essential for optimal brain function, playing different but complementary roles. To simplify hugely, DHA is critical to the proper *structure* of neuronal membranes, so adequate supplies are essential during early development to support brain growth, and throughout life to maintain membrane fluidity. EPA plays little or no structural role in the brain, but it is nonetheless essential for the moment-by-moment regulation of brain *function* via a wide range of mechanisms.

Unexpectedly perhaps, the current balance of evidence points to EPA, not DHA, as the omega-3 fatty acid most effective in improving attention, perception, memory or mood, although most studies have involved adult psychiatric disorders, as discussed in more detail elsewhere. Further research is still needed to confirm this apparent superiority of EPA over DHA for various aspects of mental health or performance – but it should be emphasised again that *both* omega-3 HUFAs are critically important for a wide range of brain and body functions, and natural foods that provide one tend also to provide the other. Any extremist claims for one over the other therefore seem more likely to reflect potential commercial influences than scientific evidence.

Standard fish oils usually contain EPA and DHA in a ratio of 3:2, although total concentrations may vary. From the available evidence, supplements with a higher ratio of EPA to DHA seem more likely to be effective for these purposes, so for current and planned trials we have chosen ratios of between 5:1 and 7:1 in favour of EPA. Pure ethyl-EPA has been used with success in a number of studies of adult psychiatric patients, but given that conversion of EPA to DHA is limited (thought to involve the same delta-6 desaturase enzymes that appear to be rate-limiting at the initial step of EFA → HUFA conversion), the inclusion of at least a little DHA in most cases seems advisable in my view.

### **Optimal dosages and monitoring response**

No dose-response studies of omega-3 fatty acids have yet been carried out in children, but the studies summarised in Table 2 suggest that benefits can be achieved with little more than the quantities recommended for general cardiovascular health. A pharmaceutical-grade, high-EPA fish oil supplying just over 500mg EPA daily, with around 100mg DHA in addition, has been chosen for our own ongoing studies in this area. In our experience, this kind of dosage may be adequate for most individuals with dyslexia, dyspraxia and milder forms of ADHD and ASD, but if behavioural problems and/or mood swings and impulsivity are severe, 1g/day of EPA or more may be indicated – a dose that has been found effective in depression and other mood disorders in adults. Higher doses of pure ethyl-EPA have been used successfully in some clinical trials of adult psychiatric disorders, but are probably best used under specialist supervision, as more is not always better. The only dose response studies to date have suggested 1g/day of EPA as the optimal dose for depression<sup>63</sup> and 2g/day for schizophrenia (where any benefits were less clear in any case).<sup>64</sup>

Dietary HUFA requirements will clearly differ between individuals, and can also change in the same individual over time, so optimal dosages are best determined from careful monitoring, with attention paid to changes in any other factors that may be relevant.

### **Treatment duration and maintenance issues**

Three months is the minimum recommended period for evaluating possible benefits from increasing omega-3 HUFA intake, because this appears to be the time needed to restore normal DHA concentrations in brain tissue following chronic dietary deficiency.<sup>65</sup> Having

said this, our clinical and research experience indicates that for those who respond best to this approach, improvements are often evident on a much shorter timescale: usually within a week or two, and sometimes within days (and in many cases, benefits seem to be lost just as quickly if supplementation is discontinued). The most notable subjective improvements usually involve better attention, concentration, mood and/or sleep.

Some popular commercial supplements make specific recommendations that daily intake can be reduced to a lower 'maintenance dose' after 3 months (usually to around one-third of the initial dosage). Insofar as any rationale is provided for this, it is usually with reference to the slow turnover of HUFA in neuronal membranes. The suggestion is that once membrane levels have been 'topped up' over 3 months, the dose can then be reduced with no loss of benefits. Unfortunately, there remains no evidence to back these kinds of recommendations, and in our experience, most people who derive any obvious initial benefits from omega-3 HUFA supplementation seem to need to continue with an intake of around 500mg/day to maintain those benefits. Furthermore, the two studies that have monitored children taking this kind of dose for up to 6 months (albeit with no placebo control beyond 3 months) do suggest that further increases in benefits may result from supplementation with the same fixed dose for longer than 3 months.

Both dosage and maintenance issues clearly need to be explicitly addressed in future studies. Until this is done, the best practical recommendation that can be made is that any dose changes should be made as systematically as possible, and the effects monitored for at least 1-2 weeks before further changes are instituted.

### Other considerations

Fish liver oils are *not* generally suitable for these purposes, as the high doses needed to deliver 500-1000 mg/day of EPA and DHA from this kind of source could lead to Vitamin A toxicity if used on a long-term basis. Having said this, the most recent UK national dietary survey revealed alarmingly low intakes of Vitamin A (and many other essential micronutrients) in a large proportion of children, as discussed elsewhere.<sup>48</sup> This is rather worrying given the critical importance of Vitamin A for immune function, vision, digestion and a huge array of other functions. Lack of Vitamin A could also contribute to poor omega-3 HUFA status by impairing EFA→HUFA conversion.<sup>66</sup> Small quantities of fish liver oil could therefore be very useful for children whose diets lack other obvious sources – although this should of course be checked to avoid possible excess. Anecdotal reports already suggest benefits of small doses of cod liver oil for some autistic children, which clearly merit proper investigation.

Quality of HUFA supplements is another crucial issue. While EU regulations should ensure that fish oils contain no harmful residues such as toxic metals, PCBs and dioxins, even the processing methods used can sometimes damage these fragile oils. The supplements used in our current studies are not only highly concentrated (so that fewer capsules are needed), but also use oils extracted via the best available technology, which is environmentally friendly as well as keeping temperatures much lower than conventional molecular distillation techniques. HUFAs are particularly susceptible to oxidation if exposed to light, heat or air. For this reason, a good intake of Vitamin E and other antioxidants is always advisable along with omega-3 and omega-6 HUFAs. Vitamin E is added to some specialist supplements, but very few include Vitamin C or other antioxidants needed to recycle this. Whole, unprocessed foods (particularly fruits, vegetables, nuts and seeds) are of course the best way to provide the full spectrum of antioxidants and other phytonutrients, as well as vitamins, minerals and

other essential micronutrients; so again, the priority should be to achieve an overall balance to the diet.

## Conclusion

Finally, it must be re-emphasised that multiple strategies are usually needed for the optimal management of difficulties in behaviour, learning or mood. Dietary interventions should always be seen as complementary to other approaches, and optimising fatty acid intake is obviously only one aspect of good nutrition, albeit a central one. Additional factors worth considering in the management of any child behaviour or learning problems include other specific micronutrients, potential toxins or adverse food reactions, other issues concerning digestion and absorption and of course blood sugar regulation, all of which are discussed elsewhere.<sup>48</sup>

Research is only just starting to illuminate many of the key aspects of fatty acid metabolism, and until better diagnostic tests become available to inform nutritional practice, there is no substitute for clinical observations and experience. Omega-3 FA intake is probably sub-optimal in most UK children and adolescents, but as this review makes clear, there are many reasons why some individuals may have unusually high dietary requirements for the pre-formed Omega-3 HUFAs, EPA and DHA. Given the evidence reviewed here, it should hardly be surprising if these individuals turn out to be over-represented among those with obvious difficulties in behaviour, learning or mood.

### About the Author

Dr Alex Richardson is a Senior Research Fellow at the University of Oxford's Department of Physiology, Anatomy and Genetics, and a Founder Director of the charity Food And Behaviour Research (FAB Research: see [www.fabresearch.org](http://www.fabresearch.org)). She is internationally known for her research into the role of nutrition in behaviour, learning and mood, and in particular for her controlled trials of omega-3 fatty acids for child behaviour and learning difficulties.

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All of the author's royalties from the sale of this book have been dedicated to FAB Research, and a special discount of **£5.00 off the RRP** is available to readers of Nutrition Practitioner. To read the latest reviews and other information about this book, and to take advantage of this special offer, visit [www.theyarewhatyoufeedthem.com](http://www.theyarewhatyoufeedthem.com) and quote discount code **NPJ889** when placing your order.



## References

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- 1 Peet, M., Glen, I., Horrobin, D.F. (eds) *Phospholipid Spectrum Disorders in Psychiatry and Neurology*. Carnforth: Marius Press, 2003.
- 2 Logan, A.C. Omega-3 fatty acids and major depression: A primer for the mental health professional. *Lipids in Health and Disease*, 2004, 3:25 (Full text of this paper is available, with the author's permission, from [www.fabresearch.org](http://www.fabresearch.org))
- 3 Vaddadi, K. Essential fatty acids and mental illness. *International Review of Psychiatry*, 2006, 18(2) 81-4
- 4 Richardson, A.J. Omega-3 fatty acids in ADHD and related neurodevelopmental disorders. *International Review of Psychiatry*, 2006, 18(2) 155-172
- 5 Recommendations of the International Society for the Study of Fatty Acids and Lipids (ISSFAL) and the UK Joint Health Claims Initiative (JHCI). Further details can be found via the FAB research website at [www.fabresearch.org](http://www.fabresearch.org)
- 6 Richardson, A.J. Fatty Acids in Dyslexia, Dyspraxia, ADHD and the Autistic Spectrum. *Nutrition Practitioner*, 2001, 3(3):18-24.
- 7 Richardson, A.J., Ross, M.A. Fatty acid metabolism in neurodevelopmental disorder: a new perspective on associations between ADHD, dyslexia, dyspraxia and the autistic spectrum. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2000, 63: 1-9
- 8 Garland, M.R., Hallahan, B. Essential fatty acids and their role in conditions characterised by impulsivity. *International Review of Psychiatry*, 2006, 18(2): 99-105
- 9 Bennett, C.N., Horrobin, D.F. Gene targets related to phospholipid and fatty acid metabolism in schizophrenia and other psychiatric disorders: an update. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2000, 63: 47-59.
- 10 Peet, M., Glen, I., Horrobin, D.F. (eds.) *Phospholipid Spectrum Disorders in Psychiatry*. Carnforth: Marius Press, 1999
- 11 Crawford, M.A. (2000). The placental delivery of arachidonic and docosahexaenoic acids: implications for the lipid nutrition of the preterm infant. *American Journal of Clinical Nutrition*. 71:275S-284S.
- 12 Bradshaw HB, Walker JM. The expanding field of cannabimimetic and related lipid mediators. *British Journal of Pharmacology*. 2005, 144(4):459-65
- 13 Arita, M., Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, Yang R, Petasis NA, Serhan CN. Stereochemical assignment, anti-inflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. *Journal of Experimental Medicine*. 2005, 201(5) 713-22
- 14 Serhan, C.N. Novel eicosanoid and docosanoid mediators: resolvins, docosatrienes, and neuroprotectins. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2005, 8(2):115-21
- 15 Schwab JM, Serhan CN. Lipoxins and new lipid mediators in the resolution of inflammation. *Current Opinion in Pharmacology*. 2006, (4): 414-20.
- 16 Bourre, J. M. 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*. 2004, 8: 163-174.
- 17 Haag, M. Essential fatty acids and the brain. *Canadian Journal of Psychiatry*, 2003, 48: 195-203.
- 18 Simopoulos, A.P., The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomedicine and Pharmacotherapy*, 2002. 56(8): p. 365-379.
- 19 Kang, J.X., The importance of omega-6/omega-3 fatty acid ratio in cell function: the gene transfer of omega-3 fatty acid desaturase. *World Review of Nutrition and Diet*, 2003. 92: p. 23-36.
- 20 Pawlosky, R.J., et al., Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. *Journal of Lipid Research*, 2001. 42(8): p. 1257-65
- 21 Brenna, J.T. Efficiency of conversion of alpha-linolenic acid to long chain n-3 fatty acids in man. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2002, 5(2) 127-32.
- 22 Schaeffer, L., Gohlke, H., Muller, M., Heid, I.M., Palmer, L.J., Kompauer, I., Demmelmair, H., Illig, T., Koletzko, B., Heinrich, J. Common genetic variants of the FADS1 FADS2 gene cluster and their reconstructed haplotypes are associated with fatty acid composition in phospholipids. *Human Molecular Genetics*, 2006, 15(11) 1745-56.
- 23 Burdge, G.C. and Wootton, S.A., Conversion of alpha-linolenic acid to eicosapentaenoic, docosapentaenoic and docosahexaenoic acids in young women. *British Journal of Nutrition*, 2002. 88(4): p. 411-20.

- 24 Burdge, G.C., Jones, A.E., and Wootton, S.A., Eicosapentaenoic and docosapentaenoic acids are the principal products of alpha-linolenic acid metabolism in young men. *British Journal of Nutrition*, 2002. 88(4): p. 355-63.
- 25 Richardson, A.J. and Puri, B.K., The potential role of fatty acids in attention-deficit/hyperactivity disorder. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2000. 63(1-2): p. 79-87.
- 26 Richardson, A.J., Cyhlarova, E., and Puri, B.K., Clinical and biochemical fatty acid abnormalities in dyslexia, dyspraxia, and schizotypy: an overview., in *Phospholipid Spectrum Disorders in Psychiatry and Neurology*, Peet M, G.I., Horrobin DF. (eds), 2003, Marius Press: Carnforth. p. 477-90.
- 27 Richardson, A.J. Long-chain polyunsaturated fatty acids in childhood developmental and psychiatric disorders. *Lipids* 2004;39:1215-22.
- 28 Colquhoun, I. & Bunday, S. A lack of essential fatty acids as a possible cause of hyperactivity in children. *Medical Hypotheses*, 1981, 7: 673-679.
- 29 Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR, Burgess JR. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. *American Journal of Clinical Nutrition*, 1995, 62: 761-8
- 30 Stevens LJ, Zentall SS, Abate ML, Kuczek T, Burgess JR (1996). Omega-3 fatty acids in boys with behaviour, learning, and health problems. *Physiology and Behaviour*. 59(4/5): 915-920
- 31 Baker SM (1985). A biochemical approach to the problem of dyslexia. *Journal of Learning Disabilities* 18(10): 581-584
- 32 Taylor KE, Higgins CJ, Calvin CM, Hall JA, Easton T, McDavid AM, Richardson AJ. Dyslexia in adults is associated with clinical signs of fatty acid deficiency. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2000, 63: 75-78.
- 33 Richardson AJ, Calvin CM, Clisby C, Schoenheimer DR, Montgomery P, Hall JA, Hebb G, Westwood E, Talcott JB, Stein JF. Fatty acid deficiency signs predict the severity of reading and related difficulties in dyslexic children. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2000, 63: 69-74.
- 34 Bell JG, Sargent JR, Tocher DR, Dick JR (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(1-2):21-5.
- 35 Bell JG, MacKinlay EE, Dick JR, MacDonald DJ, Boyle RM, Glen AC. Essential fatty acids and phospholipase A(2) in autistic spectrum disorders. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2004, 71(4) 201-4.
- 36 Brookes KJ, Chen W, Xu X, Taylor E, Asherson P. Association of Fatty Acid Desaturase Genes with Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry*, 2006. Aug 4; [Epub ahead of print]
- 37 Mitchell, E.A., *et al.*, Clinical characteristics and serum essential fatty acid levels in hyperactive children. *Clinical Pediatrics: Philadelphia*, 1987. 26(8): p. 406-11.
- 38 Arnold, L.E., *et al.*, Potential link between dietary intake of fatty acids and behavior: Pilot exploration of serum lipids in attention-deficit hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 1994. 4(3): p. 171-182
- 39 Bekaroglu, M., *et al.*, Relationships between serum free fatty acids and zinc, and attention deficit hyperactivity disorder: a research note. *Journal of Child Psychology and Psychiatry*, 1996. 37(2): p. 225-7.
- 40 Chen, J.R., *et al.*, Dietary patterns and blood fatty acid composition in children with attention-deficit hyperactivity disorder in Taiwan. *Journal of Nutritional Biochemistry*, 2004. 15(8): p. 467-72.
- 41 Young, G.S., Maharaj, N.J., and Conquer, J.A., Blood phospholipid fatty acid analysis of adults with and without attention deficit/hyperactivity disorder. *Lipids*, 2004. 39(2): p. 117-23.
- 42 Vancassel, S., *et al.*, Plasma fatty acid levels in autistic children. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2001. 65(1): p. 1-7.
- 43 Bu B, Ashwood P, Harvey D, King IB, Water JV, Jin LW. Fatty acid compositions of red blood cell phospholipids in children with autism. *Prostaglandins Leukot Essent Fatty Acids*, 2006, 74(4): 215-21.
- 44 Bell, J. G., Ross, M. A., Cyhlarova, E., Shrier, A., Dick, J. R., Henderson, R. J. & Richardson, A. J. Membrane fatty acids, reading and spelling in dyslexic and non-dyslexic adults. ISSFAL 6th International Congress, 2004. Brighton, UK
- 45 MacDonell, L.E., *et al.*, Increased levels of cytosolic phospholipase A2 in dyslexics. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2000. 63(1-2): p. 37-9.

- 
- 46 Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstat, N., Mahon, A., Zentall, S. S., Arnold, L. E. & Burgess, J. R. (2003). EFA supplementation in children with inattention, hyperactivity and other disruptive behaviours. *Lipids*, 38, 1007-1021.
- 47 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.
- 48 Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. *European Journal of Clinical Investigation*, 2005, 35(11): 691-9
- 49 Richardson, Alex – *They Are What You Feed Them*, Harper Thorson, 2006 – and see author's details.
- 50 Slade M, Priebe, S. (2001) Are randomised controlled trials the only gold that glitters? *British Journal of Psychiatry* 179 286-287
- 51 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.
- 52 Stevens, L., Zhang, W., Peck, L., Kuczek, T., Grevstat, N., Mahon, A., Zentall, S. S., Arnold, L. E. & Burgess, J. R. (2003). EFA supplementation in children with inattention, hyperactivity and other disruptive behaviours. *Lipids*, 38, 1007-1021.
- 53 Richardson, A. J. & Montgomery, P. The Oxford-Durham study: a randomised controlled trial of fatty acid supplementation in children with developmental coordination disorder. *Pediatrics*, 2005, 115, 1360-1366.
- 54 Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC (2001). A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. *Journal of Pediatrics* 139: 189-96.
- 55 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
- 56 Nemets H, Nemets B, Apter A, Bracha Z, Belmaker RH. Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *American Journal of Psychiatry*, 2006, 163(6): 1098-100.
- 57 Papolos D, Papolos J. (2001) *The Bipolar Child*. New York: Broadway Books.
- 58 Parker G, Gibson NA, Brotchie H, Heruc G, Rees AM, Hadzi-Pavlovic D. Omega-3 fatty acids and mood disorders. *American Journal of Psychiatry*, 2006, 163(6) 969-78.
- 59 Freemantle E, Vandal M, Tremblay-Mercier J, Tremblay S, Blachere JC, Begin ME, Thomas Brenna J, Windust A, Cunnane SC. Omega-3 fatty acids, energy substrates, and brain function during aging. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2006, Jul 6; [Epub ahead of print]
- 60 Yehuda S. Omega-6/omega-3 ratio and brain-related functions. *World Review of Nutrition and Diet*, 2003, 92: 37-56.
- 61 Aman MG, Mitchell EA, Turbott SH (1987). The effects of essential fatty acid supplementation by Efamol in hyperactive children. *Journal of Abnormal Child Psychology* 15: 75-90.
- 62 Arnold LE, Kleykamp D, Votolato NA, Taylor WA, Kontras SB, Tobin K (1989). Gamma-linolenic acid for attention-deficit hyperactivity disorder: placebo-controlled comparison to D-amphetamine. *Biological Psychiatry* 25: 222-228
- 63 Peet, M. and Horrobin, D.F. 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*, 2002, 59, 913-9.
- 64 Peet, M., Horrobin, D.F. and 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.
- 65 Bourre J-M, Durand G, Pascal G, Youyou A (1988). 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.
- 66 Zhou D, Zaiger G, Ghebremeskel K, Crawford MA, Reifen R. Vitamin A deficiency reduces liver and colon docosahexaenoic acid levels in rats fed high linoleic and low alpha-linolenic acid diet. *Prostaglandins Leukotrienes and Essential Fatty Acids*, 2004, 71(6) 383-9.