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Fatty Acids in Dyslexia, Dyspraxia, ADHD and the Autistic Spectrum

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Dyslexia, dyspraxia, ADHD and the autistic spectrum

Current practice within our education and health care systems involves separate diagnostic labels for dyslexia, dyspraxia, attention-deficit / hyperactivity disorder (ADHD) and autistic spectrum disorders (ASD). Each refers to a specific pattern of behavioural and learning difficulties for which the core defining features are quite different. For dyslexia these involve specific difficulties in learning to read and write; for dyspraxia, specific difficulties in the planning and coordination of movement; for ADHD, persistent and age-inappropriate difficulties with attention, hyperactivity-impulsivity, or both; and for ASD, marked social and communication deficits and a restrictive, stereotyped range of behaviours. These developmental conditions are remarkably common, affecting up to 20 per cent of the school age population to some degree, and they account for the vast majority of children with special educational needs. The associated difficulties usually persist into adulthood, with enormous consequences for the individuals affected, their families and society as a whole.

Because of the different ways in which these conditions are defined, identification and management of each is usually by different professional specialists. Dyslexia falls firmly within educational psychology, and interventions typically focus on specialist teaching of reading, spelling and component skills. Dyspraxia is usually managed via behavioural approaches aimed at improving physical coordination, such as physiotherapy or occupational therapy. The ADHD diagnosis falls within the domain of psychiatry, with stimulant medication as the standard treatment; and the diagnosis of autistic spectrum disorders also has a medical orientation, although management may involve a combination of pharmacological, behavioural and psychosocial treatments.

In none of these conditions is the possible role of nutrition considered as part of standard evaluation and management, despite its obvious and fundamental importance for optimal functioning of the brain. A whole range of micronutrients is essential in this respect, but in particular, there is mounting evidence – summarised here - that deficiencies or imbalances in certain highly unsaturated fatty acids (HUFA) of the omega-3 and omega-6 series may contribute to both the predisposition and the developmental expression of dyslexia, dyspraxia, ADHD and autism (1).

If this is so, then dietary supplementation with the relevant HUFA could help in both the prevention and the management of these kinds of behavioural and learning difficulties. Further research in these areas is still needed, and the issue of prevention is clearly not very amenable to direct investigation. With regard to management, well-designed controlled trials of fatty acid treatment in these conditions are few, but preliminary evidence from these is evaluated here, followed by consideration of the implications for clinical practice.

An overlapping spectrum of neurodevelopmental disorders

Despite their separate diagnostic labels, the clinical overlap between dyslexia, dyspraxia, ADHD and ASD is very high, and 'pure' cases are the exception, not the rule. Thus around half of any dyslexic population is likely to be dyspraxic and vice versa, and the mutual overlap between ADHD and dyspraxia is also around 50%. Dyslexia and ADHD co-occur in 30-50% of cases, although this association is stronger for inattention than for hyperactivity-impulsivity. All of these conditions also show some overlap with the autistic spectrum, although in severe cases, the autism diagnosis always takes precedence.

The problem is that these 'diagnoses' are purely descriptive labels for particular constellations of behavioural and learning difficulties. Furthermore, the traits defining each are clearly dimensional, as milder difficulties with reading and/or spelling, motor-coordination, attention and impulse control, and social and language skills are not uncommon in the general population. To view these conditions as categorical 'disease entities' is thus rather misleading, because in milder form, their core characteristics all exist as perfectly normal individual differences in behaviour and cognition.

Dyslexia, dyspraxia, ADHD and autism are all complex developmental syndromes with a biological basis. As well as co-occurring within individuals, they tend to cluster in the same families, indicating shared elements in genetic predisposition. A family history of other developmental or psychiatric disorders is also common: in ADHD these include depression, bipolar (manic-depressive) disorder, substance abuse and antisocial personality disorders, while dyslexia and dyspraxia show some degree of familial association with the schizophrenia spectrum, in which fatty acid abnormalities have been well-documented. The term 'phospholipid spectrum disorders' has recently been coined to describe a range of developmental and psychiatric conditions including those considered here (2), in recognition of both their inter-relationships and the mounting evidence that all may involve some underlying anomalies of fatty acid and phospholipid metabolism.

The potential role of fatty acids in the biological predisposition to these conditions

A genetic component to these conditions is indisputable, and the evidence in each case points to several if not many different genes acting together to increase risk. No specific genes have yet been identified, although many of the chromosomal regions identified by linkage studies contain known genes that code for enzymes involved in fatty acid and phospholipid metabolism (3). However, only environmental factors could possibly explain the apparent increases in recent years in the incidence and severity of some of these conditions, which is notable for ADHD and particularly striking in the case of autistic spectrum disorders. Increasing exposure to environmental toxins is one probable contributory factor (4) but changes affecting nutrition are likely to be equally important.

Studies of mood disorder provide a good example of the potential importance of diet for brain function. Across different countries, rates of clinical depression vary widely and are strongly inversely related to levels of seafood consumption – a proxy measure of omega-3 fatty acid intake (5). Rates of post-partum depression and bipolar disorder show exactly the same pattern. Furthermore, similar relationships hold over time: the dramatic increases in rates of depression over the last century correlate strongly with the relative disappearance of omega-3 fatty acids from the diet. Although these data cannot prove causation, they are entirely consistent with other evidence that omega-3 deficiencies are characteristic in depression (6,7,8,9), and that omega-3 fatty acids can be effective in the treatment of mood disorders (10,11). Similar changes to our food supply and dietary habits may also be acting to increase the prevalence of behavioural and learning difficulties such as dyslexia, dyspraxia, ADHD and autism.

Genetic and environmental influences are of course essentially intertwined, i.e. 'nature versus nurture' is simply not a valid question. It is our environment that determines gene expression; and conversely, our genetic makeup leads us to select certain aspects of our environments. Fatty acid and phospholipid metabolism are at the interface of gene-environment interactions: the expression of individual differences in genetic constitution will depend heavily on dietary intake of fatty acids, both during development and throughout life. For further discussion of these issues, the interested reader is referred to a recent book containing a wealth of accessible information on the importance of lipids in the evolution of the modern human brain, and the relevance of this for neurodevelopmental and psychiatric disorders (12). The central proposal is that the individual differences underlying these conditions are actually as old as humanity, but that their developmental expression will depend crucially on dietary fatty acid intake.

A number of features associated with dyslexia, dyspraxia, ADHD and the autistic spectrum are potentially explicable in terms of mild abnormalities of fatty acid metabolism. These include the excess of males affected, slightly increased tendencies for pregnancy and birth complications and minor physical anomalies, and an increased frequency of atopic or other auto-immune disorders in affected individuals and their relatives. As discussed in detail elsewhere (13), fatty acid abnormalities could not only help to account for these features (and some of the key cognitive and behavioural features of these conditions, such as anomalous visual, motor, attentional or language processing) but may also play a part in some of the associated difficulties with mood, appetite or digestion, temperature regulation and sleep.

Omega 3 and omega 6 fatty acids and the brain

Highly unsaturated fatty acids (HUFA) of the omega-6 and omega-3 series are crucial for normal brain structure and function. Two so-called essential fatty acids (EFA), linoleic acid (omega-6) and alpha-linolenic acid (omega-3) can only be provided by the diet. In theory, these can then be converted into the more complex HUFA needed for optimal brain function (DGLA and AA from the omega-6 series, and EPA and DHA from the omega-3 series), as shown in Table 1.

Structurally, AA and DHA are key components of neuronal membranes, making up 15-20% of the brain's dry mass and more than 30% of the retina. Adequate supplies of these HUFA are so essential during prenatal development that the placenta acts to double the levels circulating in maternal plasma (14), and severe deficits may have permanent effects if they occur during critical periods of neural development. AA is crucial to brain growth, and mild deficiencies are associated with low birth weight and reduced head circumference, while DHA is particularly concentrated in highly active sites such as synapses and photoreceptors, and is essential for normal visual and cognitive development.

Throughout life, adequate supplies of HUFA are crucial for maintaining the fluidity of neuronal membranes (while saturated fats and cholesterol act to reduce this). Such fluidity is essential for the optimal functioning of membrane-bound and membrane-associated proteins that include both neurotransmitter receptors and ion channels. Certain HUFA also play key roles as 'second messengers' in neurotransmitter systems as well as contributing to many other aspects of cell signalling (15).

Functionally, the omega-6 fatty acids DGLA and AA and the omega-3 fatty acid EPA deserve special mention as these 20-carbon HUFA are substrates for the eicosanoids, a highly bioactive group of hormone-like substances including prostaglandins, leukotrienes and thromboxanes. Through their regulatory influences on endocrine, cardiovascular and immune systems, these HUFA derivatives can exert profound influences on brain development and function. As noted already, AA also plays a key structural role in the brain, but the crucial importance of DGLA and EPA in the regulation of numerous processes relevant to neural functioning is sometimes overlooked owing to their relatively small contribution to the actual composition of neuronal membranes.

Possible reasons for functional HUFA deficiencies

Unfortunately, evidence shows that the process of converting EFA to HUFA is remarkably slow and inefficient in humans (16, 17). Furthermore, various dietary and lifestyle factors can further impair in-vivo HUFA synthesis. These include a high dietary intake of saturated, hydrogenated or 'trans' fatty acids (found in most processed foods), lack of vitamin and mineral co-factors (particularly zinc, magnesium and vitamins B3, B6 and C), smoking, heavy use of alcohol or caffeine, viral infections, and high levels of the hormones released in response to stress.

Difficulties in synthesising or retaining HUFA can also occur for constitutional reasons. Both diabetes and atopic conditions such as eczema are associated with impaired EFA-HUFA conversion; and males appear particularly vulnerable to HUFA deficiency, as oestrogen helps in conserving HUFA under conditions of dietary deprivation, while testosterone can inhibit HUFA synthesis (18,19). Thus for constitutional or lifestyle reasons, some individuals may have particularly high dietary requirements for pre-formed HUFA.

Functional HUFA deficiencies may also arise from inefficiencies in recycling these fatty acids. HUFA are constantly replaced and recycled, both during the normal turnover and remodelling of membrane phospholipids and in the cascades triggered by normal cell signalling processes. In particular, phospholipase A2 enzymes (PLA2)

remove HUFA from membrane phospholipids, creating potentially damaging interim products such as free fatty acids that are highly susceptible to oxidation and have to be recycled in at least two further enzyme steps. The efficiency of these processes will also differ between individuals.

Fatty acid abnormalities in dyslexia, dyspraxia, ADHD and autism

In animals, deficiencies in EFA - and therefore their HUFA derivatives – lead to physical signs including excessive thirst, frequent urination and very dry, scaly skin as well as behavioural abnormalities. Twenty years ago, noting that these signs were common in hyperactive children, Vicky Colquhoun and Sally Bunday first pioneered the theory that HUFA deficiencies could underlie behavioural problems in ADHD (20). They pointed out that this could account for the apparent intolerance shown by many ADHD children to foods containing salicylates. (These impair the cyclo-oxygenase pathway for converting HUFA into prostaglandins and would thus exacerbate any problems stemming from low levels of these key HUFA derivatives). Noting the frequency of atopic conditions and zinc deficiency in ADHD, and that fact that non-affected siblings consumed similar diets, they also proposed that the primary difficulties might lie in poor EFA-HUFA conversion.

Separately from Colquhoun and Bunday's findings, a careful case report a few years later documented results of a biochemical / nutritional approach taken with a boy diagnosed with dyslexia (21). In this child, the clinical signs of fatty acid deficiency evident from what the author called the 'mirror test' (i.e. pure observation) were so well-described as to be worth quoting: *"Michael had very dry, patchy, dull, skin. Like a matte finish on a photograph, his skin, as well as his hair, failed to reflect light with a normal lustre. His hair was easily tousled and when pulled between the fingers it had a straw-like texture rather than a normal silky feel. He had dandruff. The skin on the backs of his arms was raised in tiny closed bumps like chicken skin. His fingernails were soft and frayed at the ends. All of these findings point to an imbalance of fatty acids."* Biochemical testing confirmed this picture, and nutritional intervention to correct these imbalances was followed by clear improvements in the child's school work.

Subsequent studies showed these clinical signs of fatty acid deficiency to be elevated in both ADHD children (22, 23) and dyslexic adults (24) compared with appropriately matched controls. They also related to visual symptoms in both dyslexic and non-dyslexic adults, and to the severity of reading, spelling and working memory deficits in dyslexic children (25).

The ADHD studies included blood biochemical measures, which confirmed reduced HUFA concentrations in both plasma and red cell membranes of boys with ADHD. No EFA deficiencies were found, supporting the proposal of impaired EFA-HUFA conversion. These measures also provided validation of the simple checklist scale used to assess clinical signs of fatty acid deficiency, as high scores were indeed associated with low plasma levels of AA and DHA as well as total omega-3 fatty acids. When further analyses were carried out irrespective of clinical diagnosis (23), HUFA deficiencies assessed by either method were related to a range of behavioural, learning and health problems. However, low levels of omega-6 fatty

acids in plasma were related only to physical health measures, while low omega-3 fatty acid status was associated with both behavioural problems and learning difficulties.

In autistic spectrum subjects, recent findings indicate an even greater elevation of these physical signs of fatty acid deficiency as well as reduced levels of omega-3 HUFA in red cell membranes (26,27). These studies have also revealed that membrane HUFA of autistic subjects appear unusually vulnerable to further breakdown during storage unless samples are kept at extremely low temperatures. Preliminary evidence indicates that this may reflect an excess of a PLA2 enzyme that removes HUFA from membrane phospholipids. High levels of this enzyme have previously been reported in both schizophrenia and dyslexia (28), and in dyslexic adults, abnormal membrane lipid turnover was also suggested by the results of brain imaging with 31-phosphorus magnetic resonance spectroscopy (29).

Can fatty acid supplementation help?

In all of these conditions there is already abundant anecdotal evidence of marked benefits for some individuals following dietary supplementation with fatty acids. However, careful and systematic investigation is required to provide definitive evidence that this kind of treatment can really help. This may take various forms, but randomised, double-blind placebo-controlled trials are regarded as the 'gold standard' in treatment evaluation. Unfortunately, there are some major difficulties in designing appropriate studies of this kind, let alone the significant obstacles to conducting them in practice. As noted earlier, diagnoses of these developmental conditions rely on purely behavioural criteria, and the heterogeneity of populations defined in this way makes it unlikely that fatty acid deficiencies will seriously affect more than a subset. Furthermore, unless subjects can be pre-selected via reliable objective measures of fatty acid status, decisions on the best kind of HUFA treatment to use are difficult. By their very nature, randomised controlled trials (RCT) do not allow treatments to be individually tailored, and in evaluating treatments for mental health conditions they have other fundamental limitations (30). Only a few such studies of fatty acid supplementation in these developmental disorders have so far been reported.

In ADHD, two early RCTs of supplementation with evening primrose oil (providing the omega-6 fatty acid GLA) gave equivocal results (31,32). However, subjects were not pre-selected in any way for low fatty acid status, and one of these studies involved three different treatments taken for only one month each in counterbalanced order (32), a rather inappropriate design given the very slow turnover of HUFA in the brain (33). More fundamentally, the accumulation of evidence since then strongly suggests that omega-3 fatty acids are probably more important than omega-6 in the etiology and management of behavioural and learning difficulties.

In another RCT using mainly omega-3 but some omega-6 HUFA, ADHD children were pre-selected for physical signs of fatty acid deficiency, and an early report indicated blood fatty acid changes in the treated children that were associated with reduced ADHD symptoms (34). More recently, another well-conducted RCT showed that pure DHA supplementation was completely ineffective in ADHD (35). These

findings are consistent with other evidence that EPA rather than DHA is the important omega-3 fatty acid for these purposes, as discussed further below.

The first RCT involving dyslexic children showed that supplementation with fish oil and evening primrose oil (providing mainly omega-3 but some omega-6 HUFA) can reduce behavioural and learning problems in those with ADHD tendencies (36,37). Particular improvements were found in attention, concentration and working memory, but disruptive behaviour and hyperactivity in these children also responded to HUFA treatment, and marked reductions were seen in anxiety and withdrawal. Study numbers were small and these initial findings require replication, but the treatment effects observed across a wide range of ADHD-related symptoms were substantial. In another, larger study of clinic-referred dyslexic children, preliminary results suggest that HUFA treatment may also improve reading progress. Full analyses are still in progress, but treatment effects seem particularly pronounced in children showing either physical signs of fatty acid deficiency or visual symptoms before treatment.

No controlled trials of fatty acid supplementation in either dyspraxia or the autistic spectrum have yet been reported, although studies in both these areas are now underway. At present, firm evidence for HUFA as a useful treatment for any of these developmental conditions therefore remains very limited. Further clinical trials are needed, but given the heterogeneity and comorbidity issues, an exclusive focus on current diagnostic labels may not be the best approach. Within 'ADHD' for example, behaviour problems can reflect an underlying mood disorder. Stimulant medications are least successful when ADHD is accompanied by anxiety or depression, and could exacerbate problems if the real problem is actually bipolar disorder (38). HUFA treatment may perhaps be most effective in these subsets of ADHD children, given the mounting evidence for omega-3 fatty acid deficiency in mood disorders.

Guidance for Practitioners

As already emphasised, HUFA supplementation cannot be expected to help all individuals with dyslexia, dyspraxia, ADHD or autism. The variability within these conditions and their multi-factorial nature guarantees this, and many such individuals may already obtain all the HUFA they need from their diet. Nutritional interventions should be complementary to other management approaches, and where possible carried out in full consultation with other professionals involved, particularly if any medical treatment or supervision is ongoing. However, a high dietary intake of HUFA is associated with many positive health benefits, so there should be little if anything to lose from trying such supplementation in the context of an appropriately balanced diet, and ideally with guidance and supervision from a nutrition practitioner. The only known negative effects of HUFA supplements involve mild digestive upset, although this is relatively uncommon and can usually be minimised with attention to other aspects of the diet.

Possible indicators of a good response to HUFA supplementation

The rationale for HUFA supplementation clearly rests on there being some pre-existing functional deficiency, but at present even the best blood biochemical measures give limited information in this respect. In the meanwhile, provisional

guidelines for identifying those most likely to benefit from fatty acid supplements include:

- Physical signs of fatty acid deficiency (excessive thirst, frequent urination, rough or dry skin and hair, dandruff, and soft or brittle nails)
- Atopic tendencies (especially eczema)
- Visual symptoms (such as poor night vision or sensitivity to bright light, and visual disturbances when reading - e.g. letters and words move, swim or blur on the page)
- Attentional problems (including distractibility, difficulties with sustained concentration, working memory problems and feelings often described as like 'brain fog')
- Emotional sensitivity or lability (especially undue anxiety/tension, excessive mood swings, or temper tantrums arising from 'low frustration tolerance')
- Sleep problems (particularly if these involve difficulties in both falling asleep at night and waking up in the morning)

Omega-3 versus omega-6 fatty acids

Omega-3 HUFA appear more relevant than omega-6 to these developmental conditions, and these are more likely to be lacking from modern diets. Green leafy vegetables and some nuts and seeds can provide the omega-3 EFA, alpha-linolenic acid. However, it is the omega-3 HUFA (EPA and DHA) that the brain needs, and given that EFA-HUFA conversion may be difficult, a direct supply is preferable. Oily fish and seafood are the only major food sources of EPA and DHA, and supplements are often the only realistic option. Although omega-3 should probably take precedence, adequate supplies of omega-6 are also vital. Evening primrose oil (EPO) is the best-researched supplement source and can help with the allergies that frequently accompany these conditions, but early studies of EPO alone indicated little benefit for the central problems in learning and behaviour.

Omega 3: EPA versus DHA

EPA and DHA are both essential for optimal brain function, but for different reasons. DHA is important in the *structure* of neuronal membranes, hence adequate supplies are needed 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 its eicosanoid derivatives such as prostaglandins, leukotrienes and thromboxanes.

All the evidence now points to EPA, not DHA, as the omega-3 fatty acid most effective in improving attention, perception, memory or mood in dyslexia, dyspraxia, ADHD or ASD. Controlled trials comparing EPA, DHA and placebo showed EPA to be effective in reducing these kinds of symptoms in schizophrenia and depression, while DHA was not (39,40). In ADHD, some benefits from fish oils have been reported (34), but pure DHA was also found completely ineffective (35). Probable reasons for this superiority of EPA over DHA include:

- DHA can easily be synthesised from EPA if needed (17,41), while retroconversion may be more difficult.
- EPA can inhibit the action of PLA2 enzymes, and may therefore help to protect <u>all</u> HUFA against rapid breakdown and loss (41).

- EPA gives rise to 3-series prostaglandins that have powerful anti-inflammatory actions, and immune system over-activation is implicated in most of these conditions.
- Other eicosanoid derivatives of EPA are likely to have important regulatory effects on neuronal signalling (e.g. via other aspects of immune function, cerebral blood flow, or vascular endothelial secretions).

The speed of response to treatment with fish oils also points to EPA, not DHA, as the active ingredient. Benefits are usually apparent within 1-2 weeks, consistent with EPA's role as a substrate for the eicosanoids. If DHA were responsible, up to three months would be expected, owing to the slow turnover of brain membrane fatty acids.

Standard fish oils all contain EPA and DHA in a roughly 2:1 ratio, although their total concentration may vary. Specialist supplements with a higher ratio of EPA to DHA are likely to be most effective, and high-DHA fish oils the least suitable for these purposes.

Optimal Dosages and monitoring response

Dietary HUFA requirements will differ between individuals, and in the same individual over time, so dosages are best determined from careful monitoring, with attention paid to any changes in other factors that may be relevant. For dyslexia and dyspraxia, a high-EPA fish oil supplying 500mg EPA daily is used in our ongoing studies, and this dose may be adequate for most individuals with milder forms of ADHD and ASD. However, if behavioural problems and/or mood swings are severe, 1g/day of EPA or more may be indicated, and daily doses of 2-4g pure EPA have been used successfully in disorders such as schizophrenia and depression (11,39,40). If evening primrose is included (which it is in our developmental studies), a dose supplying 50-100mg of GLA daily should be sufficient, although more may be helpful for individuals who also suffer from atopic conditions such as eczema.

After a few months, reducing the initial dose to half or even one-third of these levels may be possible without loss of benefits, but some people appear to need high levels on a long-term basis to prevent symptoms from re-appearing. 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 suitable for these purposes owing to their high Vitamin A content, and any HUFA supplements for which premium quality cannot be guaranteed should also be avoided. These may not only be ineffective, but could contain harmful residues (from environmental pollution or from extraction and processing methods). As HUFA are particularly susceptible to oxidation, additional Vitamin E supplementation is also advisable.

Finally, it is emphasised that factors other than HUFA should always be considered in the nutritional management of behavioural and learning difficulties. An adequate supply of other essential micronutrients is crucial, and many – such as zinc – are likely to have interactive effects on fatty acid metabolism (42). In the early case report of a dyslexic child mentioned earlier (21), fatty acid deficiency was cited as the

single most important factor, but various vitamin and mineral deficiencies were also identified and corrected, and further improvements followed from reducing this child's consumption of dairy products. Unfortunately, despite the success of a biochemical / nutritional approach in this case, other 'specialists' were apparently critical, telling the child's parents firmly that 'Nutrition has nothing to do with dyslexia'. However, as the author notes: *"Improvement in Michael's school work coincided with the return of normal lustre and texture to his skin and hair. If he had been a cocker spaniel his family would have accepted the connection between his "glossier coat" and better disposition more readily. The timing was convincing. Although it is never enough to establish "proof" in a given person, Michael was convinced. He saw and felt the changes together, and he understood the idea behind the work we did with him. With a twinkle in his eye, he told his grandmother that dandruff had been the cause of his dyslexia."*

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Table 1: 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**.**

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

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 (but not DHA) are needed to manufacture *eicosanoids* - hormone-like substances including prostaglandins, leukotrienes, and thromboxanes - that play a critical role 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. However, both are essential, and 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 'anti-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.