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Review

n-3 LCPUFA improves cognition: The young, the old and the sick

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ABSTRACT

Due to the implication of docosahexaenoic acid (DHA) in neurogenesis, synaptogenesis, neurite outgrowth and to its high incorporation into the brain, this n-3 long chain polyunsaturated fatty acid (LCPUFA) is considered as crucial in the development and maintenance of the learning memory performance throughout life. In the present chapter we aimed at reviewing data investigating the relation between DHA and cognition during the perinatal period, young adult- and adulthood and neurodegenerative diseases such as Alzheimer disease (AD). In Humans, dietary DHA supplementation from the perinatal period to adulthood does not reveal a clear and consistent memory improvement whereas it is the case in animal studies. The positive effects observed in animal models may have been enhanced by using n-3 PUFA deficient animal models as controls. In animal models of AD, a general consensus on the beneficial effects of n-3 LCPUFA in attenuating cognitive impairment was established. These studies make DHA a potential suitable micronutrient for the maintenance of cognitive performance at all periods of life.

1. Introduction

Docosahexaenoic acid (DHA) is a 22-carbone polyunsaturated fatty acid (PUFA) from the n-3 series. It is synthesized from alpha-linolenic acid (ALA, 18:3 n-3), an essential PUFA, by desaturation and elongation steps. It is found mainly in marine products. Technically, humans can synthesize DHA from ALA that is found in vegetables but the conversion efficiency is very low ($< 1\%$) even in healthy adults [1,2]. Several fatty fishes are rich in DHA and can be directly provided through the diet under preformed DHA. Hence, due to its numerous properties, DHA is considered as essential for humans.

DHA is highly concentrated in the adult brain (15–20% of the lipids of the rodent brain) [3,4]. Most DHA accumulates in the brain during the perinatal period from the beginning of the third trimester of gestation to 2 years in humans and from prenatal day 7 to postnatal day 21 in rats at the same time that rapid neuronal maturation, synaptogenesis and gray matter expansion occurred [5–9]. Moreover, normal aging is characterized by a loss of memory and cognitive functions [10] and by a decrease in biomarkers of brain DHA level [11,12]. These two periods of life are then particularly sensitive to the n-3 PUFA intake. Nowadays, it is generally considered that human diet is typically unbalanced in n-3 PUFA [13]. This was reflected in the high n-6/n-3 ratio [14].

DHA is likely to affect brain by several possible mechanisms. It has been shown to cross the blood brain barrier and to play critical roles in neuroplasticity, the promotion of neurogenesis, neurite outgrowth and synaptogenesis, maintenance of membrane fluidity, the dowregulation and the resolution of inflammation but also pathological mechanisms of several neurodegenerative diseases such as Alzheimer's Disease (AD) [13,15]. All these

Abbreviations: AA, Arachidonic acid (20:4 n-6); AD, Alzheimer's disease; AHA, American Heart Association; ALA, Alpha-linolenic acid (18:3 n-3); ApoE, apolipoprotein E; APP, Amyloid precursor protein; BSID, Bayley Scales of Infant and Toddler Development; CHD, Coronary heart disease; CREB1, CAMP responsive element binding protein 1; DHA, Docosahexaenoic acid (22:6 n-3); E-DHA, Ethyl-DHA; DQ, Developmental Quotient; DPA, Docosapentaenoic acid (22:5 n-6); EPA, Eicosapentaenoic acid (20:5 n-3); E-DHA, Ethyl-docosahexaenoic acid; E-EPA, Ethyl-eicosapentaenoic acid; FTII, Fagan test of Infant Intelligence; IQ, Intellectual quotient; K-ABC, Kaufman Assessment Battery for Children; KPSDSI, Knobloch Passamanik and Sherrards Developmental Creening Inventory; LA, Linoleic acid (18:2 n-6); LCPUFA, Long chain polyunsaturated fatty acids; LTP, Long term potentiation; MDI, Mental Development Index; MRI, Magnetic resonance imaging; PDI, Psychomotor Development Index; PSD 95, Post-synaptic density protein 95; PUFA, Polyunsaturated fatty acids; RCT, Randomized controlled trial

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mechanisms may impact on learning memory performance. In this chapter, we will focus on the role of DHA in cognition from normal physiological to pathological processes, in particular in AD.

2. DHA improves cognition during the perinatal period

During late gestation and early post-natal life, the neonate's brain experiences a tremendous increase in growth and cellular proliferation termed the "brain growth spurt". For this rapidly growing infant, there is a high demand for complex lipids, such as DHA and arachidonic acid (AA), to form vital cell membrane structures [5].

Human fetuses and young infants have a limited ability to synthesize n-3 LCPUFA *de novo* and are supplied *via* maternal (placental transfer, breast milk) or external (enriched formula) sources. The recent decline in n-3 LCPUFA consumption relative to n-6 LCPUFA in many Western countries has raised concern about its potential detrimental effects on the neurodevelopment of human infants [16]. The question of whether a dietary supply of DHA and AA confers advantages to cognitive development in infants has thus been the subject of intense research for several decades (for review, [17,18]).

2.1. Evidence in humans

Lots of studies evaluated the effects of n-3 LCPUFA, like DHA, supplementation of pregnant and/or lactating women on the neurodevelopment of their children.

Levels of DHA in erythrocytes membrane is related to the DHA enrichment of brain phospholipids as demonstrated by Makrides et al. from necropsies [19]. Thus, most of the clinical studies made this extrapolation, using the child DHA phospholipids fraction in plasma (or, alternatively, in erythrocytes) as a proxy for the brain DHA concentration, and correlated it to cognitive abilities.

2.1.1. Supplementation during pregnancy (Table 1)

The studies vary according to the daily dose of n-3 LCPUFA (135–2200 mg/d) and the onset of supplementation (from 20–27 weeks of gestation). The source of the DHA is fish oil capsules [20–22], cereal-based bars enriched with DHA [23] or eggs [24]. Child neurodevelopment is assessed using different tests, such as the Bayley Scales of Infant and Toddler Development (BSID), Mental Development Index (MDI) and/or Psychomotor Development Index (PDI) [21,22], single-object attention task and a distractibility task [24], the Griffiths Mental Development Scales; Peabody picture Vocabulary test [20], the 2-step problem-solving test from Willatts and the Fagan Test of Infant Intelligence, for recognition memory [23]. All these Randomized Controlled trials (RCTs) report data on the effects of n-3 LCPUFA supplementation during pregnancy on the neurodevelopment of children at the ages of 9 months [23], 10 months [22], 12–18 months [21,24] and 30 months [20].

No harmful effect on the mother or the neonate of n-3 LCPUFA supplementation during pregnancy was ever mentioned [25]. While some of the studies revealed that n-3 LCPUFA supplementation had a significant effect on the cognitive performances (problem-solving tasks [23], attention measures and distractibility performances [24]), others could not find any differences between supplemented and control groups regarding motor, language, and cognitive development [20–22].

2.1.2. Supplementation during lactation (Table 2)

For the most part, the researchers who carried out RCTs use measures of (1) general intelligence with the BSID, MDI, Brunet–Lezine Developmental Quotient (DQ), problem solving, Knobloch Passamanik and Sherrards Developmental Screening Inventory (KPSDSI), Fagan Test of Infant Intelligence (FTII), (2) verbal ability

Table 1
Intervention studies of the cognitive development in term infants in relation to DHA supplementation during gestation.

Dose of DHA	Source of DHA	Duration	Participants	Cognitive test	Age of cognitive assessment	Outcome	Study	Effect on cognition
135 mg/egg 8463 mg total	DHA-enriched eggs	Last trimester to delivery	77	Single object attention Distractibility	12–18 mo	More mature developmental profile on single object attention. More optimal performance on distractibility	Colombo et al. [24]	+
214 mg/d	Cereal-based bars enriched with DHA (DHA/EPA 8:1)	Weeks 24 to delivery	30	2-step problem solving Fagan test of Infant Intelligence	9 mo	Beneficial effects on the performance of problem-solving tasks. No beneficial effects in Fagan test	Judge et al. [23]	+
4 g/d	Fish oil capsules (DHA+EPA)	Last trimester to delivery	249	BSID	10 mo	No beneficial effect on mental or psychomotor development	Tofail et al. [22]	No
2.2 g/d	Fish oil capsules (DHA/EPA 2:1)	Weeks 20 to delivery	72	Griffiths Mental Development Scales Peabody Picture Vocabulary test	30 mo	Eye-hand coordination favored. No clear effect on cognitive scores	Dunstan et al. [20]	No
800 mg/d	Fish oil capsules (DHA/EPA 8:1)	Weeks 19 to delivery	2399	BSID	12–18 mo	No effect on mean composite cognitive and language scores	Makrides et al. [21]	No

BSID, Scales of Infant and Toddler Development; d, day; DHA, docosahexaenoic acid; mo, months; no: no effect; +: positive effect.

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Table 2
Intervention studies of the cognitive development in term infants in relation to DHA supplementation during lactation.

Dose of DHA	Source of DHA	Duration	Participants	Cognitive test	Age of cognitive assessment	Outcome	Study	Effect on cognition
17 mg DHA/100 kcal + 34 mg AA/100 kcal	Algal or tuna oil (DHA or DHA/EPA 3:1) Fungal oil	3 or 12 mo	361	BSID	18 mo	Improvement of mental and psychomotor development	Clandinin et al. [45]	+
0.1-1.7% of total FA	Breast-fed; oil with pure DHA to mothers (DHA-rich algal oil)	From birth to 12–24 mo	52	BSID	12–24 mo	Early DHA may be positively related with BSID scores at 12 mo. No long-term effects of infant DHA status on neurodevelopment	Gibson et al. [31]	+
Unknown	LCPUFA enriched-formula from milk fat, vegetable oils and egg lipids (DHA + ARA)	From birth to 4 mo	60	Brunet-Levine graded psychomotor development test	4 mo	DHA in erythrocytes correlated with DQ	Agostoni et al. [26]	+
0.35% of total FA	LCPUFA enriched-formula from algal oil (DHA + ARA)	From < 5 d to 17 weeks	56	BSID	18 mo	Significant increase of the Mental Development Index	Birch et al. [30]	+
0.5% lipids (5% lipid diet)	Tuna fish oil (DHA/EPA 5:1) + GLA (0.9% lipids)	9 mo	238	BSID	18 mo	No difference in neurocognition outcome +5.7 points advantage in boys on MDI	Fewtrell et al. [44]	+
200 mg/d	Algal TG DHA capsules	From birth to 4 mo	230	BSID Gross motor development, language and visual-motor problem solving abilities	30 mo 12 and 30 mo	No effect on PDI. No effect on MDI No effect	Jensen et al. [38]	No
Unknown	LCPUFA enriched-formula from milk fat, vegetable oils and egg lipids (DHA + ARA)	From birth to 24 mo	81	Brunet-Levine graded psychomotor development test	24 mo	The diet/DQ association found at 4 mo was not predictive of DQ scores at 24 mo	Agostoni et al. [27]	No
0.2% of toal FA	LCPUFA enriched-formula; DHA from fish oil (DHA + EPA) ± ARA (from egg)	From < 7 d to 4 mo	274	BSID MaCArthur Communicative Development Inventories	12 mo, 14 mo	No effect on mental psychomotor neurodevelopment. Detrimental effects on language	Scott et al. [35]	No
0.32% of total FA	LCPUFA enriched-formula from egg phospholipid and triglyceride fraction (DHA + ARA)	From < 7 d to 6 mo	447	Knobloch, Passamanick and Sherrards test BSID	9 mo, 18 mo	No effect on cognitive or motor development at both ages.	Lucas et al. [32]	No
0.35% of total FA	LCPUFA enriched-formula (DHA/DHA + ARA)	From < 7 d to 12 mo	68	BSID	12 mo, 24 mo	No effect on cognitive or motor development at both ages	Makrides et al. [33]	No
0.14% of total FA	LCPUFA enriched-formula from fish oil or fungal oil (DHA + ARA)	From < 9 d to 12 mo	239	Fagan test of Infant Intelligence BSID MaCArthur Communicative Development Inventories	6–9 mo, 6–12 mo, 9–14 mo	No effect on global neurodevelopment at any age	Auestad et al. [28]	No
2.7 g/d	Fish oil capsules (60% DHA)	From birth to 4 mo	175	Means-end problem-solving test MaCArthur Communicative Development Inventories	9 mo, 1–2 y	No effect on problem solving. Passive vocabulary at 1 y lower in the supplementation group. No differences were found at 2 y.	Lauritzen et al. [39]	No
250-280 mg	Fish oil capsules (DHA/EPA 4:1)	From birth to 6 mo	420	MaCArthur Communicative Development Inventories BSID	12–18 mo	Benefits to early communicative development. No effect on global neurodevelopment at any age	Meldrum et al. [34]	No

ARA: arachidonic acid; BSID, Scales of Infant and Toddler Development; d, day; DHA, docosahexaenoic acid; LCPUFA, long chain polyunsaturated fatty acids; mo, months; no: no effect; y, year; +: positive effect.

with the MacArthur Communicative Development Inventories and (3) motor skills with the BSID PDI.

Most of the RCTs studied formula-fed infants with a dose of DHA ranging from 0.1 to 1.7% of total fatty acids. Standard formula-fed and/or breastfed infants were used as controls. Supplementation started in the first days of life and lasted from 6 weeks up to one year. The developmental impact of the diet was assessed at various time points between 3 and 30 months of age [26–37]. Two RCTs exclusively studied breastfed children. Mothers were given DHA from fish oil or algal oil capsules (200 mg or 4.5 g/day). Controls were given vegetable oil with no DHA [38,39].

These trials have yielded mixed results in term children. Relative to infants fed control formulas, infants supplemented with DHA formulas showed either improved global cognitive function [26,30,36,40] or no significant differences [27–29,31–35,37–39]. Language production and comprehension in relation to DHA supplementation have been assessed with mixed results [28,29,34,35,39]. In one study, supplemented infants who were born at term were not significantly different from those fed control formula [29,34]. However, in other studies, the group of infants supplemented with only DHA (compared with supplementation with DHA and AA) [35] or when mothers were supplemented with fish oil [39] actually showed lower language production at 12 and 14 months of age, as reported on the MacArthur Communicative Development Inventory, than did those fed the control formula. The effect was not evident when these infants were reaching 24 or 39 months of age [28,39]. Finally, in one study, the Bayley Psychomotor Development Index of the supplemented group was higher at 30 months of age, though the Mental Development Index was similar [38]. One prospective study correlated the DHA status of breast-fed term gestation infants, in the absence of any supplementation, to developmental indices [41]. They showed that the DHA status of children was significantly related to measures of language development, assessed as the ability to discriminate non-native consonant contrasts. No statistically significant relations were found between the infant DHA status and test scores for novelty preference, Bayley's MDI or PDI, or the object search task [41].

Interestingly, Cohen et al. (2005) aggregated results from eight RCTs representing ten of the publications cited above [26–28,30–33,35–37] comparing cognitive development in controls and in children who had received n-3 PUFA supplementation (seven studies of formula supplementation and one study of maternal dietary supplementation). They assigned study weights accounting for statistical precision, relevance of three endpoint domains (general intelligence, verbal ability, and motor skills) to prediction of Intellectual Quotient (IQ), and age at evaluation. The study estimated that increasing maternal DHA intake by 100 mg/day increases child IQ by 0.13 points.

Several studies specifically assessed beneficial effects of LCPUFA supplementation in preterm infants' populations. High-DHA (0.26% to 1% of total fatty acids) enteral feeds were compared with standard DHA starting the first days of life. Supplementation stopped at the term corrected age [42,43], 9 months [44] or 21 months [45]. The source of the DHA was fish oil [42–45] or algal oil [45]. All infants were tested at 6, 9, 12, 18 or 27 months corrected age using the Bayley MDI and/or PDI. One study also used the Fagan test of novelty preference [43]. Only one of these studies showed improved global cognitive function (Bayley scales) for infants supplemented with DHA formulas [45]. Global analyses showed no significant differences in the other studies [42–44]. However, when going into details, some positive effects have been shown either for girls [42], or only for boys [44] with the Bayley scales. O'Connor et al. showed no positive effects of DHA supplementation on the Bayley score but performances were greater on the Fagan test of novelty preference in LCPUFA supplemented infants compared to controls.

Table 3
Intervention studies of the cognitive development in term infants in relation to DHA supplementation during gestation and lactation.

Dose of DHA	Source of DHA	Duration	Participants	Cognitive test	Age of cognitive assessment	Outcome	Study	Effect on cognition
1.183 g	Cod liver oil to mothers	From 18 w of gestation to 3 mo after delivery	84	Kaufman Assessment Battery	4 y	Higher mental processing scores	Helland et al. [48]	+
As above	As above	As above	341	Fagan test	6–9 mo	No effect on cognitive development	Helland et al. [46]	No
As above	As above	As above	143	Kaufman Assessment Battery	7 y	No effect on mental processing	Helland et al. [47]	No

DHA, docosahexaenoic acid; mo, months; no: no effect; y, year; +: positive effect.

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2.1.3. Supplementation during both pregnancy and lactation (Table 3)

Three publications from the same group reported on the neurodevelopment of children born to mothers supplemented with cod liver oil (containing 1183 mg of DHA and 803 mg of eicosapentaenoic acid, EPA) or corn oil from the 18th week of gestation until 3 months after delivery while breast-feeding [46–48]. All of the studies assessed the same population of children but at different time points (6 months, 9 months, 4 years and 7 years). The Fagan test for novelty preference assessment was used as an indicator of cognitive function at 6 and 9 months of age and no difference were found between the two groups [46]. As part of the protocol, some of the children were invited for intelligence testing with the Kaufman Assessment Battery for Children (K-ABC) at 4 years and 7 years of age as an indicator of the child's style of problem solving and information processing. DHA compared with corn oil supplementation also did not result in significantly different attainment on all of the scales of the K-ABC at 4 years [48] and at 7 years of age [47]. However, children born to mothers who received the DHA supplementation *versus* corn oil scored higher on the Mental Processing Composite of the K-ABC at 4 years of age, yet the difference between groups was of borderline statistical significance.

2.1.4. Conclusions from clinical studies and limitations

Evidence from RCTs does not demonstrate a clear and consistent benefit of maternal n-3 LCPUFA supplementation on the neurodevelopment of the offspring. A few studies did show favorable effects of n-3 LCPUFA supplementation on some domains of child development. However, these effects often referred to only one specific aspect of infant development without affecting the others or disappeared during subsequent assessments. Several possible explanations for the inconsistent results exist, the first one being that effects do not exist. Here are other possibilities:

(1) *Lack of sensitivity of the tests*. The inconsistent results could be related to the use of inappropriate measures of cognition. Early global measures of development, such as those commonly used in research of DHA supplementation (eg, the BSID or Brunet–Lezine's Scale), are a general rubric against which one can judge overall development. These tests were originally designed to identify those who were developing non-typically as quantified by tests of age-normed milestones. As such, the global measures do not allow for the assessment of specific independent cognitive processes (such as attention, memory, inhibition, or higher-order functions), and they may not be sensitive to manipulations that produce specific effects. It is possible that differences between infants supplemented with DHA and those fed control diet may not be evident when global measures are used but might be detectable if outcomes focus on specific abilities that underlie cognitive development (for review see [49]).
(2) *Study design issues*. Most of the cited studies used inadequate sample sizes. The LCPUFA composition of enriched and control diets, the source and dose of DHA, as well as the time of exposure to DHA were highly variable, leading to heterogeneous paradigms, thus likely to heterogeneous results. Fish oils contained EPA and DHA in concentrations varying with the source and the process. They also contained other nutrients such as vitamins that are not deprived of effects per their own.
(3) *No follow-up studies:* Only one of the included studies (performed in the same group of patients) assessed the neurodevelopment of children after 3 years of age. These studies showed no benefit of n-3 LCPUFA supplementation up until 7 years of age [47,48]. There is, therefore, a need for more follow-up studies in preschool and school-age children.
(4) *Western countries only.* Most of the trials were performed in developed countries in presumably well-nourished mothers. Therefore, the lack of an effect also could be explained by a sufficient baseline n-3 LCPUFA supply to support adequate infant neurodevelopment.
(5) *Genetic background.* In addition, it should be considered that the effects of n-3 LCPUFA supplementation might be offset by the genetic background of the studied population. One study demonstrated variations in fatty acid desaturase genes, which are responsible for differences in plasma and erythrocyte lipid levels in pregnant women and in breast milk. Genetic variants can contribute to maternal-to-infant n-3 fatty acids transfer; thus, it is possible that to obtain the clinical effect of DHA supplementation, the dose must be tailored to the subject's genetic background [50].
(6) *Consider the developmental stage of children and not their actual age*. It is the general view that girls with respect to most skills mature faster than boys. The test has to be in accordance with the maturational stage of the children and may better detect differences between infants at a specific stage of development. Moreover, the apparent sex difference noted in some of the publications may be a coincidence not reflecting a difference in cognitive abilities, but rather small sample size or other sex differences, e.g. in accordance with the test.

2.2. Evidence in animals

Due to the urgency of the topic, effects of n-3 PUFA deficiency and supplementation on cognitive development have been extensively researched in basic experimental studies with rodents [18,51]. A significant advantage of animal studies is that more experimental control over factors such as maternal or pup nutritional status or genetic background can be achieved, without the complicating aspects of demographic status. Furthermore, factors that potentially confound a valid measure of cognitive performance, such as anxiety, can be more easily controlled. On the other hand, animal studies are often biased towards the male sex, but studies suggest that there could be important sex difference in effects of n-3 intake on cognition [14].

In general, brain DHA deficiency is induced by feeding an n-3 fatty acid-deficient diet *in utero* (*via* the maternal intake) and throughout life for two to three generations. Most DHA accumulation in the brain takes place during brain development from prenatal d7 to postnatal d21 in rats. Dietary restriction of only n-3 fatty acids (ALA, DHA and metabolic intermediates) does not grossly affect development or growth, but leads to a decrease of the brain and other organ levels of DHA, region specifically (frontal cortex and hippocampus being more susceptible), with a reciprocal increase in the n-6 docosapentaenoic acid (DPA) in the adult nervous system [51–57].

2.2.1. Behavioral observations (Table 4)

Cognitive assessments in rodents were performed with maze-tests such as the Barnes circular maze or the Morris water maze but also passive/active avoidance. All these tests depend on the activity of the hippocampus.

In the Morris water maze, animals need to find a hidden platform in a circular tank filled with water and remember its position using the extramaze cues (place or spatial version) or intramaze cues (cued version). Because of the motivation of escaping from the water as quickly as possible, the Morris water maze is a good tool for assessing hippocampus-based spatial learning memory performance [58]. The spatial learning ability test (place or spatial version) may address

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Table 4
Studies on the effect of developmental n-3 supplementation/deficiency on cognition in rodents.

Nutritional intervention period	DHA concentration	Form of DHA	Duration	Strain/species	Cognitive test	Age of testing	Outcome	Study	Effect on cognition
Gestation+Post-natal supplementation	40 mg/100 g diet	Pellets (DHA+ARA 2:1 or 1:1)	From G0 to adulthood	Swiss OF1 mice	Morris Water Maze Active avoidance	7–11 w, 9–11 mo, 17–19 mo	Spatial memory improved in mature mice. Improvement in avoidance test in juvenile	Carrié et al. [3]	+
Gestation+Post-natal deficiency	1.3 g/100 g diet	Pellets (DHA)	Over 3 generations	Long Evans rats	Morris Water Maze	9–13 w	n-3 adequate diet restored impairment at both ages.	Moriguchi and Salem [67]	+
Post-natal supplementation	1% total FA	Gavage (DHA+ARA)	From 8 d to weaning	Wistar rats	Passive avoidance	Adults	Repletion with DHA restored cognitive performances	Garcia-Catalayud et al. [63]	+
Post-natal deficiency	0.36 g n-3 LCPUFA/100 g milk (lactation) 3.2 g n-3 LCPUFA/100 g diet (at weaning)	Artificial rearing (lactation) Pellets (at weaning) (DHA+n-6 DPA)	From birth to 9 w	Long Evans rats	Morris Water Maze	9 w	Repletion with DHA restored cognitive performances	Lim et al. [64]	+
Gestation+Post-natal supplementation	7.7% total FA	Pellets (DHA/ALA 1:3)	From G0 to 60 d	Sprague-Dawley rats	Morris Water Maze	60 d	Spatial and working memory best in supplemented rats	Fedorova et al. [60]	+
Post-natal supplementation	2.5% total FA	Artificial rearing (DHA ± ARA)	From >5–18d to 9 w	Long Evans rats	Morris Water Maze	6–9 w	Performance on spatial learning and memory was not different between groups	Wainwright et al. [66]	No
Gestation+Post-natal supplementation	1 g/kg body weight of n-3 LCPUFA	Gavage with juice (DHA/EPA 1:2)	From G0 to 60 d	Sprague-Dawley rats	Passive avoidance	21–90 d	No effect on learning and memory performances	Coluccia et al. [65]	No
Gestation+Post-natal deficiency	1.28 g/100 g diet	Pellets (DHA)	From G0 to 8 w	Long Evans rats	Barnes Maze	8 w	Slight differences between groups in the initial learning phase. Both groups performed equally well by the last day of training	Fedorova et al. [59]	No
Post-natal deficiency	1% Total FA (lactation); 2.5% n-3 LCPUFA of total FA (at weaning)	Artificial rearing (lactation), Pellets (at weaning) (DHA/EPA 40:60)	From birth to 7 w	ICR mice	Barnes Maze	7 w	Impaired learning in the reference-memory version. No differences in the cued and working memory version.	Chung et al. [53]	−

d, day; DHA, docosahexaenoic acid; DPA: docosapentaenoic acid; FA, fatty acids; LCPUFA, long chain polyunsaturated fatty acids; mo, months; no: no effect; w, week; +: positive effect; −: negative effect.

working memory, i.e., memory for the specific details of a particular session, or reference memory, which refers to learning the rules associated with a task. In the cued version of the water maze, the location of the platform is indicated by some prominent visual cue attached to the platform. A difference in the performance on this task is used as an indication of alterations in the sensory, motor or motivational attributes of the animal. The latter control is even more important considering that clinical and animal studies have demonstrated that n-3 PUFA were essential for normal development of vision [17]. A disadvantage of the Morris water maze is that the stress, evoked by the water, may interfere with memory performance. Thus, compounds that reduce stress, such as n-3 PUFA could affect memory performance indirectly, rather than having a direct cognitive-enhancing effect. Conversely, deficiency of n-3 PUFA would have a stronger effect in the water maze [59,60].

The Barnes circular maze is similar to the Morris maze in that both tests require an escape response [61]. The maze consists of a circular platform raised above the floor level with holes evenly spaced around the circumference. Animals are trained to locate a black escape tunnel beneath one of the holes in response to an aversive sound and light stimuli. The basic function of Barnes maze is to measure the ability of a mouse to learn and remember the location of a target zone using a configuration of distal visual cues located around the testing area. This task is dependent on the intrinsic inclination of the subjects to escape from an aversive environment and on hippocampal-dependent spatial reference memory.

Avoidance tasks are widely used to investigate the effects on learning/acquisition or memory processes. They evaluate the memory of an aversive event. The stimulus is generally a mild foot shock and the response is avoidance of the location in which the footshock was received. There are two types of avoidance tasks, active and passive avoidance. Passive avoidance usually uses a step-through-type apparatus, consisting of two compartments, one dark and one illuminated. An animal is placed in the illuminated compartment and allowed to enter the dark one where an electroshock is delivered through the floor. The next day an animal is again placed in the illuminated compartment and the step-through latency to enter the dark compartment is measured. Natural rodent behavior is to look for a dark hidden place but the negative experience associated with the dark compartment should prevent the animal from entering it or at least delay the entry. This task is called passive avoidance, because the animal is not required to make any active response, it may remain in the same compartment in order to avoid electroshock. An active avoidance test also uses a two-compartment apparatus the animal is expected to respond to the electroshock by actively escaping to the other compartment.

As for clinical studies, regarding the mode of administration, the dose, the time of exposure or the form of LCPUFA, animal studies are highly heterogeneous:

In supplementation experiments, the source of DHA varies between fish oil [53,62], high-DHA containing milk [63,64], high-DHA containing fruit juice [65] or single cell microbial oil [66]. In n-3 deficiency experiments, LCPUFA are provided through flaxseed oil [59,60,67] to get n-3 adequate diets.

In most studies, dams are fed during pregnancy and lactation with diets under the form of pellets [59,62,64,67] or by gavage [53,65]. After weaning, pups are maintained under the same pellet diet [59,60] or fruit juice diet [65] as their dams. In some cases, pups are fed through an artificial rearing method during the lactating period [60,64,66], employing a custom-designed bottle-nipple system to hand feed them. In supplementation experiments, DHA level varies between 1% and 27% of total fatty acids [53,62–66]. In deficiency experiments, adequate diets present a n-6 LCPUFA/n-3 LCPUFA ratio between 4.1 and 6.2 [59,60,67]. Diets starts either in the first days of gestation [59,62,65,67] or after birth [53,60,63,64,66]. Animals are all tested for behavior at adulthood.

Overall, dietary depletion of n-3 PUFA causes detrimental effects on cognition in the Morris water maze [63,64,67] and in the Barnes maze [59,60]. However, the learning deficits observed in the Barnes maze are less pronounced compared with that in the Morris water maze, suggesting that the increased stress reactivity of n-3 deficient animals is a contributing factor to their impaired performance [59]. Moreover, DHA cannot be replaced by its closest long-chain equivalent, DPA n-6, as pups fed a diet rich in LA and DPA but low in DHA had impaired spatial memory performance compared to rats fed a diet rich in DHA [64].

On the other hand, supplementation with n-3 PUFA of a normal non-depleted diet during the early stages of development has demonstrated benefits on cognitive performance [53,62–64], although lack of effect on cognition has been found as well [62,65,66]. Thus, in general, the strongest effects of n-3 PUFA supplementation are observed in conditions of deficiency or in animals displaying memory deficit. Whether increased dietary DHA can improve memory of animals with normal memory has been poorly addressed in rodent models [12]. This point constitutes a limitation in these studies as it remains unclear whether DHA supplementation is protective or is a “normal” setting. Nevertheless, a lesson learned from these investigations is that improvement in cognitive performance is clearly associated with higher brain DHA concentrations [68]. Finally, it is of importance to note, that no evidence has been demonstrated that deficiency or supplementation with EPA alone has effects on cognitive development. DHA appears to be the critical PUFA for cognitive enhancement, at least during development.

In conclusion, we would like to emphasize the possible role of non-cognitive factors like emotionality and attention in the impaired performance on different types of learning tasks of n-3 deficient animals. This idea was first suggested by Wainwright who said that “it is important to realize that performance on cognitive measures (learning, memory) may be confounded by alterations in non-cognitive functions (emotionality, arousal) or by inadequate sensory and motor skills” [66]. In any case, if brain DHA status affects performance, this is of importance since performance plays a crucial role in adaptation and therefore survival.

2.2.2. *Cellular and molecular substrates*

Indirect clues about the developmental effects of n-3 PUFA on cognition can also be obtained from neurophysiological studies.

2.2.2.1. Neurogenesis, synaptogenesis, myelinogenesis. The spatio-temporal events of rat fetal brain neurogenesis and synaptogenesis are quite well characterized. Although minor differences exist, the bulk of neuronal “birth”, i.e., the period after neuron precursors have stopped dividing is between E14 and E17 for most brain regions. Synaptogenesis starts after neurons have undergone terminal mitosis, usually after E17. In 1999, Green et al. elegantly studied the accretion of fatty acids in the developing brain [69]. They described two surges in the accumulation of lipid, the first at E14–E17 coinciding with peak neurogenesis and the second starting at the second postnatal week, representing synaptogenesis. At this second time point myelinogenesis also commences, giving rise to the well-known “growth spurt” [70]. Thus, depletion of DHA during these critical periods of brain growth could dramatically interfere with neurogenesis and synaptogenesis [71].

In light of these results, recent *in vitro* and *in vivo* experiments have directly linked DHA deficiency or supplementation to neurogenesis. In 2006, Kawakita et al., showed on neural stem cells cultures that DHA application significantly increased the number of cells and the newborn neurons were morphologically more

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mature than in the control [72]. This was confirmed *in vivo* by Coti-Bertrand [71]. They used a model of dietary n-3 LCPUFA deprivation in rats that they previously found to reduce embryonic brain DHA accretion [41]. The diets were fed from 2 weeks prior to mating, and then throughout gestation until E19. Morphometric analyses performed at E19 showed that the changes in the embryonic brain fatty acids were accompanied by increased thickness of proliferative zones and decreased size of target regions such as the cortex or the hippocampus [71]. The factors that regulate adult neurogenesis are highly conserved among species, and Beltz et al. (2007) showed that short-term augmentation of dietary n-3 relative to n-6 fatty acids in the lobster results in significant increase in the numbers of dividing cells as well [73]. Experiments performed on hippocampal neurons in culture showed that application of 1 μM of DHA increased significantly the total number of synapses compared to control cultures [74]. This confirmed previous results from Cao et al. showing that 10 days of *in vitro* supplementation with DHA at 1 μM significantly promotes synaptogenesis whereas *in vivo* DHA-depletion in fetal hippocampi from E2 to E16 resulted in decrease in the number of synapses [75]. They also demonstrated that maternal dietary depletion of DHA impairs long-term potentiation (LTP) in offspring mice [75]. Interestingly, in neonates, Salvati et al. injected a single dose of EPA or DHA into brains of rat pups, and myelin development was assessed 3 days later by evaluating myelin protein expression in different brain regions. They showed that EPA rather than DHA plays an important role in myelinogenesis [76].

2.2.2.2. Neurite outgrowth, neuron size. As for neurogenesis, several experiments showed the beneficial effects of DHA on neuronal growth. In 2004, Calderon and Kim performed fatty acid analyses and neurite measurements in hippocampal neurons after 6 days *in vitro* with or without 1.5 μM DHA supplementation in the culture medium. DHA increased the total neurite length of hippocampal neurons. This effect was specific to DHA since DPA, AA or oleic acid was unable to reproduce the same effect. They also studied the impact of n-3 LCPUFA deficiency *in vivo*. They compared the effects of an n-3 fatty acid deficient diet formulated with safflower oil because of its low content of ALA and compared to an n-3 fatty acid adequate diet supplemented with flaxseed oil as a source of linoleic acid (LA) to achieve the final ALA composition to be 2.6 mole % of total fatty acid. They found that *in vivo* DHA deficiency from E2 to E18 decreases neurite growth of hippocampal neurons [52]. These results were confirmed later on by a report from Cao et al. (2009) showing that after 10 days *in vitro* supplementation with DHA at 1 μM increased neuronal length as well as the arborization complexity [75]. On the other hand, *in vivo* DHA-depletion in fetal hippocampi from E2 to E16 resulted in inhibition of hippocampal neuronal development in culture as shown by the decrease of dendritic length and arborization complexity [75]. A recent study showed that LCPUFA have significant neurotrophic effects on rat primary sensory neurons at early stages of development. On rat dorsal root ganglion primary cultures prepared from P3 and P9 pups, they showed that DHA and EPA, in a physiological PUFA concentration range, increase neurite outgrowth during the developmental period [77]. Finally, Ahmad et al. (2002) showed a decrease in neuron size in the CA1 region of the hippocampus in n-3 LCPUFA deficient rats compared to supplemented rats [78].

2.2.2.3. Synaptic proteins expression. A recent study investigated changes in the synaptic plasma membrane proteome of DHA-adequate or -depleted mice cortices from E2 to adulthood. They found that proteins involved in synaptic transmission such as munc 18–1, PSD-95, synaptic vesicle protein, synapsin 1a/b, contactin 2, bassoon, GluA2 and GluN2B subunits were downregulated. Many of these down-regulated proteins belong to the CREB1 and caspase-3 network pathways, suggesting that both transcription and degradation activity is under the control of the DHA status in the brain. No concurrent up-regulation of proteins was apparent, possibly reflecting the diminished synapses under DHA-depleted conditions, which is consistent with the reduced synaptogenesis discussed above [79].

3. DHA improves cognition at adulthood

DHA is an essential fatty acid for the brain as already mentioned. DHA may play an essential role in brain functioning, due to the very high level of DHA in the brain and to the difficulty to achieve a DHA deficiency in this organ despite its limited capacity to synthesize DHA. DHA is involved in mood and emotional state, locomotor and exploratory activities and cognitive functions. Optimal cognitive functions are components of well-being quality of life.

The role of DHA in cognitive function has been extensively studied during the perinatal period, the most sensitive period in term of brain development and DHA accretion and aging, the period during which cognitive decline and dementia occured. However, few studies dealt with the effect of n-3 PUFA on cognition during the stage of life in between, during young or advanced, healthy adulthood [18]. In this chapter we will focus on the role of DHA in cognition at adulthood. We first described studies in humans and then in animals, mainly rodents. The cognitive functions were assessed by neuropsychological test in humans and by learning behaviors in rodents.

3.1. Evidence in humans

Observational and interventional studies have been conducted in healthy children, young adults and adults.

Table 5
Observational studies in young children and adults reporting the effect of n-3 PUFA supplementation on cognition.

Characteristics of the participants	Outcome	Study	Effect on cognition
Children (6–16 y), boys and girls	Positive association between n-3 fatty acids and cognitive performance Contribution of dietary n-3 PUFA: women > men	Lassek and Gaulin [14]	+
Adults (30–70 y), men and women	Positive association between DHA blood levels and scores on cognitive performance tests	Muldoon et al. [80]	+
Adults (45–70 y), men and women	↘ risk of impaired overall cognitive function and speed	Kalminjn et al. [81]	+
Adult women non-pregnant	Positive association between DHA and slower learning curve. But ↗ in cognitive performance after 22 wks	De Groot et al. [82]	+ and −

DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; +: positive effect; −: negative effect.

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Table 6
Interventional studies in young children and adults reporting the effect of n-3 PUFA supplementation on cognition.

Characteristics of the participants	Experimental design	Outcome	Study	Effect on cognition
Adults (33 y) Women and men Low dietary intake of LC n-3 PUFA (< 200 mg EPA+DHA/wk)	DHA supplementation (1.16 g DHA+0.17 g EPA/d) for 6 months	Women: improvement of the accuracy of episodic memory Men: improvement of the reaction time of episodic memory	Stonehouse et al. [15]	+
Adults (22–51 y) Women and men	EPA and DHA supplementation 1.6 g and 0.8 g/d, respectively, for 35d	Improvement of attention and physiological functions (vigor, anxiety, fatigue, depression, confusion)	Fontani et al. [83]	+
Children (8–10 y), boys	DHA supplementation (400 or 1200 mg/d) for 8 weeks (DHA)	Positive correlation between erythrocyte DHA composition and prefrontal cortex activation Negative correlation between erythrocyte DHA composition and reaction time	McNamara et al. [84]	–
Adults (18–35 y) Women and men	DHA-rich fish oil (1 g) for 12 weeks (DHA/EPA 5:1)	No positive effects on cognitive performance	Jackson et al. [85,86]	No
Children (10–12y), girls and boys	DHA supplementation (400 or 1000 mg/d) for 8 weeks	No positive effects on cognitive performance	Kennedy et al. [87]	No
College-aged adults (20 y), Women and men	DHA and EPA supplementation (480 mg and 720 mg/d, respectively, for 4 weeks)	No positive effects on cognitive performance	Karr et al. [88]	No
Adults (45–77 y)	DHA and EPA supplementation 252 mg and 60 mg/d, respectively, for 90d	No positive effects on cognitive performance	Stough et al. [89]	No

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; no: no effect; +: positive effect; –: negative effect.

3.1.1. *Observational studies (Table 5)*

Associations between cognitive performance and fatty acid status were based on cognitive measures and either plasma fatty acid analysis or food frequency questionnaire associated to food database. Lassek and Gaulin (2011) found that dietary n-3 fatty acids are positively related to cognitive performance in children 6–16 year of age [14]. The contribution of dietary n-3 PUFA to cognitive performance is much greater in females than in males. In adults 30–70 years, DHA was related to cognitive functioning, with higher blood levels associated with better scores on tests of nonverbal reasoning, mental flexibility, working memory and vocabulary [80] and with decreased risk of impaired overall cognitive function and speed [81]. In contrast, de Groot et al. [82] reported a slower learning curve on general speed information processing although there was a significant increase in cognitive performance over 22 weeks in 54 non-pregnant women [82].

These inconsistencies may be due to a different demographic background or to differences in evaluating the DHA status and revealed the complexity of observational studies.

3.1.2. *Interventional studies (Table 6)*

In most interventional studies undertaken in adults, DHA was provided as capsules. Studies have provided mixed results regarding the effect of DHA intake on cognitive performance in adults. They showed either improved cognitive function or no beneficial effects.

In a recent randomized clinical trial, Stonehouse et al. [15] showed that a DHA supplementation (1.16 g DHA+0.17 g EPA/d) for 6 months improved memory and reaction time of memory assessed with the Computerized Mental Performance Assessment System in healthy young adults (mean age 33 years old) whose habitual diet was low in DHA [15]. DHA improved the reaction time of episodic memory and this response was modulated by gender. In women, it was the accuracy of episodic memory that was improved whereas in men it was the reaction time of working memory that was ameliorated. This study points out the importance of considering gender differences in the relation between DHA and cognition. In 2005, Fontani et al. used also a mixed n-3 PUFA supplementation but with twice more EPA than DHA (1.6 g EPA+0.8 g DHA) for 35 days in healthy subjects aged 22–51 years (males and females) [83]. They found an improvement of attention and physiological functions (vigor, anger, anxiety, fatigue, depression, and confusion). The possible mechanisms involved may be related to the influence of the n-3 PUFA on neuronal excitability. Conducting a neuroimaging study, McNamara et al. (2010) aimed at determining the effects of DHA supplementation (400 or 1200 mg/d) for 8 weeks on functional cortical activity during sustained attention in healthy boys aged 8–10 years [84]. This low- or high-dose DHA significantly increased functional activation in the prefrontal cortex during performance of an attention task (identical-pairs version of the continuous performance task) compared with placebo. Two years later, Jackson et al. [85] found that a supplementation with DHA-rich fish oil (1 g) for 12 weeks resulted in a significant increase in the concentrations of oxygenated hemoglobin, indicative of increased cerebral blood flow during the cognitive tasks [86].

In contrast to the beneficial effects of n-3 PUFA described, other studies have shown limited or no positive effects of DHA supplementation on cognitive performance, either in children aged 10–12 years supplemented with 400 or 1000 mg/d DHA for 8 weeks [87], nor college-aged adults (20 years old) supplemented with 480 mg DHA +720 mg EPA/d for 4 weeks [88], nor healthy young adults (18–35 years old) supplemented with 1 g EPA-rich fish oil for 12 weeks although this supplementation may reduce subjective mental fatigue at times of high cognitive demand [85], nor in healthy adults aged 45–77 years supplemented with 252 mg DHA+60 mg EPA/d for 90 days [89].

These differences may be due to the daily dose used, the lengths of intervention, the source of n-3 PUFA (mainly EPA or mainly DHA), the dietary n-3 PUFA history of the patients and the cognitive function assessed. As recently discussed by Dangour and Allen, the relevance of the cognitive tests used need to be better addressed [90]. In addition, larger studies with a clear definition of primary endpoints would help to decipher the beneficial effect of n-3 LCPUFA on memory.

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Table 7
Effect of n-3 PUFA supplementation on cognition in adult rodents.

Species	Test	Experimental design	Outcome	Study	Effect on cognition
Long Evans rats	Morris water maze	Depletion of n-3 PUFA over 3 generations. Male offsprings resupplemented at birth or at weaning or at 7 weeks with DHA (0.13%). Behavioral testing at 9 and 13 weeks (DHA).	- Impairment of the Morris water maze learning and retention with the n-3 PUFA deficient diet. - Restored performance with n-3 adequate diet at birth and weaning. - When repletion occurred at 7 weeks, restored performance at 13 weeks only.	Moriguchi and Salem [67]	+
Wistar rats	Radial arm maze	Depletion of n-3 PUFA over 3 generations. Male offsprings resupplemented at 5-weeks with DHA (300 mg/kg/day) for 10 weeks (DHA).	Improvement of the reference but not working memory errors in the maze	Gamoh et al. [92]	+
Sprague-Dawley	Morris water maze	2-month old male rats fed a diet with appropriate (150-300 mg/kg) or high doses (600 mg/kg) DHA for 1 month (DHA).	Improvement of the spatial learning performance and retention with the appropriate dose. Impairment of the performance with the higher dose	Pan et al. [93]	+
Crj:CD-1 mice	Maze	3-week old male mice fed a diet supplemented with ethyl-DHA (2%) for 5 months	Better performance	Lim and Suzuki [99]	+
Wistar rats	Morris water maze	Male adult rats fed a diet supplemented with ethyl-EPA (0.2 or 1%) for 8 weeks	- No improvement of water maze performance - Improvement of an Il-1-induced impairment of memory	Song and Horrobin [94]	+
Sprague-Dawley rats	Morris water maze	2-month old rats fed a diet supplemented with EPA (1%) for 7 weeks.	- No improvement of water maze performance - Improvement of an Il-1-induced impairment of memory	Song et al. [95]	+
Wistar rats	Morris water maze	3-4 months rats fed a diet supplemented with ethyl-EPA or DPA (200 mg/kg/day) for 8 weeks	No improvement in memory performance	Kelly et al. [97]	no
C57Bl6 mice	Morris water maze	6-week old male mice fed a diet supplemented with ethyl-EPA (1%) for 12 weeks.	No improvement in spatial learning or retention compared to control.	Luchtman et al. [98]	no
Swiss OF1 mice	Morris water maze; passive avoidance	7-week female mice fed a diet supplemented with phospholipid-DHA (0.05%) for 2 months	No improvement in memory or passive avoidance performance	Carrié et al. [3]	no

DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; no: no effect; PUFA, polyunsaturated fatty acids; +: positive effect.

Table 8
n-3 long chain polyunsaturated fatty acids in animal models of aging.

Species of rodents and age	Treatment and length *Context*	Brain regions	Outcomes	Study	Effect on cognition
Mice, 3 months and 22 months	10% EPA and 7% DHA, 2 months, *Aging, inflammation and cognition*	Hip and Brain	↑n-3 LCPUFA ↓cytokines expression in old mice Changes in astrocytes morphology in old mice ↑spatial memory in old mice	Labrousse et al. [12]	+
Rats, 100 weeks	Fish oil-deficient diet (3 generations), DHA-EE 300 mg/Kg/day, 5 weeks, *Aging and cognition*	Hip	↓reference memory and working memory errors ↓LPO	Gamoh et al. [121]	+
Mice, young (7–11 weeks), Mature (9–10 months), old (17–19 months)	Fish oil diet (DHA 9.4 g/Kg diet). Palm oil diet (DHA 0 g/Kg diet), whole life, *Aging and cognition*		↑exploratory and locomotor activity in young mice No change in mature and old mice ↓locomotor activity in old mice and↑in youg mice ↑performance only on the probe trial of the Morris water maze in mature mice	Carrié et al. [3]	+
Mice, 14 months	DHA and EPA 1.14 mmol/Kg/ day vs ALA 1.5 mmol/ Kg/day	EC neurons	↑DHA, ↓AA and ↑cellular capacitance with DHA diet, Membrane hyperpolarisation and ↑sEPSC, ↑syntaxin-3 and translocation ratio of drebrin	Arsenault et al. [147]	+
Rat, birth, 3 weeks and 7 weeks	n-3 adequate diet (n-3 Adq, 2.6% ALA +1.3% DHA) or n-3 deficient diet (n-3 Def), 3 generations of n-3 Def diet and n-3 Adq for 2, 6 or 9 weeks, *Aging*	Half brain	↓DHA and ↑DPA n-6 with n-3 Def, Fatty acid profile of n-3 Adq diet at birth ≈ n-3 Adq reference group, ↑DHA and ↓DPA n-6 with n-3 Adq, % DHA of 3 weeks of age > of 7 weeks of age, ↑time to reach the platform in Morris water maze with n-3 Def, ↑time for 7 weeks of age to restore brain DHA, Nearly full recovery on the probe trial and spatial learning task after 6 weeks of n-3 Adq diet of 7 weeks mice	Moriguchi and Salem [67]	+
Rat, 3–4 months and 20–22 months	E-EPA or DPA (200 mg/Kg/day), 2 weeks, *Aging, inflammation and cognition*	Cx, Hip	E-EPA ↑cortical DPA and DHA, ↓microglial activation, ↓coupled activation of sphingomyelinase and caspase 3, ↑spatial learning and long term potentiation	Kelly et al. [97]	+
Mice, 4 months and 20 months	DHA 0.9 g/Kg/day [14C]–DHA, [14C]–EPA, *Aging and BBB*	Whole brain	DHA and EPA cross the BBB by diffusion, n-3 LC-PUFA deprivation increase brain DHA uptake in old mice	Ouellet et al. [131]	n.d.
Rats, 2 months and 2 years	11% DHA, 2.8% EPA, 1 month, *Aging*	Whole brain	↑DHA, ↓AA, No difference in Morris water maze test	Barcelo-Coblijn G et al. [122]	no

AA, arachidonic acid; Adq, adequate; ALA, alpha-linolenic acid; BBB, blood-brain barrier; Cx, cortex; CxFr, cortex frontal; Def, deficient; DHA, docosahexaenoic acid; DHA-EE, DHA ethyl ester; DPA, docosapentaenoic acid; EC, enthorinal cortex; EPA, eicosapentaenoic acid; Hip, hippocampus; IL-6, interleukin-6; LCPUFA, long chain PUFA; LPO, lipid peroxide; n.d.: not determined; no: no effect; PUFA, polyunsaturated fatty acid; vs, versus; +: positive effect; −: negative effect.

3.2. *Evidence in animals (Table 7)*

Lots of studies dealing with DHA and cognition conducted in animals started the n-3 PUFA deficiency or supplementation during the perinatal period and observed the effects at adulthood (see the previous paragraph). Few studies dealt with the relation between DHA and cognition with deficiency or supplementation started at adulthood. In this part, we considered only the studies whose deficiency or supplementation started in young adult- and adult- animals. Moreover we focused on animals, mainly rodents, without any pathology. Studies dealt with the effect of DHA either on n-3 PUFA deficient diet animals or on adequate n-3 diet animals. In young and adult rodents submitted to an n-3 PUFA deficient diet, DHA was decreased in the brain and associated with an increase in DPA n-6 [4,91]. This loss of DHA was independent of age whereas the increase in DPA n-6 was faster in young animals due to higher desaturase activities [4]. Cognitive assessments were performed with the same tests than those described in the

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Table 9
n-3 long chain polyunsaturated fatty acids in animal models of Alzheimer's disease.

Species of rodents and age	Treatment and length *Context*	Brain regions	Outcomes	Study	Effect on cognition
Rats, 20 weeks	Ethyl-DHA 300 mg/Kg/day, 7 weeks, *Alzheimer's disease*	Cx	↓Aβ, ↓cholesterol, ↓reference memory error	Hashimoto et al. [140]	+
Rats, 25 weeks	Ethyl-DHA 300 mg/Kg/day, 12 weeks, *Alzheimer's disease*	Cx, Hip	↓avoidance learning ability, ↑DHA/AA ratio, ↓neuronal apoptotic products, ↓oxidation	Hashimoto et al. [142]	+
Rats, 20 weeks	Ethyl-DHA 300 mg/Kg/day, 12 weeks, *Alzheimer's disease*	Cx, Hip	↑DHA/AA ratio, ↓reference and working memory errors	Hashimoto et al. [143]	+
Mice, 8 months and 15 months	DHA 3.5 g/Kg diet, 6 or 13 months, *Alzheimer's disease*	CxFr, Cx, Hip, Acg	No change in rCBV in 8 months old mice, ↓Aβ in 15 months old mice, ↑spatial memory in 15 months old mice, ↑rCBV in 15 months old mice	Hooijmans et al. [145]	+
Mice, 6 months	DHA 0.4%, EPA 0.4%, 3-4 months, *Alzheimer's disease*	Hip, CxFr, Cx and Cer	↓Aβ, ↓activated microglia, ↑exploration activity, No change at spatial learning in Morris water maze	Oksman et al. [146]	+
Mice, 12–14 months	DHA 0.6 g/Kg/day (DHA/EPA 4:1), 8–10 months, *Alzheimer's disease*	EC neurone, CxFr, Cx	↑DHA and ↓AA, ↑object recognition, ↓seizure-like akinetic episodes, ↑cell capacitance, ↓firing rate *versus* injected current	Arsenault et al. [147]	+
Rats, 25 weeks	Ethyl-DHA 300 mg/Kg/day, 12 weeks, *Alzheimer's disease*	Cx	↑membrane lateral and rotational fluidity, ↑DHA, ↓cholesterol and lipid peroxidation	Hashimoto et al. [141]	n.d.
Mice, 17 months	DHA 0.6 % , 103 ± 5 days, *Alzheimer's disease*	CxFr, Cx and hemi brain	↑drebrin, ↓oxidation, ↓caspase-cleaved actin, ↑antiapoptotic BAD phosphorylation	Calon et al. [144]	n.d.
Mice, 17 and 19 months	DHA 0% or 0.09% or 0.6%	Cx, Hip, parietal Cx	↓Aβ and Aβ42, ↓Aβ plaques, ↓α- and β-APP C-terminal fragment	Lim et al. [64]	n.d.
Mice, 3 months	DHA 0% or 0.6%, 3 months, *Alzheimer's disease*	Cx, HipV, Str, Hip, liver	↑DHA and ↓AA, ↓Aβ plaques, ↑drebrin	Perez et al. [149]	n.d.
Mice, 3 months	DHA 1.3 g/100 g diet and DPA n-6 0.5 g/100 g diet, 3, 6 or 9 months, *Alzheimer's disease*	Whole brain	↓intraneuronal Aβ and Tau, ↓PS1, DPA n-6 ↓early-stage phospho-tau and↓of phosphorylated c-jun N-terminal kinase	Green et al. [150]	n.d.

Mice, 12 and 20 months	n-6/n-3=25 (4.6 Kcalories/g diet), *fat-1* transgene, Whole life, *Alzheimer's disease*	Cx, CxFr	↑n-3/n-6 ratio and DHA at 20 months, ↓soluble Aβ42 at 20 months, ↓soluble and insoluble phosphorylated tau at 20 months, ↓CaMKII and GFAP at 20 months	Lebbadi et al. [151]	n.d.
Mice, 17 months	DHA 0.6%, 3-5 months, *Alzheimer's disease*	Cx, Hip	↑NMDA receptor subnit (NR2A and NR2B), ↑CaMKII, ↓caspase/calpain activity	Calon et al. [161]	n.d.
Mice, 13 months	DHA 0 g/Kg diet and n-3/n-6= 0.01, 9 months, *Alzheimer's disease*	CxFr, Cx	↓n-3/n-6 ratio, ↑insoluble Aβ40 and β42, ↑insoluble and soluble tau, ↓drebrin	Julien et al. [162]	n.d.
Mice, 4 and 12-13 months	Young vs old mice, *Alzheimer's disease*	CxFr, Cx, Hip	DHA in brain young > old mice, NPD1 in brain young > old mice, ↓inflammatory signaling, amyloidogenic APP cleavage and apoptosis	Zhao et al. [174]	n.d.

AA, arachidonic acid; Aβ, β-amyloid; Acg, anterior cingulate gyrus; APP, amyloid protein precursor; CaMKII, calcium/calmodulin-dependent protein kinase II; Cer, cerbellum; Cx, cortex; CxFr, cortex frontal; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EC, enthorinal cortex; Hip, hippocampus; HipV, ventral hippocampus; GFAP, glial fibrillary acidic protein; n.d.: ‚not determined ; NMDA, N-methyl-D-aspartate; PS1, presenilin 1; rCBV, relative cerebral blood volume; Str, striatum ; + +: positive effect.

previous paragraph concerning the perinatal period. Moriguchi and Salem (2003) studied the reversibility of an n-3 PUFA deficiency induced on 3 generations of rats with supplementation of DHA at different ages: birth, 3 and 7 weeks of age [67]. They found that brain function can recover from a severe and extended DHA deficiency by a dietary supply with DHA. The performance in spatial tasks was closely related to the level of brain DHA. Younger animals (3 weeks of age) restored brain DHA at a faster rate than older ones (7 weeks of age), when brain formation is ongoing. The normalization of brain DHA induced the total recovery of the performance as compared to the n-3 adequate group (containing a LA/ALA ratio of 6.2 and 1.3% DHA) although the recovery in brain DHA was not total for the rats supplemented at 3 weeks (93%) and at 7 weeks (60%). No critical period in development was observed in this experiment during which DHA must be supplied. However, an earlier intervention appears to be more effective in restoring brain DHA than a later one.

The same result was obtained in the study of Gamoh et al. [92] who worked on rats fed with a fish oil deficient diet (without DHA) instead of an n-3 PUFA deficient diet for 3 generations [92]. The authors failed to mention the fatty acid composition of the different diets they used. However, perorally administration of DHA (300 mg/kg/day) to these rats caused a significant increase in DHA in the cerebral cortex and hippocampus but not in the cerebellum and brain stem. This increase is associated to the improvement of the reference memory-related learning ability without affecting working memory.

Only one study tested a supplementation of DHA on rats fed an adequate n-3 PUFA diet. Here again the authors did not disclose the fatty acid composition of the adequate n-3 PUFA diet. They showed that supplementation with DHA (150 and 300 mg/kg) significantly improved learning and memory in the Morris water maze task but a higher dose of DHA (600 mg/kg) increased the risk of memory impairment [93]. Hence DHA deficiency or excess (600 mg/kg) might impair spatial learning and memory function.

The effect of a diet supplemented with pure EPA or DHA (as ethyl-EPA, E-EPA or ethyl-DHA, E-DHA) was compared to the one of an n-3 PUFA deficient diet on memory impairment. The chronic administration of E-EPA, the precursor of DHA, for 5–7 weeks did not significantly enhance memory in rats [94–96]. However, it attenuated the effects of intracerebroventricular injection of interleukin-1β (15 ng/10 μL/rat) on spatial memory by suppressing inflammation and reducing the decrease of acetylcholine release. Luchtman et al. (2012) found in mice that the E-EPA diet only increased tissue EPA and DPA levels and not DHA whereas Kelly et al. (2011) found in rats that E-EPA administration increased cortical DPA and DHA [97,98]. Thus, it is not clear whether EPA acts through a higher DHA incorporation in the brain or not. Nonetheless, E-EPA by itself can affect inflammation-induced cognitive impairment and normalize neurotransmitter release.

The beneficial effects of DHA on cognition were counterbalanced by few studies reporting no effect of DHA supplementation (started at 3 weeks of age for 5 months) in young mice as shown by Lim and Suzuki [99]. They only found an enhancement in maze-learning ability in old mice. The study of Carrie et al. (2000) examined the effects of a supplementation at 7 weeks of age with phospholipids rich in n-3 PUFA for 2 months on behavior, learning, and phospholipid fatty acid composition of brain regions in n-3 PUFA deficient mice (deficiency induced in mums 3 weeks before mating) [3]. They did not find any differences between n-3 PUFA deficient diet, control diet and diets supplemented phospholipids rich in DHA on Morris water maze or passive avoidance although the brain DHA levels were different in the deficient group and the others.

The discrepancies in the efficiency of DHA supplementation on cognitive deficit may be explained by the brain DHA levels before the

supplementation. Indeed, the "dietary history" of the animals under study is very important: adequate diets, n-3 PUFA deficient or supplemented diets, time at which the specific diet is started, the duration of the specific diet. The age of the animals when the cognitive tests were performed may also have an importance. We should also keep in mind that other factors like emotionality and attention, affected by brain DHA levels, could interfere with the cognitive tests on memory and leaning.

4. DHA improves cognition: clues from animal models of cognitive impairment

4.1. Cognitive decline in normal aging: effect of n-3 LCPUFA (Table 8)

Normal aging is associated with a decline in cognitive functions including memory [10,100]. Memory loss is a prominent health concern in older individuals either due to "normal" aging or underlying pathological processes such as vascular dementia or neurodegenerative diseases. The most important of such diseases is Alzheimer's disease (AD), which affects over 24 millions people worldwide [101]. The undergoing pathological process in AD is different from normal aging, in part because it is much faster and widespread. Thus, much effort has been devoted to identify early AD stages, such as mild cognitive impairment, to make a clear distinction with normal aging [102–104].

Epidemiological studies have pinpointed an association between consumption of n-3 LCPUFA with slower cognitive decline in elderly individuals without dementia [105–108]. For example, an association was found between red blood cell n-3 LCPUFA and a decreased risk of white matter hyperintensities and smaller brain volume in old study participants [109]. RCTs performed in cohort of old individuals were less conclusive. Two relatively large studies with 302 and 867 healthy adults, respectively, detected no change in cognitive function scores after supplementation with supplements combining EPA and DHA [107,110]. In contrast, results from a RCT involving 485 healthy subjects showed that a treatment with pure DHA improves episodic memory and learning [108]. Memory enhancing effect of n-3 LCPUFA in non demented older subjects was also shown in 2 smaller RCTs [111,112]. One of these smaller study ($n=30$) also reports improved beneficial effects of n-3 LCPUFA on magnetic resonance imaging (MRI)-determined brain structural endpoints in old subjects, such as white matter integrity and gray matter volume [112]. Finally, independent RCTs performed in individuals with mild cognitive dysfunction adds support to the postulate that n-3 LCPUFA exert a benefit on cognition [113–116]. However, another RCT detected effects of n-3 LCPUFA mostly limited to improvement of depressive symptoms [117]. The apparent conflict between the results of these RCT may stem from variables such as cognitive reserve, dietary habits, pre-study n-3 LCPUFA status, the type of LCPUFA supplement given, and population heterogeneity [68,106], and underscore the challenges of performing clinical trials in this population [104,118]. However, selection of the most relevant primary endpoints in cognitive studies remains a challenge [90]. Larger studies with clearly defined *a priori* outcomes are needed before using the results of published study for health recommendation.

The effects of n-3 LCPUFA treatments were also assessed in animal models [12,119]. The study of Labrousse et al. (2012) indicated that diet-induced accumulation of EPA and DHA in the brain protects against neuroinflammation and cognitive impairment linked to aging in an animal model, further reinforcing the idea that increased EPA and DHA intake may provide protection to the brain of aged subjects [12]. Consistent ameliorating effects on cognition or neuroinflammatory endpoints following n-3 LCPUFA supplementation on age-related cognitive deficits are reported in old rodents [97,120,121], although not confirmed by other investigators [122,123].

4.2. Alzheimer's disease n-3 LCPUFA: animal models

In the past 20 years, animal models have been generated to pinpoint how the neuropathology of brain disorders like AD can lead to readily measurable cognitive deficits. The most widely used strategy is to transgenically express in the brain of mice mutant genes known to cause AD in humans [124,125]. Although none of these mice develop the frank neuronal or synapse losses pathognomonic of AD, they exhibit various behavioral anomalies reminiscent of AD symptoms, as well as an extensive AD-like neuropathology. Among the 20 autosomal-dominant amyloid precursor protein (APP) mutations, the Swedish mutation facilitating APP cleavage near the β-secretase site was the first to be used to generate a transgenic model of AD (Tg2576) [126]. Such strategy was successful to generate series of transgenic mice bearing APP mutation(*s*) and developing amyloid plaques and cognitive deficits [124,125]. In addition, transgenes have been added to recreate neurofibrillary tangles, another neuropathological hallmark of AD [127]. One example is the now widely used 3xTg-AD mouse which develops both plaques and tangles [128]. While these transgenic mice fail to replicate the full neurodegenerative spectrum of human diseases, they are extensively used to model the preclinical phases of AD. They also offer an excellent opportunity to study the impact of nutraceutical interventions.

Indeed, in the past 10 years, preclinical trials in transgenic AD mice have been performed with controlled diets and designed to assess specific behavioral and molecular endpoints. It was long known that fatty acids (especially DHA) ingested through the diet directly impact upon concentrations of corresponding fatty acids in the cerebral tissue [4,68,129,130]. Indeed, circulating DHA readily crosses the blood-brain barrier to enter the brain [131], where it displays a very slow turnover rate [132,133]. Therefore, dietary manipulation provides a direct means of studying the effect of fatty acids on brain function, and n-3 LCPUFA have accordingly been the subject of series of investigations on their impact on cognition and AD-like neuropathology in animal models [68,134–136].

There is a general consensus on beneficial effects of n-3 LCPUFA on cognition in animal models of AD (Table 9). The first series of evidence come from the work of Hashimoto et al. using rat intracerebrally infused with Aβ40 to quickly recreate AD neurodegeneration [137]. Although this model relies on a direct neurotoxic effect of Aβ monomers, which is of debatable AD relevance [138,139], the data generated clearly support improving effects of dietary DHA on memory and learning ability [140–143]. Then, using the Tg2576 animal model of AD in the Morris water maze paradigm, DHA was shown to protect against cognitive impairment caused by an APP transgene bearing the Swedish mutation [144]. DHA intervention studies were also performed in APPswe/PS1dE9 mice, which in addition to the Swedish mutant APP express a presenilin variant known to potentiate Aβ plaque deposition. Memory improvement after exposure to DHA-enriched diets was detected in old but not young APPswe/PS1dE9 mice, again using the Morris water maze paradigm [145,146]. More recently, it was found that long term DHA treatment improved object recognition and reduced akinetic periods in 12-month-old 3xTg-AD mice [147].

The main advantage of investigations with animal models is to provide insights on the direct relationship between cognitive behavior and underlying molecular mechanisms. Aβ pathology remains the most studied neuropathological hallmark of AD and it has been shown to be sensitive to brain DHA levels. Decreases in brain Aβ load after DHA treatment have been reported in at least

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Table 10
n-3 long chain polyunsaturated fatty acids and miscellaneous brain and synaptic markers in normal animals.

Species of rodents and age	Treatment and length *Context*	Brain regions	Outcomes	Study
Mice, 18 days	DHA 0.9%, At 2 days of pregnancy to after lactation period, *Molecular signaling*	Hip	↑Neurite growth, synaptogenesis, synapsin, glutamate receptor expression and glutamatergic synaptic function	Cao et al. [75]
Rats, 2 months	DHA 1.25% (DHA/EPA 5:1), 12 days, *Cognition and molecular signaling*	Hip, whole brain	↑syntaxine-3, ↑NR2B, ↑learning in Morris water maze	Chytrova et al. [166]
Rats, 110 days	DHA 0.3%, Whole life, *Neurophysiology*	Hip	↑neurons size	Ahmad et al. [78]
Rats, 90 days	DHA 18% and EPA 12%, Whole life, *Neurotransmission*	Hip, Cx	↑BDNF, ↑5-HT of 90 day-old rats	Vines et al. [179]
Mice, 5-6 months	DHA 0.7g/Kg/ day (DHA/EPA 4:1), 3 months, *Inflammation*	Whole brain	↓microglial activation, ↓ischemic lesion size, ↑Bcl-2 and ↓Cox2 and IL-1β	Lalancette-Hébert et al. [176]
Rats, 6-7 weeks	DHA 1.25% (DHA/EPA 4:1), 12 days, *Neurotransmission*	Hip	↑spatial learning, ↑BDNF and synapsin 1, ↓oxydation, ↑Akt and CaMKII	Wu et al. [180]
Mice, 8 weeks	Diet rich in LA and ALA (n-3/n-6) or diet rich in LA (n-6), Gestation to 8 weeks, *Inflammation*	Cx (in PC and PE), Hip	↓DHA and↑DPA n-6 in PC and PE, No difference for AA, ↑social exploration with n-6 diet, ↑IL-6 with n-6 diet in Hip, ↑expression of IL-6 mRNA with time with n-6 diet in Hip, ↓LPS-induced STAT1, STAT3 and JAK2 activation with n-6 diet in Hip	Mingam et al. [91]
Rats, 5 weeks	Fish oil deficient diet for 3 generations, DHA 300 mg/Kg/day or vehicule, Over 10 weeks	Cx, Hip, Cer and brain stem	↑DHA in Cx and Hip, ↑reference memory-related learning ability	Gamoh et al. [92]
Rats, 2 months	DHA 150 and 300 mg/Kg/day, DHA 600 mg/Kg/day, 1 month, *Cognition*	Primary Hip, neuronal culture	↑learing and memory with 150 and 300 mg/Kg/d, ↑ the risk of memory impairment with 600 mg/Kg/d, Upregulation of CB1 and TRPV1 with a dose-dependence	Pan et al. [93]
Rats, 5 weeks	Coconut oil or soybean oil diet or coconut oil diet enriched with E-EPA (0, 0.2 and 1%), 8 weeks, *Inflammation and cognition*	Hip	E-EPA attenuates memory impairment induced by IL-1β	Song and Horrobin [94]
Rats, 2 months	1% EPA, 7 weeks, *Inflammation and cognition*	Hip, Amy, HipTha and PVN	E-EPA improved spatial memory, ↓CRF expression and corticosterone secretion, ↑NGF expression	Song et al. [95]
Rats, 5 weeks	Pure E-EPA, Injection of IL-1β (15 ng/10μL/rat), 7 weeks, *Inflammation and cognition*	Hip	E-EPA improved memory, ↑Ach release, ↑NGF and ↓IL-1β expression	Taepavarapruk and Song [96]

5-HT, serotonin receptor; AA, arachidonic acid; Ach, acetylcholine; Akt, kinase; ALA, alpha-linolenic acid; Amyg, amygdale; Bcl-2, antiapoptotic molecule; BDNF, brain-derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase II; CB1, cannabinoid receptor 1; Cer, cerbellum; COX2, cyclo-oxygenase 2; CRF, corticotrophin-releasing hormone; Cx, cortex; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; E-EPA, ethyl EPA; Jak, Janus kinase; Hip, hippocampus; HipTha, hippocampe thalamus; IL-1β, interleukin-1β; LA, linoleic acid; LPS, lipopolysaccharides; NGF, nerve growth factor; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PVN, paraventricular nucleus; STAT, Signal Transducers and Activators of Transcription; Str, striatum; TRPV, Transient Receptor Potential Vanilloid.

4 studies in APP transgenic mice [145,146,148,149], albeit to a lesser extent in the 3xTg-AD model [147,150]. Tau-laden tangles are equally important in AD but appear to respond less to DHA treatment. Nonetheless, DHA-induced decreases in phosphorylated soluble tau, with unchanged levels of insoluble tau, have been reported by 2 groups [147,150]. Finally, 3xTg-AD mice genetically altered to increase brain DHA levels using the *fat-1* transgene had less Aβ and tau pathologies [151], further underscoring the positive impact of increasing brain DHA concentrations on AD neuropathology.

Preclinical intervention studies have perhaps shown even more convincingly a protective effect of n-3 LCPUFA on synaptic proteins. Postsynaptic dendrites and proteins located therein are affected particularly early in the progression of AD. Losses of postsynaptic proteins such as drebrin (developmentally regulated brain protein), glutamate receptors and PSD95 have been described in AD [144,152–160] and animal models [144,161,162]. Deleterious effects of DHA deprivation on synaptic markers are remarkably striking in the Tg2576 mouse [144,161], but are also detected in the 3xTg-AD model when combined with a high-fat diet [162], as well as in young mice [75] and old rats [163]. On the other hand, DHA exerts upregulating effects on various synaptic proteins such as PSD-95, syntaxin-3 or drebrin in different transgenic models [144,149,161,164] and normal rodents [165,166]. Because accumulating data indicate that synapse defects underlie clinical symptoms of AD, the enhancing effect of DHA on these synaptic markers is likely to have clinical relevance.

Still, evidence of effects of LCPUFA on neuronal function remains scarce. We recently reported that chronic consumption of DHA alters basic electrophysiological properties of entorhinal cortex neurons, thereby correcting anomalies found in the 3xTg-AD mouse [147,164]. More specifically, treatment with DHA prevented the decrease in cellular capacitance observed in aged 3xTg-AD mice [147,164]. These electrophysiological effects cannot be reproduced with an equimolar dose of a precursor of DHA, ALA [164]. Since the capacitance of a given membrane surface area is a constant value for all cells [167], cell capacitance directly reflects the total membrane surface [147,164]. DHA-induced enlargement of neurons is in agreement with previous reports of increased hippocampal neuron size in DHA-treated animals, using cresyl violet staining and stereology [78]. Interestingly, both syntaxin-3 and drebrin, two key synaptic markers, correlated well with cell capacitance readouts [164]. Accordingly, DHA-induced neurite outgrowth and membrane expansion has been shown to depend on syntaxin-3 [168]. Such electrophysiological data combined with synaptic marker assessment in mice altogether support the hypothesis that DHA incorporation in brain tissue can improve synaptic integration and neuronal function.

Beside the aforementioned effects on AD markers, molecular studies also reveal the pleiotropic action of n-3 LCPUFA in the brain (Table 10). Indeed, DHA plays a critical role in regulating membrane fluidity [169], cell signaling [144,161,170], oxidative stress [144,171], gene expression [172], APP metabolism [148,173,174], and inflammatory cascades [12,175–177]. In addition, we and others have recently shown that n-3 LCPUFA can stimulate the secretion of neurotrophic factors in the brain [178–180]. These last observations are of particular interest, as neurotrophic factors remain the only compounds known to date to show neurorestorative properties *in vivo* [181].

4.3. Alzheimer's disease and n-3 LCPUFA: clinical evidence

The clinical evidence supporting n-3 LCPUFA use as a supplement or in the food is generally considered stronger for cardiovascular disease outcomes [182,183], including coronary heart disease (CHD) [184], albeit still controversial [185]. The available data has led to recommendation from the American Heart Association (AHA) for higher intake of DHA and EPA. However, clinical evidence for dementia is more difficult to gather, mainly due to the elusive nature and heterogeneity of neurodegenerative diseases, the lack of reliable surrogate markers, and rising evidence that early treatment is necessary [68,136]. On the positive side, it is estimated that an intervention delaying dementia onset by only a few years would result in a dramatic reduction in AD prevalence [186,187], suggesting that a treatment with a mild neuroprotective effect can have a significant global health impact.

The question is whether n-3 LCPUFA can have such an impact. Numerous observational studies have highlighted a possible association between dietary intake of fish and n-3 LCPUFA and a lower risk of dementia [188–191]. The results of these investigations also tell us that the origin (fish *versus* vegetable oil), dietary combination and ApoE status critically influence such an association [192–195]. Similarly, the relative impact of each n-3 LCPUFA subtype (ex EPA *versus* DHA) remains difficult to decipher [196,197]. Epidemiology and preclinical data have naturally provided an irresistible incentive to start clinical trials in patients with a diagnosis of AD, which are reviewed in details elsewhere [68,136,188–191,198]. In short, RCTs do not lend much support to a therapeutic role for n-3 LCPUFA supplementation in the treatment of established AD [114,199]. In retrospect, however, it should have been obvious that beneficial effects of n-3 LCPUFA could hardly be expected when the neurodegenerative process is already well engaged. Long and costly RCTs in preventive settings are clearly required to determine whether DHA or other fatty acids can protect from age-related dementia or alter AD progression [68,200,201].

4.4. Conclusion

Despite drawbacks detailed above, preclinical studies in animal models of AD have taught us that DHA and other dietary fats can modulate fatty acid concentration in cerebral tissue, and consequently key neuropathological markers of neurodegenerative disease. Most importantly, such discoveries are raising the hope that nutritional interventions can exert disease-modifying effects in neurodegenerative diseases. Two major research axes appear to be particularly important. First, the pleiotropic effects of n-3 LCPUFA makes it difficult to assess which therapeutic target is the more relevant. Thus, the main mechanistic pathways by which n-3 LCPUFA impact the brain cognitive function needs to be identified. Second, clinical and neuropathology research must go hand in hand aiming at identifying subgroups with a high chance of benefiting from n-3 LCPUFA treatment. Indeed, it is unlikely that one single drug will benefit all elderly individuals or all AD patients. The traditional “one size fits all” approach used in evidence-based medicine can hardly apply to a complex, elusive disease such as AD. Nevertheless, data accumulated so far strongly suggest that the optimization of brain lipid profile might translate into a realistic strategy to enhance cognitive performance and/or to prevent neurodegenenerative diseases. Therefore, in the years to come, research effort has to be devoted to define the optimal lipid dietary intake for the aging brain and who are the individuals who might benefit the most for it.

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