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REVIEW

Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children

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Abstract ω-6 and ω-3 polyunsaturated fatty acids (PUFAs) play a central role in the normal development and functioning of the brain and central nervous system. Long-chain PUFAs (LC-PUFAs) such as eicosapentaenoic acid (EPA, C20:5ω-3), docosahexaenoic acid (DHA, C22:6ω-3) and arachidonic acid (AA, C20:4ω-6), in particular, are involved in numerous neuronal processes, ranging from effects on membrane fluidity to gene expression regulation. Deficiencies and imbalances of these nutrients, not only during the developmental phase but throughout the whole life span, have significant effects on brain function. Numerous observational studies have shown a link between childhood developmental disorders and ω-6:ω-3 fatty acid imbalances. For instance, neurocognitive disorders such as attention-deficit hyperactivity disorder (ADHD), dyslexia, dyspraxia and autism spectrum disorders are often associated with a relative lack of ω-3 fatty acids. In addition to a high ω-6 fatty acid intake and, in many cases, an insufficient supply of ω-3 fatty acids among the population, evidence is increasing to suggest that PUFA metabolism can be impaired in individuals with ADHD. In this context, PUFA imbalances are being discussed as potential risk factors for neurodevelopmental disorders. Another focus is whether the nutritive PUFA requirements—especially long-chain ω-3 fatty acid requirements—are higher among some individuals. Meanwhile, several controlled studies investigated the clinical benefits of LC-PUFA supplementation in affected children and adolescents, with occasionally conflicting results.

Keywords Omega-3 fatty acids · EPA · DHA · Fatty acid metabolism · Childhood developmental disorders · Attention-deficit hyperactivity disorder (ADHD)

Abbreviations

ABC	Aberrant Behaviour Checklist
COX	Cyclooxygenase
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
CBCL	Child Behaviour Checklist
CDI	Children's Depression Inventory
CDRS	Children's Depression Rating Scale
CGI	Clinical Global Impression
CTRSL	Conners' Teacher Rating Scales, Long Version
FADS	Fatty acid desaturase
LOX	Lipoxygenase
PL	Phospholipase A2
PUFAs	Polyunsaturated fatty acids
IVA/CPT	Intermediate Visual and Auditory/Continuous Performance Test
LC-PUFAs	Long-chain polyunsaturated fatty acids
TOVA	Test of Variables of Attention

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Introduction

Polyunsaturated fatty acids (PUFAs) are essential nutrients for humans, and must be obtained from food. ω-6 and ω-3 long-chain PUFAs (LC-PUFAs) are structural and functional components of cell membranes. Likewise, LC-PUFAs are precursors of eicosanoids, which exert hormonal and immunological activity. The properties of the long-chain ω-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have met with considerable interest in the last few years. In particular, the vascular-protective effects of long-chain ω-3 fatty acids are well documented. EPA und DHA are known to affect the lipid profile, vascular tone and blood coagulation [44, 45]. Owing to their anti-inflammatory effects, another possibility is to positively affect inflammatory disorders such as rheumatoid arthritis [46]. In addition to these properties, which have been known for some time, it is apparent that ω-3 fatty acids also play a central role in the functioning of the brain and central nervous system. Together with ω-6 fatty acids, they are not only involved in the development and maturation of neuronal structures, but are essential throughout the entire life span for maintaining normal brain and nervous system function [129].

The supply of long-chain ω-3 fatty acids EPA and DHA in the overall population, as well as in children and adolescents, is often inadequate. In the eating habits prevalent in western industrial countries, food tends to be rich in ω-6 fatty acids such as linoleic acid (LA) and arachidonic acid (AA), and low in long-chain ω-3 fatty acids such as EPA and DHA. Furthermore, there is evidence that the fatty acid metabolism could be impaired in some individuals [21, 23, 24, 72, 102, 103].

Consequently, it is not surprising that a lack of ω-3 fatty acids, or an imbalance between ω-3 and ω-6 fatty acids, is associated with a number of behavioural abnormalities, as well as neurological and psychiatric disorders in both children and adults. Corresponding associations can be found with attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorders, as well as with unipolar and bipolar disorders [42, 96, 97]. Here, we describe the importance of polyunsaturated fatty acids, in particular ω-3 fatty acids, in relation to the development and functioning of the brain and central nervous system, as well as their clinical relevance in the prevention and treatment of neurological and psychiatric disorders among children and adolescents.

Metabolism of PUFAs and implications of metabolic disorders

In contrast to the rational chemical nomenclature, PUFAs are classified from a nutritional point of view according to the position of the double bonds from the methyl end of the molecule. Depending on the position of the first double bond, PUFAs are classified as either ω-3 fatty acids or ω-6 fatty acids. The first double bond of ω-3 fatty acids such as α-linolenic acid (ALA, C18:3ω-3) and its long-chain derivatives, eicosapentaenoic acid (EPA, C20:5ω-3) and docosahexaenoic acid (DHA, C22:6ω-3), is located at the third carbon atom (Fig. 1). In contrast, the first double bond of ω-6 fatty acids is located at the sixth carbon atom; the most well-known fatty acids in this group are linoleic acid (LA, C18:2ω-6), γ-linolenic acid (GLA, C20:3ω-6) and arachidonic acid (AA, C20:4ω-6).

Unlike plants, mammals are not able to synthesise the parent compounds of both fatty acid families, the ω-6 fatty acid LA and the corresponding ω-3 fatty acid ALA. Therefore, they must be obtained through the consumption of food. In contrast, humans are capable of synthesising the long-chain derivatives of these fatty acids, in particular AA, EPA and DHA, based on LA and ALA in a multistage

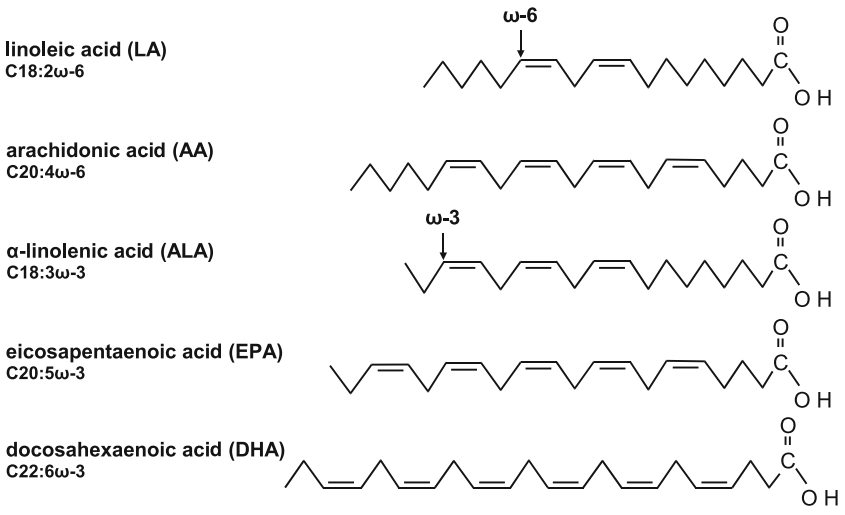

Fig. 1 Structure of ω-6 and ω-3 fatty acids

conversion process, which primarily takes place in the endoplasmic reticulum of liver cells [116]; Fig. 2). Although ω-3 fatty acids have the greatest affinity for the corresponding enzyme systems, the synthesis of EPA and DHA from ALA is extremely slow and low yielding [91, 106]. It is estimated that an intake of approximately 20 g pure ALA is necessary to obtain 1 g EPA [19]. The synthesis of DHA in humans appears to be more complicated then was long thought, since it is clear that another pathway also exists [135]. According to the alternative pathway, docosapentanoic acid (C22:5ω-3) is elongated to become tetracosapentanoic acid (C24:5ω-3) followed by a Δ6 desaturation. The next reaction step occurs after transfer of the fatty acid to peroxisomes, where a specific β-oxidation shortens the chain to a C22 product. The complexity of this conversion may be another reason for its ineffectiveness.

The conversion process is regulated by various endogenous and exogenous factors such as genetic factors, the intake of saturated fatty acids, vitamins and mineral cofactors as well as stress hormone levels. Various studies argue for genetically induced differences in the conversion of precursor substances [21, 72, 110]. For instance, SNPs (single-nucleotide polymorphisms) have been identified in the *FADS1* and *FADS2* (fatty acid desaturase) gene clusters [72, 110]. Likewise, Brookes et al. [21] observed a significant association a SNP in the *FADS2* gene in a population of ADHD children compared with the control population. *FADS1* and *FADS2* genes code for the enzymes delta-5 desaturase and delta-6 desaturase, which play a major role in the conversion of LA and ALA into the long-chain derivatives. The potential functional effects of these SNPs are still unclear. However, the activity of these key enzymes is the limiting factor in the conversion process. Carriers of the SNPs have greatly elevated AA contents in their serum phospholipids.

Conversion efficiency also appears to be gender-specific dependent on sex hormones. For instance, in vivo metabolisation studies have shown that the conversion of ALA into EPA and DHA is much more efficient in young women than in young men [23, 24], which might explain the higher prevalence of specific neuropsychiatric disorders such as ADHD and autism among boys as opposed to girls. Other studies also point at sex hormone effects. High testosterone levels in the amniotic fluid, for example, have an influence on the structure and function of neuronal tissue in foetuses [68] and are associated with reduced social development and attention in developing children [67]. Results of experiments performed on rats also suggest that male animals are particularly at risk for PUFA deficiencies or imbalances, as testosterone inhibits the synthesis of LC-PUFAs, whereas oestrogens protect them from breaking down [54, 76]. Apart from genetic factors, the status of mineral cofactors also appears to have an influence on the conversion and status of ω-3 fatty acids. Minerals such as magnesium [43] and zinc [8] are crucial desaturase enzyme cofactors. A lack of these micronutrients results in an inhibition of enzyme activity. Furthermore, the conversion of ALA into EPA and DHA is competitively lowered by a high supply of LA [91, 106].

On the other hand, oxidative stress is discussed as being a potential influencing factor for an elevated metabolism rate of LC-PUFA, and in particular ω-3 fatty acids [102, 103]. For example, Ross et al. [103] detected increased

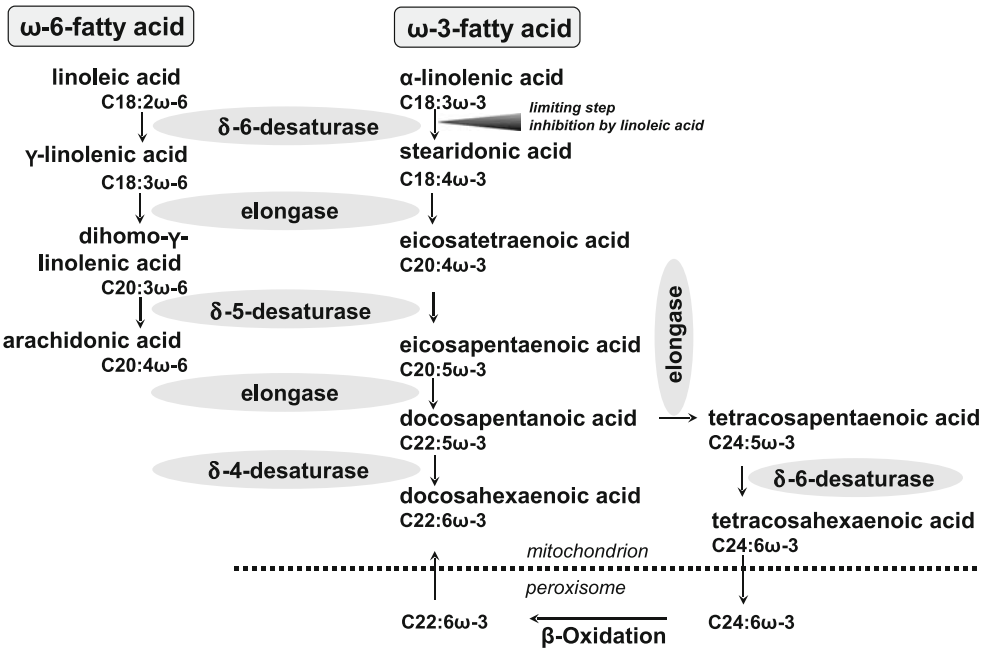

Fig. 2 Synthesis of long-chain ω-6 and ω-3 fatty acids from parent compounds LA and ALA. The 18-carbon ω-6 and ω-3 fatty acids derived from plant sources can be converted to their longer chain and metabolically active forms AA, EPA and DHA. Through a series of desaturations and elongations, LA is converted to AA, while ALA is converted to EPA and further to DHA. In this conversion, ω-3 and ω-6 fatty acids compete for the same enzyme systems, whereas a higher initial concentration of the respective parent compounds reduce the formation of the long-chain derivatives from the other series

ethane levels, a non-invasive marker for the elevated oxidation of ω-3 fatty acids, in respiratory air among children with ADHD symptoms.

Overall, the various observations are likely causal factors for the formation of PUFA imbalances and ω-3 fatty acid deficiencies and possibly neurodevelopmental disorders. Despite a supposedly adequate supply of the precursor molecule ALA, a lack of EPA and DHA and associated functional impairment may therefore result. Moreover, it must be considered that an inefficient conversion and an elevated PUFA metabolism rate increase the nutritive needs of pre-formed, long-chain ω-3 fatty acid. In view of the extremely low conversion rate into EPA and DHA, debate is increasing on whether the long-chain ω-3 fatty acids (EPA and DHA) should also be considered essential and be supplemented with food.

Physiological relevance of PUFAs in the nervous system

ω-3 and ω-6 fatty acids possess many physiological functions based on similar mechanisms (Table 1). The influence of LC-PUFAs on the development and function of the nerve tissue is due to their involvement in numerous processes (Table 2), ranging from gene transcription regulation to effects on cellular signal processes. While some of these influences have long been known, others have recently become evident.

LC-PUFAs play a central role in the normal functioning of the brain and nervous system [17, 35, 128, 129]. They are biochemically involved in the development of the brain and neuronal structures and exert their effects on various processes within the nervous system. DHA is a major structural component of the membrane-based phosphoglycerides in the photoreceptors of the retina and consequently involved in the development of sight. Accordingly, sufficient amounts of ω-3 LC-PUFAs such as EPA and DHA, as well ω-6 LC-PUFAs such as AA and dihomo-gamma-linolenic acid (DGLA, C20:3ω-6), are essential during the embryonal stage and early phase following birth [73, 134]. From the beginning of the second half of gestation, especially in the third trimester, the foetus is most dependent on an adequate supply of these PUFAs [33, 77, 78]. During this cerebralisation phase, which extends to the first few months after birth, the CNS develops rapidly.

Table 1 Physiological functions of LC-PUFAs

Integral components of cell membranes
Affects membrane fluidity
Regulation of ion channels
Modulation of endocytosis and exocytosis
Modulation of hormonal activity
Immunological effects
Influences gene expression (development)

Table 2 Effect of ω-3 fatty acids on neuronal mechanisms (according to [42])

Mechanism of action	Author
Cerebral development	[128, 129, 133, 134]
Development of vision	[75, 80, 88, 104, 128]
Component in neuronal membrane phospholipids	[17, 18, 82, 106]
Effects on neurotransmitter systems	[1, 37, 69, 119, 142, 143]
Regulation of corticotrophin-releasing hormone	[50]
Inhibition of protein kinases	[79, 113]
Modulation of heart rate variability via vagal mechanism	[131]
Improved cerebral circulation and oxygen supply	[127]
Prevention of neuronal apoptosis	[63, 64]
Influence on energy exchange	[137]
Influence on neurite growth	[27]
Regulation of gene expression	[9, 60, 65, 101]
Anti-inflammatory effects	[62, 77, 90, 119]

In this phase of rapid growth, the brain is very sensitive to a lack of nutrients. An adequate supply of ω-3 fatty acids-especially DHA—is therefore indispensable for maintaining optimal tissue function. Normal visual and cognitive development is dependent on this supply due to the central structural role of DHA in synapses and photoreceptors [19, 25, 55, 107, 118, 124]. Infants from mothers supplemented with DHA during pregnancy had significantly improved visual acuity at 4 and 6 months of age [59].

Likewise, in randomised controlled trials, impaired mental performance (e.g., childhood IQ scores) and visual function (e.g., visual acuity and stereo-acuity) was reported in healthy term infants due to a lack of dietary supply of DHA and DHA+AA [14, 15, 136]. Similarly, animal studies with rhesus monkeys demonstrate that a ω-3 fatty acid deficiency during gestation and postnatal development caused considerably reduced DHA levels in the retina and cerebral cortex compared to control animals. This was accompanied by psychomotor and cognitive deficits as well as impaired visual function (e.g., visual acuity) [86, 87].

As structural components of neuronal cell membranes, LC-PUFAs—in particular AA and DHA—have a considerable influence on signal transduction. Studies with rats, for example, demonstrated that chronic ω-3 fatty acid deficiency induces abnormalities in dopaminergic and serotonergic neurotransmission systems [1, 29, 37, 38], which are closely involved in the modulation of attention, motivation and emotion. The exact mechanisms explaining

these effects are not completely understood. However, these studies suggest that an increasing proportion in favour of ω-3 fatty acids modifies the physical properties of the neuronal cell membranes, which influences the proteins (receptors, transporters) enclosed in the membrane [30, 31]. The effect of the ω-3 fatty acid content on membrane composition and function in particular has been investigated in various animal and experimental studies [1, 16–18, 82, 106]. The incorporation of DHA in the neuronal tissue membrane increases with its supply [29, 40, 61]. As a result of changes in the properties of the lipid phase, DHA plays a significant role in maintaining optimal membrane integrity and fluidity [52, 61, 81, 126, 139], which is necessary for signal processes within the cell. The double phospholipid membrane forms the matrix in which membrane proteins, receptors and ion channels are embedded and bound to membrane-associated proteins such as those of the second messenger system. An altered fluidity of the neuronal membrane phospholipids affects the tertiary and quaternary structure of the membrane-bound receptors, which, in turn, has an effect on their function and activity [139]. Owing to this biophysical model of action, LC-PUFAs are able to influence cellular signal processes and transmissions, for example by changing the binding or release of neurotransmitters [2, 30, 74, 139]. Consequently, optimal physiological membrane function—being a precondition for corresponding intercellular communication—is dependent on optimal ratio of ω-6 and ω-3 fatty acids.

Another mechanism by which LC-PUFAs—especially ω-3 fatty acids—exert their function in the nervous system is their potential to regulate brain gene expression, as experimental studies conducted in recent years have shown [12, 66, 108]. LC-PUFAs are therefore a prime example of the close interaction between nutrients and genetic factors.

The nutritionally relevant role of long-chain ω-6 and ω-3 fatty acids as eicosanoid precursors is also significant with regard to their effect on brain function. Eicosanoids are oxidation products derived from 20-carbon polyunsaturated fatty acids (Greek: “Eicos” = 20). In extremely low concentrations, eicosanoids (prostaglandins, thromboxanes and leukotrienes) act as local mediators. As a result of their hormone-like action, eicosanoids have an effect on numerous metabolic processes. When metabolised, ω-3 and ω-6 fatty acids compete for the same enzyme systems and are able to reciprocally displace each other (cf. Fig. 3; [125]). Depending on the precursor substance, different series of eicosanoids are formed, all of which vary greatly with respect to their range of action. In general, the eicosanoids formed from ω-3 fatty acids (Series 3 and 5) are attributed with more favourable effects (for example anti-inflammatory) than those formed from ω-6 fatty acids (Series 2 and 4). The formation of mediators depends on the content of respective precursors supplied in the diet. This is thus the basis for the dietetic influencing of physiological processes regulated by eicosanoids [125].

In summary, it is of particular importance to note that an adequate supply of both ω-3 and ω-6 fatty acids is critical for brain development and function. However, not only the absolute level of these fatty acids is crucial for mediating cognitive and biochemical functions, but also the ω-6:ω-3 ratio [134, 139].

Effect of LC-PUFAs on the development and behaviour of children

The many functions of polyene fatty acids suggest that deficiencies and imbalances of these nutrients in the developmental phase present far-reaching consequences in terms of brain function. Neonates with a low birth weight run the greatest risk of impaired neuronal development. A low birth weight and smaller head circumference are often associated with AA and DHA deficiencies. However, a low birth weight is usually due to an inadequate maternal diet. Conversely, it is known from observational studies that an increase in the consumption of fish during pregnancy lowers the risk of preterm delivery and low birth weight [89].

The numerous effects in particular of ω-3 fatty acids on neuronal mechanisms (Table 2) explain that a lack of these fatty acids leads to an impairment of various cerebral functions (Table 3). A number of studies have demonstrated a connection between ω-3 fatty acids and mental health [reviewed in 92]. In addition to observational studies investigating the connection between the intake of ω-3 fatty acids and neuronal function and specific psychiatric disorders, clinical trials substantiating the effects of ω-3 fatty acids are also available. In particular, childhood disorders such as ADHD and autism spectrum disorders are associated with a relative lack of ω-3 fatty acids [5, 42, 96, 99].

Effect of LC-PUFAs on ADHD, dyslexia and dyspraxia

ADHD is the most common neurocognitive disorder in children [105]. Based on estimates pooled from all over the world, it can be assumed that 5.29% of all schoolchildren are affected by ADHD [93] and that functional impairment persists in up to 70% of all children affected through to adulthood [114]. ADHD symptoms are more common in young boys than in young girls [109]. Disorders accompanying ADHD are dyslexia (reading and writing disorder), dyspraxia (coordination and developmental disorders where the coordination of motivation and action is problematic), oppositional behavioural disorders and impaired social behaviour, as well as anxiety and tic disorders. The three primary symptoms of ADHD are inattentiveness (distractibil-

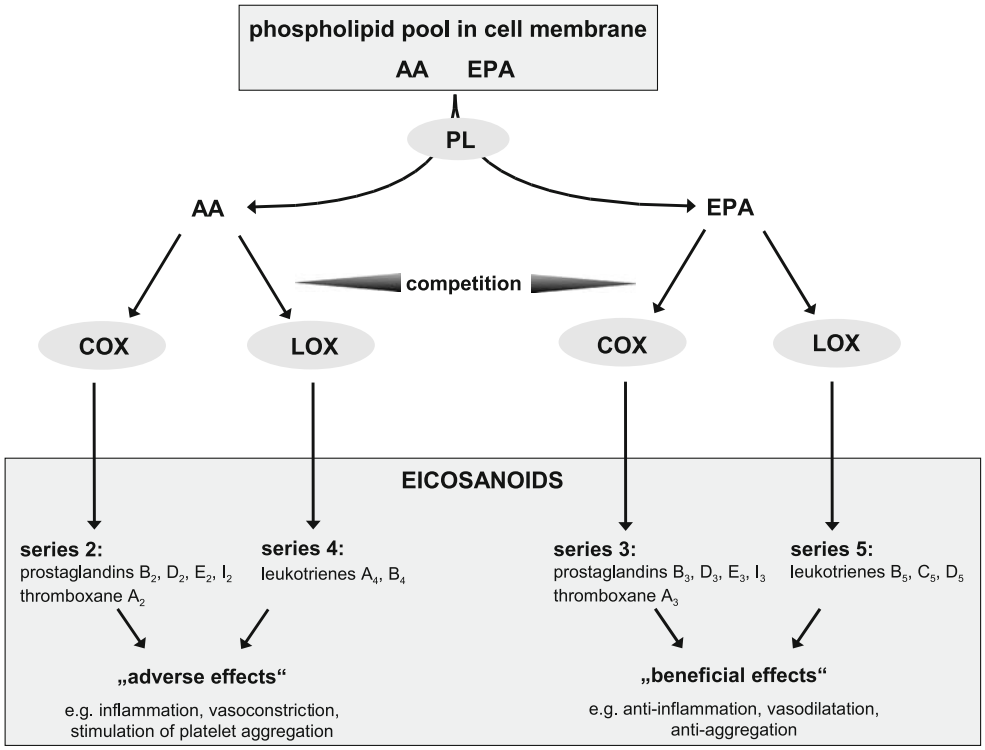

Fig. 3 ω-6-fatty acid AA and ω-3-fatty acid EPA compete for the eicosanoid forming enzyme systems. AA and EPA reside in the membrane phospholipid bilayer of cells and can be released as free fatty acid through the action of the calcium-dependent phospholipase A2 (*PL*). The fatty acids are then converted to eicosanoids of different series via the cyclooxygenase (*COX*) or lipoxygenase (*LOX*) pathways, dependent on the enzymatic setting of the cell. The highly active series 2 and 4 eicosanoids metabolised from AA can promote adverse effects such as inflammation, vasoconstriction, and stimulation of platelet aggregation. EPA is a precursor to the less metabolically active "counterpart" series 3 prostaglandins and thromboxanes and series 5 leukotrienes, which promote beneficial effects such as anti-inflammation, vasodilatation and anti-aggregation. AA and EPA compete for the COX or LOX enzymes to form these eicosanoids. Thus, an adequate EPA concentration in the phospholipid pool hinders the amount of AA derived eicosanoids by reducing the amount of enzyme available for conversion of AA to prostaglandins and leukotrienes; likewise EPA has a higher affinity to COX and can therefore displace AA competitively from the enzyme system

ity, poor concentration), hyperactivity and impulsiveness. Children with ADHD are often restless, have problems following instructions and executing tasks which require prolonged self-regulation. In addition, they are often poorly organised, function according to the pleasure principle and suffer increasingly from low self-esteem. As a result, these children usually have substantial problems at school and difficulty in dealing with routine problems. This can put a considerable strain on the whole family and also has a negative effect on their relationship with educators or teachers.

Table 3 Potential consequences of PUFA imbalances or a relative ω-3 fatty acid deficiency for brain function

Impaired circulation and oxygen supply
Reduced incorporation of DHA in photoreceptors (sight)
Reduced incorporation of DHA in synapses (stimulus transmission and cognitive function)
Abnormal immune response with heightened proneness to inflammation (change in neurotransmitter concentrations)
Impaired development and psychiatric disorders (including depression, schizophrenia, dementia, ADHD)

The aetiology of the disorders as well as the pathogenetic mechanisms are, to a large extent, unknown [28, 41, 56, 105]. However, various studies point to a multi-factorial process. For example, environmental influences such as smoking during pregnancy or premature birth are possible risk factors that might lead to the development of the disorders as are genetic factors. There is increasing evidence that changes in PUFA metabolism lead to impaired phospholipid metabolism, which, in turn, is seen to be connected to such neurodevelopmental disorders [96, 99]. Further symptoms, such as extreme thirst, increased desire to urinate as well as dry hair and skin have been reported in some children with ADHD [5]. These symptoms might suggest an under-supply of essential fatty acids [5, 47]. Some psychiatric disorders among adults, such as depression, bipolar disorders, schizophrenia, as well as personality disorders, are also linked to constitutional fatty acid and phospholipid metabolism abnormalities [11, 13, 49, 53, 95].

Results from observational studies

It is known from observational studies that the levels of ω-3 fatty acids such as ALA and DHA, but also of ω-6 fatty acids such as AA, are lower in the erythrocytic membrane phospholipids and plasma of children and adults with ADHD symptoms as opposed to healthy individuals [5, 32, 34, 83, 84, 121, 123, 141]. The PUFA levels in the phospholipids of the erythrocytic membranes are most suitable for assessing the PUFA status within the organism. They correlate well with the levels in the brain [138] and also reflect the fatty acid supply of the last month in comparison to the fatty acid levels in the plasma, which merely reflect the last 24 h [70]. In a study involving 96 young boys (with and without ADHD symptoms), Stevens et al. [122] established a connection between low ω-3 fatty acid levels in plasma phospholipids and an increased occurrence of behavioural problems and learning difficulties. The same working group also observed an increased occurrence of symptoms synonymous with a lack of essential fatty acids in abnormally behaved ADHD children and significantly lowered AA and DHA concentrations in plasma phospholipids than in healthy children [121]. Although the results of such studies suggest a connection between paediatric neurodevelopmental disorders such as ADHD and PUFA imbalances, the interpretation of blood analyses, however, remains challenging. They reflect complex chemical interaction between the effect of diet, environmental influences, genetic variations and other factors.

Results from clinical trials

In addition, data from various clinical trials is available, in which children with ADHD symptoms have received different polyene fatty acids. We have critically reviewed relevant controlled clinical trials published prior to January 2009 (summarised in Table 4). Medical and health databases were searched for trials according to the following criteria: English-language, randomised, double-blind placebo-controlled trials, where children (or teenagers) with ADHD symptoms and/or associated syndromes such as dyslexia and dyspraxia were supplemented with different polyene fatty acids. In these studies, fatty acids were administered individually or in combination, as monotherapy or as an add-on to existing pharmacotherapy.

Early studies on the effect of the sole administration of the ω-6 fatty acid GLA to hyperactive and ADHD children established merely a minimal therapeutic benefit [3, 6, 7]. Likewise, the administration of ω-3 fatty acids in monotherapy form was ineffective. For example, two randomised clinical trials, in which children with specific-learning difficulties such as dyslexia and ADHD received either DHA alone or combined with EPA, showed no effect on behavioural parameters such as attentiveness, impulsiveness and other associated symptoms [51, 132]. However, two more recent studies demonstrated a therapeutic benefit following the administration of ω-3 fatty acids as monotherapy. An Indian study established significant improvements in ADHD symptoms following supplementation with a daily dose of 0.4 g ALA from flax oil in combination with 0.5 g vitamin C [58]. Significant improvements were observed in the ADHD symptoms of nine children who had been supplemented for 8 weeks with ω-3 fatty acids in relatively high doses (10.8 g EPA/5.4 g DHA) in an American pilot study [120]. Effects were observed primarily in behavioural parameters such as inattentiveness, hyperactivity, oppositional and defiant behaviour and were accompanied by a significant rise in EPA and DHA levels as well as a drop in the AA:EPA ratio in plasma phospholipids.

However, the combination of long-chain ω-3 fatty acids EPA and DHA together with the ω-6 fatty acids LA, GLA or AA appears to be most effective. Various (randomised controlled trial) RCTs demonstrated a decrease in ADHD-associated symptoms following a supplementation comprising a mixture of fish oil rich in ω-3 fatty acid and evening primrose oil rich in ω-6 fatty acid, especially GLA [97, 100, 121, 123]. In one pilot study, Richardson and Puri [97] observed a decline in cognitive disorders and general behavioural abnormalities following the supplementation of dyslexic ADHD children with four LC-PUFAs (EPA, DHA, AA and GLA) compared with placebo. The effects were particularly pronounced with regard to general behavioural abnormalities and psychosomatic symptoms such as anxiety, shyness, cognitive problems, inattentiveness, hyperactivity and impulsiveness. Similarly, the supplementation of ADHD children with DHA and EPA in combination with AA and GLA led to a decline in numerous ADHD behavioural symptoms such as oppositional behaviour and destructive behaviour in two further clinical trials [101, 103].

In several studies, the effects were accompanied by a considerable rise in the EPA/DHA levels in erythrocytic plasma phospholipids [100, 121, 123]. Whereas a 3-month supplementation with a mixture comprising ω-3 and ω-6 fatty acids (DHA, EPA, LA) had no effect in the majority of the children and teenagers taking part in an RCT conducted by Johnson et al. [57], a sub-population among the test subjects experienced a decline in ADHD behavioural symptoms. These responders in the active treatment group were primarily young boys. Since the symptoms also declined in the placebo group, no significant difference was observed. Following a one-way cross-over, all test subjects were treated with the active preparation, which resulted in a significant decline of ADHD behaviour patterns in 47% of all test subjects.

Table 4 Summary of controlled clinical trials investigating the effect of LC-PUFAs on ADHD and its associated syndromes

Treatment groups	PUFA composition and dose (per day)	Form of therapy	Duration of trial (weeks)	Results	Author(s)
Children with ADHD *n*=30	ω-3 and ω-6 fatty acids rich in flax oil	Add-on[a]	12	Significant effects for LC-PUFAs as opposed to placebo according to teachers, opposing results according to parents Improvement in hyperactivity and impulsiveness No significant differences between the groups in respect of inattentiveness (parents' and teachers' assessment)	[22]
Children with ADHD *n*=50	480 mg DHA 80 mg EPA 96 mg GLA 40 mg AA	Add-on[a]	16	No definite effects for LC-PUFAs as opposed to placebo Significant treatment effects in merely 2 out of 16 measures of success (aggressive behaviour according to parents' assessment and problems paying attention according to teachers' assessment) Effects for LC-PUFAs as opposed to placebo: decrease in oppositional behaviour and destructive behaviour Considerable rise in EPA and DHA levels in plasma phospholipids and total erythrocytic lipids	[123]
Children with ADHD *n*=63 6–12 years	345 mg DHA	Add-on[a]	16	No significant effects for DHA compared with placebo (TOVA, DSM-IV, CBCL, Conners' Rating Scales) DHA level in plasma phospholipids rose significantly in the active drug group	[132]
Children with ADHD *n*=20 7–12 years	120 mg DHA 180 mg EPA 45 mg GLA[b]	Monotherapy Nutrient supplement with LC-PUFAs vs. Ritalin®	4	Significant effects for both nutrient supplement with LC-PUFAs and Ritalin® Therapeutic effects in both treatment groups similarly pronounced (IVA/CPT)	[48]
Children with ADHD *n*=132 7–12 years	174 mg DHA 558 mg EPA 60 mg GLA	PUFA vs. PUFA/ micronutrients	15	No clear effects for LC-PUFAs as opposed to placebo (Conners' Rating Scales) Significant treatment effects as opposed to placebo merely in the case of hyperactivity, impulsiveness and inattentiveness, according to parents' assessment No significant effects according to teachers	[118]
Children with ADHD *n*=30 average 7.75 years	400 mg ALA (flax oil)	Monotherapy	12	Significant effects for ALA as opposed to placebo (parents' assessment DSM-IV) Improvements in ADHD symptoms such as inattentiveness, hyperactivity, learning and social problems Significant increase in EPA/DHA and decrease in AA levels in erythrocytic membranes	[58]
Children with ADHD *n*=18 6–12 years	2800 mg LA 320 mg GLA	Monotherapy Evening primrose oil (Efamol®) vs. D-amphetamine (Dexedrin)	12	No clear effects for Efamol® as opposed to placebo or D-amphetamine Conners ADHD index (parents' and teachers' assessment) Parents' ratings were non-contributory Significant Efamol® effect between placebo and D-amphetamine merely in respect of hyperactivity in teachers' assessment	[6]

Table 4 (continued)

Treatment groups	PUFA composition and dose (per day)	Form of therapy	Duration of trial (weeks)	Results	Author(s)
Children with ADHD *n*=31 average 8.86 years	2160 mg LA 270 mg GLA	Monotherapy	4	No clear effects for ω-6 fatty acids as opposed to placebo No significant effects in 40 out of 42 variables Significant effects merely in the case of inattentiveness and hyperactivity, teachers' assessment	[3]
Children with ADHD *n*=40 6–12 years	514 mg DHA 100 mg EPA	Monotherapy	8	No significant effects for ω-3 fatty acids compared with placebo No effects on ADHD symptoms (DSM-IV), aggressive behaviour as well as other applied success measures	[51]
Children with dyslexia and ADHD *n*=41 8–12 years	480 mg DHA 186 mg EPA 96 mg GLA 42 mg AA	Monotherapy	12+12 (one-way cross-over)	LC-PUFAs significantly more effective than placebo (in 3 out of 14 measures for success) Significant treatment effects in 7 out of 14 measures for success (baseline) Decline in cognitive disorders and general behavioural abnormalities (global Conners' ADHD index), inattentiveness (parents' assessment DSM-IV), psycho-somatic symptoms Following cross-over, same effects as in the case of children previously treated with placebo	[98]
Children with ADHD and dyspraxia *n*=117 5–12 years	558 mg EPA 174 mg DHA 60 mg LA	Monotherapy	12+12 (one-way cross-over)	LC-PUFAs significantly more effective than placebo Significant treatment effects in 11 out of 13 ADHD measures for success (only teachers' assessment) Improvement in reading and writing, articulation (Wechsler Objective Reading Dimensions), ADHD symptoms (CTRSL) as well as other behavioural problems (aggressive and anxious behaviour) Following cross-over, same effects as in the case of children previously treated with placebo No effects on motor functions (Movement Assessment Battery for Children)	[100] Oxford–Durham study
Children/ teenagers with ADHD *n*=75 8–18 years	558 mg EPA 174 mg DHA 60 mg LA	Monotherapy	12+12 (one-way cross-over)	No significant effects for LC-PUFAs compared with placebo (DSM-IV; CGI) 25% decline in ADHD behavioural symptoms with 26% after 12 weeks and 47% after 24 weeks Following cross-over, same effects as in the case of children previously treated with placebo	[57]

[a] Additional treatment to drug treatment

[b] Part of a micronutrient supplement comprising multi-vitamins, multi-minerals, phytonutrients, probiotics and amino acids

Dyspraxia symptoms among children include gross and fine motor deficits as well as difficulties learning and adapting psychosocially. In the methodologically convincing *Oxford–Durham Study*, a supplement comprising 80% fish oil and 20% evening primrose oil was tested for its effectiveness on the abnormal behaviour of children with these symptoms in a randomised, double-blind and placebo-controlled study [100]. Of the 60 children in the active treatment group, 55 exhibited significant reading/ writing weaknesses and 50 had pronounced ADHD

symptoms, whereas all 57 children in the placebo group had considerable reading/writing difficulties while 52 had pronounced ADHD symptoms. Similarly, the supplementation of the EPA, DHA and GLA mixture in this RCT caused significant improvements in the reading/writing difficulties, ADHD symptoms as well the aggressive and anxious behaviour. All scales used for recording ADHD symptoms featured changes, although no improvements were observed with regard to motor functions. At the end of the 3-month treatment, clinically relevant ADHD symptoms were evident in only 23% of all children. Following a one-way cross-over, the same effects were also observed in the children previously treated with placebos.

Effect of ω-3 fatty acids on autism spectrum disorders in children

Autism spectrum disorders are far-reaching perceptual and information-processing changes of the brain, which become noticeable during early childhood. They are characterised by social interaction and communication weaknesses as well as by stereotypical behaviour. In addition to these primary symptoms, children often display behavioural abnormalities such as self-harm, aggression and fits of rage. However, children suffering from autism spectrum diseases frequently possess marked strengths in perception and attention, as well as memory and intelligence. The moderate success of drug treatment with psychotropics from a whole range of active substance classes is often disproportionate to their unacceptable side effects [94]. As is the case with ADHD, dyslexia and dyspraxia, it has become clear that autism spectrum disorders are also connected to fatty acid deficiencies and imbalances [99, 130]. For instance, children with autism spectrum disorders show lowered ω-3 fatty acid levels in plasma [130] and in erythrocytic membrane phospholipids [10] compared with healthy children. An observational study involving 861 autistic and 123 healthy children established a relationship between the low DHA and AA levels in infant formula and the occurrence of autism spectrum disorders [112]. Children receiving infant formula low in DHA and AA are at a much greater risk of developing autism spectrum disorders than children who are breast-fed (odds ratio 4.41, 95% CI 1.24, 15.7).

In a non-controlled study investigating a ω-3 fatty acid supplement, parents of children with autism spectrum disorders reported a general improvement in the health of their children [10]. The children were able to sleep better, concentrate more easily, displayed improved cognitive and motor abilities, were more sociable and less irritable, aggressive and hyperactive. Due to the absence of a placebo control, the outcome of the study at best points to certain effects. However, it does provide a reason for further studies. Data from a small randomised, double-blind and placebo-controlled study, in which 13 autistic children aged 5–17 were treated over a period of 6 weeks with ω-3 fatty acids (1.5 g/day) have since become available [4]. Supplementation had a considerable positive effect on hyperactivity and stereotypy (Aberrant Behaviour Checklist, ABC) as opposed to placebo. In order to explore the therapeutic potential of ω-3 fatty acid supplementation, further studies involving larger patient populations are needed.

Effect of ω-3 fatty acids on infantile depression

Major depression and dysthymia are more common among children and teenagers than is generally assumed. The American Academy of Child and Adolescent Psychiatry estimates that the prevalence of infantile depression lies at roughly 2–4%. Infantile depression is often accompanied by panic attacks as well as anxiety or obsessive behaviour and is characterised by various behavioural abnormalities. Prepubescent depressive and dysthymic disorders often occur in comorbidity with ADHD. Children and teenagers with such symptoms display poor psychosocial competence and are often suicidal. The early detection and treatment of such disorders is therefore crucial.

As numerous studies have demonstrated that ω-3 fatty acids have a positive effect in the treatment of major depression among adults, the effect of EPA/DHA treatment on infantile major depression was investigated in a study conducted by Nemets et al. [85]. During the study, the children (aged between 6 and 12 years) were given a supplement consisting of ω-3 fatty acids (0.6 g/d) over a period of 16 weeks. Treatment had a significant effect in all three assessment scales used (CDRS; CDI; CGI) as opposed to the control and led to a considerable decline in depressive symptoms.

Dosage recommendations and supply situation for children and adolescents

According to the state of knowledge today, a minimum amount of the ω-3 fatty acids EPA and DHA, i.e., 0.1 to 0.2 g/d, is needed in order to maintain essential body functions; in contrast, intake amounts of 0.3 to 0.4 g per day are regarded as nutritionally desirable [117]. To guarantee adequate neuronal development in the foetus or infant, requirements for maternal diet during pregnancy and breast-feeding rise by 0.15 up to 0.35 g ω-3 fatty acids per day [36]. Beyond that, several international perinatal medicine associations recommend that in particular pregnant and lactating woman consume not less than 0.2 g DHA per day [71, 73]. According to the recommendations of nutrition societies from Germany, Austria and Switzerland, children,

teenagers and adults should, while reducing their fat consumption to 30% and taking a ω-6 to ω-3 ratio of 5:1 into account, derive roughly 0.5% of their total energy in the form of ω-3 fatty acids [36]. This is equivalent to energy target values of 1,000 and 2,400 kcal, to a requirement of approx. 0.5 and 1.3 g ω-3 fatty acids and 2.6 or 6.3 g ω-6 fatty acids a day. The reference values cited are based on estimates and refer in each case to the supply of ALA and LA. The British Nutrition Foundation [20], on the other hand, applies the 0.5 total energy percentage in their intake recommendations to purely EPA/DHA.

There is often a difference between the desired recommended intake and actual intake, as the content of ω-3 fatty acids in the prevailing diet in modern industrial countries is extremely low. Quantitatively significant concentrations of the long-chain ω-3 fatty acids EPA and DHA are only found in a few types of high-fat cold-water fish such as salmon, mackerel or herring, whereas ALA can be found in a number of green vegetables as well as in certain nuts and seeds. According to the diet report of the German Nutrition Society [39], children between the ages of 4 and 10 consume roughly 0.1 g EPA and DHA a day. By adding a supply of 1.39 g ALA/day and an assumed conversion rate of 5–10%, an additional EPA and DHA intake of 0.05 to 0.1 g/day results.

Nutritionally, ω-6 fatty acids are equally essential. However, the supply of most ω-6 fatty acids in both children and adults is sufficient, as there are many sources of ω-6 fatty acids in people's food compared to ω-3 fatty acids. The majority of vegetable oils contain very high amounts of ω-6 fatty acids (usually LA). The typical diet in western countries is high in meat, which gives rise to a high supply of pre-formed AA and, consequently, an imbalance between ω-3 and ω-6 fatty acids. Physiological cell function is optimal at a 3:1 ratio between ω-6 and ω-3 fatty acids. The ω-6 and ω-3 ratio has shifted in the last 50 years, due to the changes in eating habits in western countries, from an initial 3:1 to more than 20:1 [115], thus resulting in an insufficient latent supply of ω-3 fatty acids.

With respect to the low conversion rate and the comparatively low consumption of fish in western countries, the ω-3 fatty acid supply for children and teenagers—in particular EPA and DHA—can to be regarded as inadequate and should be improved. The recommendation to eat more fatty types of sea fish (one to two times a week) is, however, in conflict with the reluctance of many children to eat fish at all. In order to improve the supply situation, micro-capsuled ω-3 fatty acid products are therefore a consideration in addition to the use of supplements containing sea-fish oil rich in ω-3, or even enriched functional foods [111].

Summary and conclusions

Polyunsaturated fatty acids are of central importance for the development and functioning of the brain and nervous system, especially during childhood development. An adequate supply of long-chain ω-3 fatty acids, such as EPA and DHA in particular, is therefore indispensable for normal brain development during foetal growth in the cerebralisation phase, as well as for visual and cognitive functions in neonates. Likewise, sufficient amounts of these fatty acids are essential for small children and school-children, too. It should be considered that in normal diets, the supply of these fatty acids is extremely limited.

It has been shown that ω-3 fatty acids and some ω-6 fatty acids such as GLA are also directly involved in the synthesis, release and re-uptake of neurotransmitters and, as a result, might induce behavioural disturbances. Owing to the great involvement of ω-3 fatty acids in processes within the brain and nervous system, is seems likely that a relative ω-3 fatty acid deficiency or an imbalance between ω-3 and ω-6 fatty acids leads to impaired neurological functioning, which manifests itself among children, for example, in the form of developmental and behavioural disorders. Genetic and gender-specific differences with regard to the metabolism of PUFAs in conjunction with the overall rather scarce nutritive supply of long-chain ω-3 fatty acids are therefore regarded as a potential risk factor for neurodevelopmental disorders [35, 140].

The number of studies investigating the therapeutic use of LC-PUFAs in the treatment of neuropsychiatric disorders among children is limited. Data from observational studies, as well as controlled clinical trials, suggest that the administration of specific combinations of LC-PUFAs can have a positive effect in children with ADHD, dyslexia, dyspraxia and autism spectrum disorders. Sometimes, considerable differences arise between the individual fatty acids and their dose effects. For instance, the sole administration of DHA in the case of ADHD had no effect on behaviour, learning or disposition, whereas the combination of EPA and DHA with certain ω-6 fatty acids improved the outcome. This fact is currently still incomprehensible, as the ω-6 fatty acid intake via normal food is usually very high. Consistent with the results of clinical trials conducted on adults suffering from psychiatric disorders, EPA and DHA also have a significant effect on infantile depression.

Even though a number of methodologically convincing studies have demonstrated a significant benefit for LC-PUFA supplementation with respect to an improvement in clinical symptoms among children with neuropsychiatric disorders such as ADHD, some individual studies have shown considerable shortcomings [26]. Apart from inconsistencies in the methodology, primarily diagnostic discrep-

ancies between the various studies were criticised, since the classification of symptoms in relation to comorbidities of the various neuropsychiatric clinical pictures in particular, varied from one study to another. In order to assess the clinical benefit of LC-PUFA administration, in particular ω-3 fatty acids, further-controlled clinical trials are needed. In this context, more attention should be paid to the following points:

- Long-term studies with larger patient populations and uniformly defined clinical characteristics need to be conducted in order to obtain assured findings on potential effects and to investigate long-term effects.
- The optimum LC-PUFA composition and dose (combinations of EPA, DHA, AA and GLA) needs to be established. The additional administration of mineral cofactors such as zinc, for example, should also be included in treatment strategies.
- It must be clarified whether supplementation with LC-PUFAs might be of potential use for a sub-group of affected patients with dysfunctional fatty acid metabolism. Investigations should be made in the process to establish which PUFA imbalances constitute the greatest risk factor for specific neuropsychiatric disorders among children and which causative factors affect these risk factors (e.g., choice of food, inefficient conversion from precursor substances, genetic differences, elevated PUFA metabolism rate, status of enzymatic cofactors, etc.). Investigations should be carried out to determine what duration of supplementation is required in order to correct such deficiencies or imbalances, and whether LC-PUFA supplementation is *generally* successful or *only* in the case of existing deficiencies or imbalances.
- Similarly, it is not known whether prophylactic LC-PUFA supplementation is able to lower the risk of neuropsychiatric disorders in children.
- Further studies on the combined treatment with LC-PUFAs and pharmaceutical drugs would be worthwhile, since LC-PUFA supplementation as monotherapy is—based on the current state of knowledge—not able to be recommended as *first-line treatment* for DSM-IV ADHD.
- The further investigation of correlations between biomarkers in the blood—such as lowered ω-3 fatty acid levels in erythrocytic membranes—and ADHD-associated behavioural changes following LC-PUFA supplementation are desirable.

Even though a conclusive assessment of many facts and exact information on the desirable supply of LC-PUFAs in each instance are still open, much research suggests that ω-3 fatty acids in particular play a significant role in respect to normal neurological functioning. Moreover, LC-PUFAs obviously possess therapeutic potential with regard to their effect on neuropsychiatric disorders in children. Additionally, LC-PUFAs could possibly reduce the side effects of psychotropic drugs when administered as additional treatment. On the basis of this potential, diet is growing in significance as a preventative and therapeutic means of managing such disorders. The additional consumption of LC-PUFAs therefore appears very promising in terms of their importance for the brain and nervous system of children and teenagers.

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