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Omega-3 fatty acids and brain function

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Summary

It is generally accepted that omega-3-fatty acids (n3-FAs) are important for the development, physiology and (presumably) also the perfusion of the human brain. On the other hand, the available studies do not demonstrate that n3-FAs can protect against age-related loss of cognitive performance - even though this is supported by positive epidemiological correlations. It has not been shown that n3-FAs lead to improved cognitive performance or reduce the incidence of dementia. This may be due to the host of methodological problems, rather than any inherent lack of activity. Epidemiological studies on the correlation between n3-FA intake with food and the incidence of Alzheimer's disease do not provide any valid evidence. Supplementation does not influence the incidence of Alzheimer's disease in healthy subjects and has no clinically relevant effects on patients with the disease. The same applies to Parkinson's disease. Depression is the only neuropsychiatric disease that can be demonstrably influenced by supplementation with eicosapentaenoic acid (EPA).

Future studies on the role of n3-FAs in age-related loss of cognitive performance should lay greater weight on the multifactorial pathogenesis of these conditions. They must employ realistic observation periods, and with pharmacologically based dose finding. In the near future, we can expect numerous studies on the role of n3-FAs in neuropsychiatric diseases, as indications such as depression, attention deficit hyperactivity disorder (ADHD) and learning difficulties in children open new vistas in nutritional science and are potentially of considerable economic importance.

Keywords: omega-3 fatty acids, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), fish oil, dementia, cognitive function, brain function

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Introduction

Although interest in the omega-3-fatty acids (n3-FAs) has mostly been concentrated on their possible cardiovascular effects (see article on page M596 in this issue), increasing attention is now being paid to their putative significance for cognitive function and in neurodegenerative diseases. As the prevalence of these diseases has been rising for years, we can expect a lively discussion of the role of nutrition and, particularly, of the n3-FAs in this context. The present review article presents the current state of research and explains the developments in this area.

Physiological significance

Neuronal development and brain structure

n3-FAs are essential elements in the assembly, maturation and physiological function of neuronal structures [1] (◆ Figure 1). Docosahexaenoic acid (DHA) accumulates in the brain of the fetus during neuronal development already in the third trimester of pregnancy; this process continues during the first two years of life [2, 3]. Optimal neuronal development is then highly dependent on the supply of long chain polyunsaturated fatty acids (LCPUFAs) [1]. During this maturation and growth phase, the most important LCPUFAs are DHA und arachidonic acid (AA). The breastfed baby receives these and other n3- and n6-FAs in the mother's milk [4–7]. Particularly high levels of DHA, eicosapentaenoic acid (EPA) and AA are accumulated in the phospholipids of the lipid bilayer in the brain and retina [1]. The adult human brain eventually con-tains 10–15 % DHA [8].

Neuronal function

Aside from the integral importance of DHA in brain structure, the n3-FAs EPA and DHA are also important in normal neuronal function. For example, they participate in the synthesis and activity of neurotransmitters, such as serotonin, noradrenaline and dopamine and regulate their intracellular and synaptic signal transduction. In this way, they have decisive influences on fundamental processes such as memory, cognition, emotions, sleep rhythm, pain sensitivity and sexual behavior [2, 9–14].

When the proportion of DHA in the phospholipids of neuronal membranes increases, the physicochemical properties of the membranes change, including their fluidity. This directly influences the activity of membrane-bound receptor and transport proteins, leading to changes in intercellular signal transmission [11, 12]. The n3-FAs also play an important part in other complex physiological processes in the brain, including the adaptation of the brain to external influences (neuroplasticity) and the regulation of neuronal gene expression [9–16]. Although most of these findings come from animal experiments, more recent studies in humans seem to support them [17, 18].

After the brain, the second highest concentration of DHA in the body is in the pigmented epithelium of the retina and in the photoreceptors, where DHA plays an essential role in the projection of optical stimuli to the subcortical centers [17]. As in the brain, DHA is enriched in the retina towards the end of pregnancy and during early child development. This concentration process is highly dependent on the nutritional supply of n3-FAs [17]. It has also recently been suggested that DHA may have a protective role in the pathophysiology of age-related macular degeneration (AMD) and in various retinopathies [19].

Cerebrovascular blood flow

The brain requires high levels of energy, but has low storage capacity for energy substrates. It follows that it is very important for healthy physiological brain function that both cerebrovascular perfusion and the functional reactivity of the cerebral blood vessels are adequate [18]. The importance of cerebrovascular perfusion also becomes clear on considering the pathophysiological relationships in neurodegenerative and cerebrovascular diseases, such as atherosclerosis, stroke and vascular dementia.

Glossary

antiapoptotic = acting against programmed cell death (apoptosis)

cholinergic deficit = here: impairment of the synthesis or release of the neurotransmitter acetylcholine into the synaptic gap

membrane fluidity = According to the so-called fluid mosaic model, all membrane components (lipids, proteins) continuously change their positions within the lipid double layer. If membrane fluidity increases, this means that the membrane becomes more flexible, but also that the protein complexes (e.g. receptors or transport proteins) that are embedded and stored in the lipid layer of the membrane change their positions and configuration more rapidly.

nitric oxide synthase = This enzyme catalyzes the formation of nitric oxide (NO) from the amino acid L-arginine. NO reduces blood pressure (i.a.).

presynaptic = When electrochemical stimuli pass between nerves, they must cross the so-called synaptic gap. Presynaptic means before the gap. The opposite is postsynaptic, which is after the gap.

tau protein = (from the Greek letter *tau*); a structural protein in nerve cells

The most recent human data confirm that the perfusion of defined areas of the brain is enhanced when DHA supply is increased [18, 20]; this confirms the results of animal studies [21, 22]. Possible mechanisms for this effect include an interaction between DHA and the cerebral cholinergic system and induction of NO synthase; this could lead to increased NO formation and thus to local vasodilatation [18].

According to current knowledge, this DHA-dependent increase in cerebrovascular perfusion mainly affects the cerebral cortex and the thalamus – areas of the brain involved in complex thought (cortex), personality and consciousness

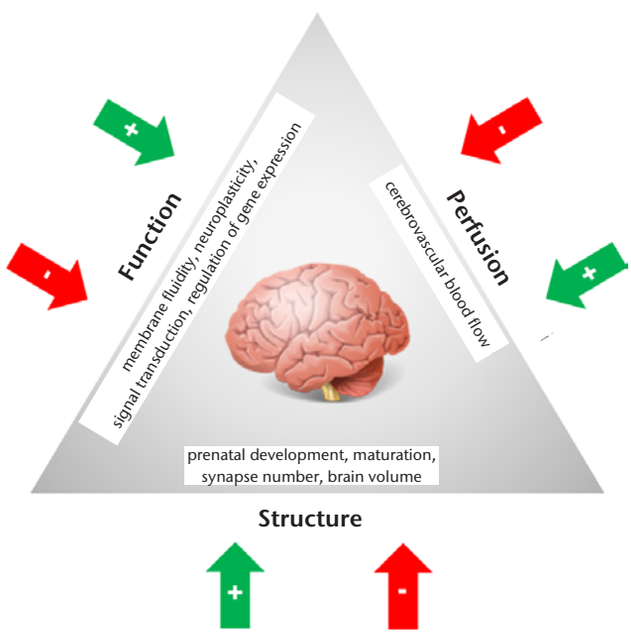

Fig. 1: **Model of the influence of different types of fatty acids on the brain** (postulated by HAAST and KILIAAN, modified in accordance with [18])
Green arrows: long chain polyunsaturated fatty acids (LCPUFAs), particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); red arrows: saturated fatty acids (SFAs). Enhancement or intensification of a parameter is marked with a (+); weakening or reduction is marked with a (-). While LCPUFAs seem to have favorable effects on the structure, function and perfusion of the brain, the effects of SFAs may be the opposite.

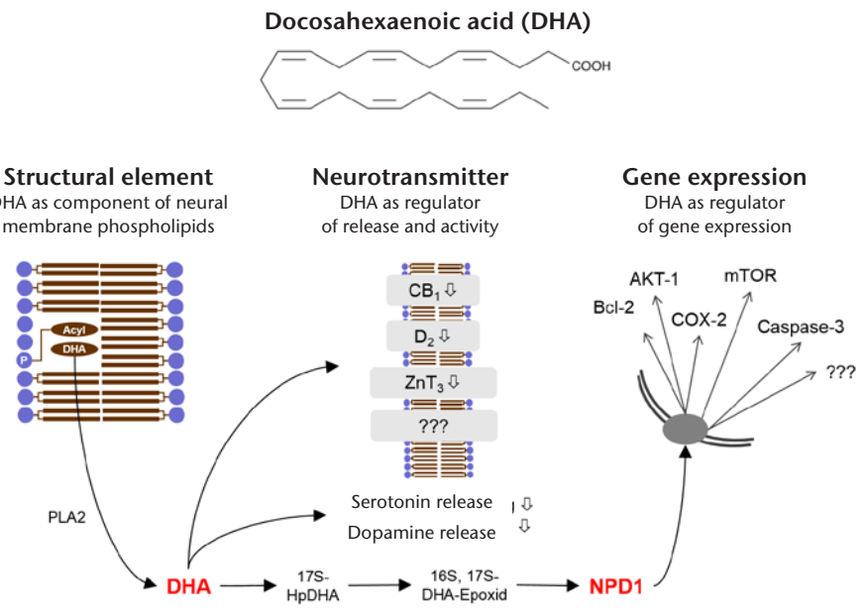

Fig. 2: **Neurophysiological functions of docosahexaenoic acid (DHA)**
Greatly simplified and schematized. DHA is a structural element of the neuronal lipid bilayer; DHA can be released from the membrane; this process is regulated by neurotrophins and catalyzed by phospholipase A2 (PLA2). DHA can regulate the activity of various neurotransmitters, either by reducing their synaptic release (serotonin, dopamine) or by acting on the expression and function of various receptors and transport proteins (CB_1: cannabinoid receptor 1, D_2: dopamine receptor 2, ZnT_3: zinc transporter 3). Through the intermediates 17S-HpDHA (17S-hydroperoxyDHA) and 16S,17S-DHA epoxide, neuroprotectin D1 (NPD1) can be formed and this influences the gene expression or post-translational modification of various regulatory proteins.
AKT-1: AK-strain transforming factor-1, neuronal survival factor, inhibits neuronal apoptosis
Bcl-2: B-cell lymphoma 2-Protein, proto-oncogene, participates in apoptosis regulation
Caspase-3: Effector caspase of apoptosis regulation
COX-2: Cyclooxygenase-2, regulator of angiogenesis and enzyme that catalyzes the formation of prostaglandin H2 from arachidonic acid
mTOR: mechanistic target of rapamycin, a key protein in the regulation of cellular survival, growth, proliferation and motility

formation [23]. This is particularly interesting in the context of cognition and the development of dementia, as recent studies indicate that cerebrovascular perfusion is reduced in those very regions during the pathogenesis of Alzheimer's disease [23]. The effect of DHA on membrane fluidity could also be relevant here. If the supply of DHA is increased, the fraction of DHA in neuronal membranes also increases, as does membrane fluidity and thus the activity of membrane-bound proteins [11, 12].

Haast and Kiliaan have proposed a model that portrays the interrelationships between fatty acid supply and the three pillars of brain health – structure, function and perfusion [18] (◆ Figure 2). According to this, LCPUFAs have favorable effects on structure, function and perfusion, while saturated fatty acids may have the opposite effects.

As n3-FAs, particularly DHA, are of considerable importance in the development, structure and evidently also the perfusion of the human brain, it is obvious to think that n3-FAs may also be involved in neuropsychiatric and neurodegenerative diseases. There is good pathophysiological evidence for the role of neuroprotectin D1 (NPD1), which is formed in the brain from DHA [19] (◆ Figure 2): NPD1 protects neurons, as it exhibits anti-apoptotic and anti-inflammatory activity and enhances neuronal resistance to oxidative stress [24–26]. In addition, NPD1 reduces the formation of die β-amyloids [24], which are components of senile plaques. The metabolic disorder linked to these plaques is regarded as the principle cause of Alzheimer's disease and other forms of dementia – together with other factors, such as changes in tau protein, reduced anti-oxidative reserves and a presynaptic cholinergic deficit [27]. It was therefore postulated that a deficit in DHA might contribute to these diseases by reducing NPD1 formation [28].

Age-related loss in cognitive performance

During physiological aging, there are decreases in the number of synapses, the number of neurons and brain volume [27]; there is a parallel decrease in cognitive performance [29–33]. Thus, gray matter starts to decrease at the age of 20 and white matter at about the age of 40 [27]. The DHA concentration in the brain also decreases with increasing age. Because of the known neurophysiological functions of DHA, a causal relationship would be conceivable, as DHA is known to be a neurotrophic growth factor [34], which improves neuroplasticity and stimulates the formation of new synapses [35–37].

On the other hand, there have been very few studies on the possible effect of n3-FA supplementation on the cognitive performance of healthy old people [38]. In fact most of the available data on the improvement of cognitive performance have been taken from animal experiments [39, 40]. The available human data on the effect of nutritional DHA supply on brain structure do in fact demonstrate an increase in gray matter

and a greater brain volume after an increase in DHA uptake. On the other hand, there were no clinically relevant endpoints in these studies, which were restricted to radiological volume measurements [23]. It is nevertheless interesting that the increase in gray substance after a DHA-enriched diet was particularly marked in the so-called corticolimbic loop, an area of the brain that is decisive in the generation and processing of emotions; when this area is malfunctional, this apparently plays a dominant pathophysiological role in various psychiatric diseases [27]. Parallel studies with a diet rich in trans-fatty acids demonstrated that this form of diet led to a decrease in brain volume and accelerated brain atrophy in healthy adults [41].

There have only been a few interventional studies in man which have examined the effect of n3-FA (DHA alone or DHA+EPA) on cognitive performance in age. These have given inconsistent results, with respect to both the presence of any effects and their size [42–47]. This conclusion was confirmed by a Cochrane review in 2012. In healthy subjects aged over 60 years, no efficacy was found with respect to improvements in cognitive performance or reduced incidence of dementia [48].

Some recent meta-analyses have found different results and may indicate that EPA/DHA does exhibit efficacy. On the other hand, these meta-analyses too could not rectify the methodological problems of the corresponding original studies. For example, Abubakari et al. performed a meta-analysis of the available studies and concluded that low dosed n3-FA supplements (< 1.7 g/d) improved memory, but not high doses (> 1.7 g/d) [49]. The value of these conclusions does however appear questionable when, as in this case, no distinction was made between the different n3-FAs, fish oil and combination preparations, or between Alzheimer's disease and other forms of dementia. In addition, the authors of a current meta-analysis show that supplementation with DHA can improve the episodic memory of healthy subjects, best at dosages between 500 and 1,000 mg/d [50]. However, this conclusion only applies to healthy subjects with mild memory complaints, not to subjects without subjective memory problems or to patients with diagnosed dementia.

Alzheimer's disease

Brain tissue from Alzheimer's patients contains not only raised concentrations of β-amyloids, but decreased concentrations of DHA and NPD1 [19, 27]. This mainly affects areas involved in learning and memory [51].

Although there is extensive neurophysiological knowledge that is intended to demonstrate the importance of DHA for Alzheimer's pathogenesis, this comes exclusively from studies on mouse models [21, 52–54]. However, observational studies with Alzheimer patients indicate that there may be a converse relationship between the quantity of DHA ingested daily with food and the prevalence of Alzheimer's disease [55, 56]. There is also evidence that a Mediterranean diet may reduce the risk of developing Alzheimer's disease [57–60]. However, the results of even these purely observational studies are inconsistent [61–66].

The possible inter-relationships are highly complex and certainly cannot be reduced to the simple conclusion that "more n3-FA in food corresponds to a reduced risk of Alzheimer's disease" [67].

Methodological problems

Aside from the possibility that n3-FAs have in fact no efficacy on age-related loss of cognitive ability, there are numerous methodological reasons for the observed negative result (see text).

Firstly, the intervention period was always only a few weeks to a maximum of 24 months.

Secondly, a wide variety of doses were used (DHA: 176–1,720 mg/d; EPA: 200–1 500 mg/d). More reliable conclusions may be possible if future long-term studies employ dosages that have previously been differentiated by testing. In this context, there are particular problems with studies that do not employ isolated n3-FA at a defined dose, but unspecified fish oil. This contains not only n3-FA, but numerous other components (e.g. vitamin D) that might be active or influence activity. Moreover, the composition of fish oil preparations may depend on the type of fish, area of catch and purification procedures, so that it is virtually impossible to compare the results.

Thirdly, it is difficult to measure human "cognitive ability" in a valid manner. There are in fact numerous different test procedures that are intended to record either overall cognitive aspects or specific individual abilities, such as recognition or vocabulary [17]; it is therefore hardly possible to compare the results of different test procedures.

Fourthly, there is considerable heterogeneity between the cognitive function of the subjects or patients examined (baseline function) and this makes it more difficult to identify subgroups who might benefit. Because of the methodological difficulties, there are no epidemiological observational studies on correlations between nutritional habits (including the ratio of n3-/n6-FAs) and the endpoint of age-related loss in cognitive performance, although this has been attempted for Alzheimer's disease (see below).

This is even more the case when the role of Mediterranean nutrition is discussed. Even future epidemiological studies are not expected to provide any important new insights, as there are multifactorial links between the pathogenesis of Alzheimer's disease and the neurophysiological activity of n3-FA. Bearing in mind that a host of factors are now recognized and that the pathogenesis of Alzheimer's disease extends over decades, it would be methodologically practically impossible to plan a randomized controlled study in which all relevant lifestyle factors were held constant aside from n3-FA supply.

The results of interventional studies are less ambiguous than those of observational studies. They consistently show no effect of n3-FA supplementation – either for the incidence of Alzheimer's disease [48] or for clinically relevant endpoints for patients already diagnosed with Alzheimer's disease [55, 56, 68–70]. Nevertheless, the significance of these results is also restricted by the fact that the interventions lasted for a maximum of a few months. As with the studies on age-related loss of cognitive performance, future studies on the interaction between n3-FAs and Alzheimer's disease must consider both the multifactorial pathogenesis and the length of the observational period [71].

Parkinson's disease

The situation is similar for the studies on the possible efficacy of n3-FAs in Parkinson's disease. Numerous laboratory studies and work on mouse models have shown that DHA shows neuroprotective effects on dopaminergic neurons and also exhibits anti-inflammatory activity [72–78]. Moreover, DHA can reduce dopamine deficiency dyskinesia in animal models of Parkinson's [79, 80]. However, as yet there has been no reliable study that demonstrates that n3-FA supplements or n3-FA rich nutrition have a protective or even therapeutic effect in patients with Parkinson's disease.

Neuropsychiatric diseases

The best available data on the clinical efficacy of n3-FAs are on the use of EPA supplements in depression. Thus, several large meta-analyses of placebo-controlled interventional studies have shown that the daily administration of EPA (200–2 200 mg/d), but not of DHA, causes a measurable reduction in the symptoms of depression [81–83]. For combined supplements, the dosage is important, as is the ratio of the individual n3-FAs; the EPA/DHA ratio must be at least 60 % [81]. There is currently intensive research on the underlying mechanisms.

Because of this favorable data on the treatment of depression, the efficacy of n3-FA supplementation has now been examined for virtually all neuropsychiatric diseases, including bipolar disorders [84], borderline disorder [85], schizophrenia [86], autism [87], learning disorders in children [88] and attention deficit hyperactivity disorder (ADHD) [89]. As yet, there is no proof that n3-FA nutrition or supplementation exhibits clinical activity for any of these indications. On the basis of the current data, it is impossible to predict whether any practicable therapeutic benefit will be identified in future.

Pregnancy

In contrast, there is comprehensive proof that an adequate supply of n3-FAs – particularly DHA – is important for the visual and cognitive development of the child [17, 19]. The importance of DHA in vision and the dependency on DHA concentration in photoreceptors have already been discussed (vide supra). Thus, above average supply of DHA during pregnancy has favorable effects on the child's visual acuity, cognitive functions, sleep patterns and fine motor skills [6, 90–92].

However, recent studies have called this view into question and have shown that the advantages of DHA supplementation can only be established for the first months of a child's life. They level off in older children and are presumably negligible in the first years of life in comparison to environmental effects [93]. These conclusions must be confirmed by further studies. Until then, pregnant and nursing mothers should ensure that their children receive at least 200 mg DHA daily. If this value cannot be reached through regular consumption of fish, appropriate supplements should be used [90, 94].

Conflict of Interest
Prof. Smollich has received lecture fees from Bayer Vital AG.

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