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The Role of Omega 3 Fatty Acids in Memory Improvement: Possible Mechanisms and Therapeutic Potential

Amare Abera Tareke* Wondu Reta Demissie Moyeta Barisso Gare
Department of Biomedical Sciences, Institute of Health, Jimma university, Jimma, Ethiopia

Abstract
Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) from fish and plant sources are promising dietary supplements to improve brain functions and slow down the progression of memory loss. Previous findings of preclinical, clinical and epidemiological research indicated there is a potential for consideration in therapeutic agent. We summarized the most relevant works literature in understanding the mechanism of omega 3 fatty acids induced memory improvement. The first part of this review focuses on discussion of omega 3 fatty acids and mechanism of memory, emphasis is given to the role of omega 3 PUFAs on memory at different stages/sites of memory formation: including effect on neuronal membrane, neurotransmitter exocytosis, concentration of neurotransmitters, receptors, and signaling molecules as well as neural plasticity for long term memory. The therapeutic potential of omega 3 PUFA in neurocognitive disorders is also summarized from recent clinical trials.
Keywords: Omega 3 fatty acids, memory, neurotransmitters, signaling molecules, therapeutic potential
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1. Introduction: Omega 3 fatty acids

Fatty acids containing a double bond are unsaturated fatty acids, (ω-3) or Omega 3 fatty acid is a family of PUFA, where the number representing the position of the double bond, the occurrence of multiple double bonds in FA also considered by addition of the word "poly"[1]. The synthesis of fatty acids from linoleic acid requires desaturase enzymes because some of these desaturase enzymes are absent in animals including human beings, they are unable to form ω-3 or ω-6 fatty acids de novo and must obtain from their diet. But they can metabolize α-linolenic acid to other longer chains, more unsaturated (ω-3) fatty acids, including Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA), and Arachidonic acid (AA) [2,3].

α-Linolenic acid conversion to EPA, DPA, and DHA is reduced in humans, in particular, conversion to the end product DHA appears to be especially is inadequate, summerized in Figure 1 [4]. EPA, DPA, and DHA are often collectively mentioned as very long-chain (ω-3) PUFA.

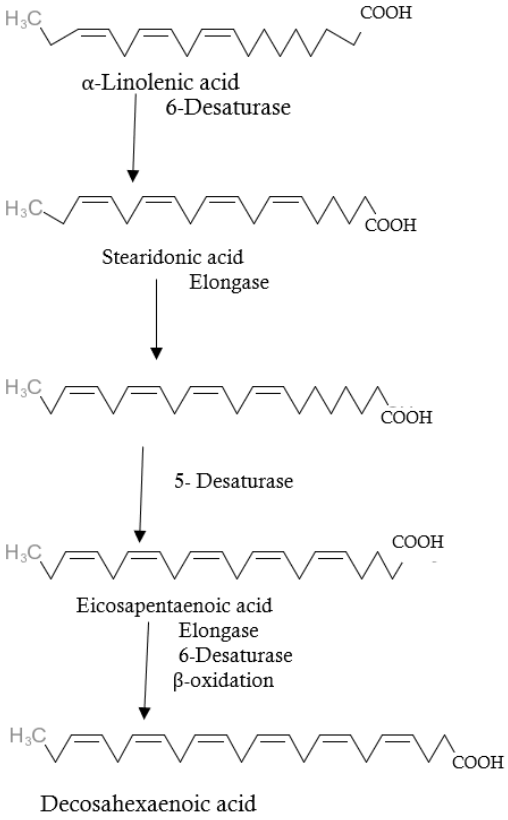

Figure 1. Pathways of α-Linolenic acid conversion to longer chain, more unsaturated omega-3 fatty acids

EPA and DHA, are Omega-3 long-chain PUFA dietary fats with a range of health benefits [6], principally integrated into the membranes confer important properties to cell membranes [7], providing DHA for brain tissue growth and function [8]. Play a role in anti-inflammatory processes and alter the fluidity of cell membranes [9,10]. EPA and DHA are the indispensable component of proper development and healthy aging [11]. Several lipid mediators are produced from EPA and DHA metabolites [12], these lipid mediators together with the parent compound revealed by many authors as advantageous in the prevention or management of numerous diseases.

In this review we will focus on the role of omega 3 fatty acids on memory: emphasis will be given to effect omega 3 fatty acids on neurotransmitters and signaling molecules in memory pathways.

2. Introduction: Mechanism of memory

Memory refers to the storage of learned information in the brain, and is crucial for adaptive behavior in animals, and is associated with gene expression, protein synthesis, and the growth of new synaptic connections at least in long term [13]. Several neurotransmitters are involved in memory, including cholinergic, serotonergic, dopaminergic, GABAergic and noradrenergic neurotransmitters [14]

2.1. Short term and intermediate memory

The stimulus in short term memory formation leads to the activation of modulatory neurons that release neurotransmitter (serotonin) onto the sensory neuron [15]. The serotonin will act on the receptors, increases the concentration of cyclic adenosine monophosphate (cAMP) in the sensory cell [16]. cAMP increment is crucial, it is witnessed [17] injecting cAMP directly into the sensory neuron produces temporary strengthening of the sensory-motor connection.

In presynaptic terminals cAMP recruits the cAMP-dependent protein kinase A (PKA) by binding to the regulatory subunits, causing them to dissociate from and free the catalytic subunits [18]. These subunits can then phosphorylate channels and exocytosis machinery in the presynaptic terminals, causing greater neurotransmitter release and availability [19]. This, in turn, causes momentary increase excitability and widening of the action potential by decreasing specific K^+ currents, to allow greater Ca^{2+} influx into the presynaptic terminal with each action potential [20]. The greater Ca^{2+} influx contributes to the enhanced transmitter release like glutamate. Glutamate released into the synaptic cleft, temporarily strengthening the connection between the sensory and motor neuron.

Today the best possible explanation for calcium-dependent presynaptic neurotransmitter release is through synaptotagmin, an integral protein of synaptic vesicles [21]. Cytoplasmic domains of some identified synaptotagmins have two repeating structures, called C2 domains. Calcium binds with the C2A and C2B domains of synaptotagmin, Ca^{2+} binding to acidic residue on the C2 domains of synaptotagmin enhances the association between synaptotagmin and the plasma membrane Soluble NSF Attachment Protein Receptor (SNARE), syntaxin [22,23].

The effects of serotonin on memory depend on the activation of serotonergic receptors located on distinct subsets of neurons [24]. Many of these effects are produced through the modification of cholinergic, dopaminergic, GABAergic or glutamatergic transmission [25]. Facilitation during intermediate-term sensitization involves both presynaptic (PKA, Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII)) and postsynaptic ($Ca2^+$, CaMKII) covalent modifications, as well as both presynaptic and postsynaptic protein synthesis [26]. Short-term and intermediate-term memory correspondences synaptic strengthening that lasts from minutes to hours, and long-term memory parallels synaptic strengthening that persists from days to weeks [27].

2.2. Long term memory

Protein synthesis and gene expression are required for long-term memory formation [28], after repeated release and long-term sensitization by serotonin [29]. To demonstrate the pathway for long term memory formation various previous works of literatures revised [30–34], repeated and long term sensitization by serotonin increases the release of glutamate, then bind to AMPA receptors postsynaptically and depolarizes the membrane allowing Ca^{2+} entry accompanied by stimulation of N-methyl-D-aspartate (NMDA) type glutamate receptors [35]. Adenylyl cyclase activation by Ca^{2+} or by modulatory inputs through G-protein-coupled receptors results in long term potentiation (LTP). A cascade of molecules including PKA activated in response to increase in cAMP level then translocates into the nucleus and phosphorylates cAMP response element binding protein (CREB). In addition, the persistent increase in cAMP recruits mitogen-activated protein kinase (MAPK) [36,37]; through catalytic subunit of cAMP-dependent protein kinase (PKA).

CREB and MAPK then move to the nucleus phosphorylates transcription factors and activates the gene expression required for long-term memory, PKA activates gene expression by means of the cAMP response element binding protein of CREB-1 [38]. CREB-1 induces the transcription factor CCAAT-enhancer binding

protein (C/EBP), which is critical for long-term facilitation and leads to the second wave of gene expression that produces the growth of new synaptic connections [39], brain-derived neurotrophic factor (BDNF) and tissue plasminogen activator (tPA) are among the effectors activated [33].

Several kinases and phosphatases modulate CREB mediated responses including PKA, CaMKII, CaMKIV, RSK2, MAPK, and PKC, suggesting involvement and extensive cross talk of different pathways [40]. Ling Du and Joel D. Richter conducted a functional assay to identify Activity-dependent polyadenylation of brain-derived mRNAs in neurons injected into surrogate Xenopus oocytes and found many mRNAs undergo activity-dependent polyadenylation in neurons corresponding with increased translation in the synapto-dendritic compartment [41]. Among them gamma CaMKII, ABP, ELK2, Map2, RCM3, alpha CaMKII showed activity-dependent phosphorylation, all the proteins encoded by them (ABP, dCaMKII, aCaMKII, RCM3/calmodulin, Map2) are found in dendrites, the proteins encoded by two of the mRNAs, Map2 and ABP, are synthesized in synaptoneurosomes treated with glutamate [41].

Activation of CREB-1 and inhibition of CREB-2 accelerate long term memory formation, both excitatory and inhibitory transmitters can activate signaling pathways that activate/inhibit transcription via CREB-1 and CREB-2 and subsequently affect the structure of nucleosomes through acetylation and deacetylation of the residues of histone proteins in chromatin [42]. Agents that decrease the activity of CREB-1 specifically block the formation of long-term memory, whereas agents that increase the amount or activity of the transcription factor accelerate the process [43].

3. Omega 3 fatty acids and memory

Recent researches are examining the neurocognitve aspects of omega-3 fatty acids (alpha-linolenic, eicosapentaenoic, docosahexaenoic) and the critical role of these essential fats in the functioning of the central nervous system. Investigations have linked omega-3 fatty acids to a number of neurocognitive disorders, omega 3 fatty acids generally investigated for their effect on memory [44–47].

3.1. Omega 3 fatty acids and neurotransmitter exocytosis

Action potential arriving at a nerve terminal allows Ca^{2+} entry through voltage-dependent Ca^{2+} channels [48]. Calcium ions then bind to synaptotagmins [49]. The release of neurotransmitter involves the recruitment of the SNARE protein complex which provides the driving force to initiate the fusion of secretory vesicles with the plasma membrane [50]. Accordingly, the presence of several important proteins, such as SNARE proteins (SNAP25, Syntaxin, and VAMP2), Munc18, Synaptophysin and synaptotagmins [51–53], has been observed during exocytosis. It was proposed that segregation of these proteins into different membrane may have a regulatory role on neurotransmitter release [54].

Synaptophysin, which reflects synaptic density and synaptic vesicle formation, shown to increase expression in omega 3 PUFAs supplementation [55]. In another study, although, genes encoding for synaptotagmin1, syntaxin1A and synaptobrevin1 not affected by PUFA incorporation in the membrane, increases exocytosis and neurotransmission was observed [56].

3.2. Omega 3 fatty acids and neurotransmitters

3.2.1. Serotonin

Serotonin synthesized from its precursor amino acid tryptophan, released from the presynaptic neuron and act on its receptors. The amino-acid l-tryptophan reduction can cause weakening of serotonin activity [57], but researches are deficient on the role of omega 3 fatty acids and tryptophan concentration. Diet-induced perinatal omega-3 fatty acid depletion is associated with significant alterations in 5-HT and 5-HIAA content in the bain of rats [58]. Arachidonic acid an omega 6 fatty acid can generate prostaglandin E2, which are potent inhibitors of serotonin discharge [59]. Generation of E_2 series prostaglandins can be inhibited by EPA in both young and old individuals [60]. Because of this action EPA in the brain might be important for normal serotonin release, which is evidenced by the positive correlation between human plasma omega-3 levels and serotonin metabolite in cerebral spinal fluid [61].

Since serotonin has G-protein coupled receptor and membrane lipid composition affects the receptor activity [62], Omega-3 fatty acids can influence serotonin function through membrane composition. Membrane fluidity is well maintained by DHA [63]. As the membrane becomes more fluid to a certain extent the serotonin receptors become accessibility can bind with ease [64]. Supporting this idea, a decrease in omega-3 fatty acids were linked with diminished serotonergic neurotransmission [65], and DHA deficiency decreases the concentration of serotonin in the frontal cortex [66]. Diet rich with fish tends to restore normal serotonin activity by increasing serotonin transporter proteins [67]. Besides serotonin, fish oil supplementation stabilizes the endocannabinoid 2-arachidonylglycerol (2-AG), dopamine (DA), neuropeptide Y (NPY), and CaMKII, silent mating type information regulation 1 (SIRT-1), and BDNF [68].

3.2.2. Glutamate

Since its discovery the function of glutamate in synaptic transmission, plasticity and development are well well-known; acting through three three receptor classes, NMDA receptor, the AMPA receptors (AMPARs) and Metabotropic glutamate receptors (mGluRs) involved in memory [69]. Omega 3 fatty acids deficiency decrease vesicular glutamate transporter 1 (VGlut-1) and vesicular glutamate transporter 2 (VGlut-2) with alteration in glutamate discharge amount in old rats [70]. Glutamate uptake in the synapse by astrocytes via glutamate transporters is well inhibited by DHA, which increase glutamate concentration at the synapsed by slow down removal regulates synaptic efficiency [71]. Age-induced deprivation of glutamatergic transmission in the hippocampus and memory deficit is aggravated by ω-3 PUFA deficiency, making clear the possible importance in this manner [70].

In transgenic mouse model of Alzheimer's disease, dietary n-3 PUFA reduction was coupled with initiation caspases and reduction in NMDA receptors in the brain [72]. Dyall SC. and his colleagues [73], noted dietary supplementation of old animals with omega-3 PUFA reverts GluR2 and NR2B glutamate receptor deficits, and improve phospholipid fatty acid profiles, with relevant changes in glutamatergic transmission. Ontogenetic experiments in rats [74], and glutamic synapse, omega 3 PUFA deficiency delayed ontogenic development of NMDA, AMPA, CaMKII contents, although normalized later in adulthood, hippocampal phospholipid DHA content reduction was also associated with decreased brain function and neural plasticity.

3.2.3. Acetylcholine

Acetylcholine is also indicated as one of neurotansmitters in different stages of memory formation [75]. Acetylcholine in different brain areas could augment LTP and nicotinic enhancement of LTP [76]. In memory impairment induced by IL-1β adimistration, which is directly related to memory deficits by diminishing acetylcholine release, ω-3 fatty acids considerably enhanced memory by overturning [77]. The (ω-3) PUFA insufficiency caused a significant loss of DHA in the membrane and accounted for 10% drop in muscarinic receptor binding [78]. Thus, diet lacking ω-3 PUFA decreased cholinergic neurotransmission, perhaps by altering membrane composition.

3.2.4. Other neurotransmitters

ω-3 PUFA deficiency during lactation can alter neural activity including dopaminergic transmission [79]. It has been postulated that DHA restores dopamine receptor density in disease conditions affecting dopamine receptors [80], also dopamine-containing vesicles decrement were associated with ω-3 PUFA deficiency [81], accompanied by decreased neurotransmitter concentration, alteration in membrane characteristics and monoamine transporters.

3.3. Omega 3 fatty acids and Neural plasticity

In the formation of long term memory, which, accomplished by new protein synthesis and gene expression, synaptic plasticity will take place, either in the form of long-term potentiation (LTP) or long-term depression (LTD) in various brain areas with multiple signaling molecules [82]. LTP and LTD are a result of modifications in postsynaptic AMPAR phosphorylation [83]. LTP is linked with ser-831 of CaMKII and PKC [84,85], on the other hand, LTD was found to be associated with ser-845, devoid of any alteration in ser-831 [86].

Morphological changes in LTP consist of growth of new dendritic spines, enlargement of preexisting spines and their associated postsynaptic densities (PSDs), and the splitting of single PSDs and spines into two functional synapses [87,88]. On the other hand, Roberto Malinow and Robert C. Malenka in 2002 published a review on AMPA receptor trafficking and synaptic plasticity putting together shreds of evidence on activity-dependent changes in synaptic function lie behind in memory formation, there was AMPA receptor endocytosis in LTD and transport of AMPA receptor to synapses during LTP [89].

NMDA receptors stimulate the generation of phospholipase A_2, which is important in LTP, arachidonic acid act presynaptically to modify neurotransmitter release in LTP [90], deficiency of arachidonic acid decreases phospholipase A_2 activity and diminishing in LTP [91]. Deficiency of arachidonic acid can be reversed by dietary supplementation of DHA, DHA not only stabilizes arachidonic acid, but also restores normal neurotransmitter release and the diminishing in LTP in old rats [92]. DHA is vital for the initiation of LTP [93] and blocks LTD in vitro [94]. Numerous writings estabilished dietary deficiency of ω-3 PUFA accelerates the aging by declining longevity and learning ability in rats [95,96].

In doing so, DHA could act on postsynaptic sites [97], inhibiting the K^+ channel [98]. Since the K^+ channel blockers, can induce NMDA-independent long lasting modulation in the Schaffer collateral of hippocampal slices [99], it is probable that DHA may act through this channel. Besides, other pieces of vidence also support this concept [100–102], K^+ channel regulates backpropagation of action potentials [103]. Because the back-propagation is identified to regulate synaptic plasticity[104], limiting back propagation [105,106], DHA may contribute to LTP by changing membrane excitability.

The diet containing DHA enhanced levels BDNF, CREB and synapsin I, Akt, and CaMKII, and reduced hippocampal oxidized protein levels [107]. Akt and CaMKII signaling are decisive in BDNF action on synaptic

plasticity and memory [108]. Contrary to this study, ω-3 deficiency disturbed BDNF and components of BDNF signaling pathway (TrkB, CaMKII, Akt and CREB) [109]. Putting together enrichment of diet with omega-3 FA could stabilize the levels BDNF, and thus, regulate neural plasticity [110].

3.4. Omega 3 fatty acids and gene expression

Kitajka K et al. conducted extensive measurement on changes of rat brain gene expression by dietary ω-3 fatty acids, a number of genes over expressed and some under expressed [111]. The ATP-generating machinery of the brain increased to ω-3 fatty acids intensively, maintaining ionic balance and maintaining Na-K ATPase activity is important in nerve transmission [112]. Amplification of proteins involved in signal transduction (calmodulins, etc.) and plasticity has been suggested [113]. Genes encoding synuclein α and gama also were overexpressed [111]. Synuclein α involved in neural plasticity and is related to learning in the brains of songbirds, its role in synaptogenesis has also been proposed [114], and it is discussed previously plasticity involves morphologic changes, synaptogenesis in the cerebellar cortex of adult rats was shown [115].

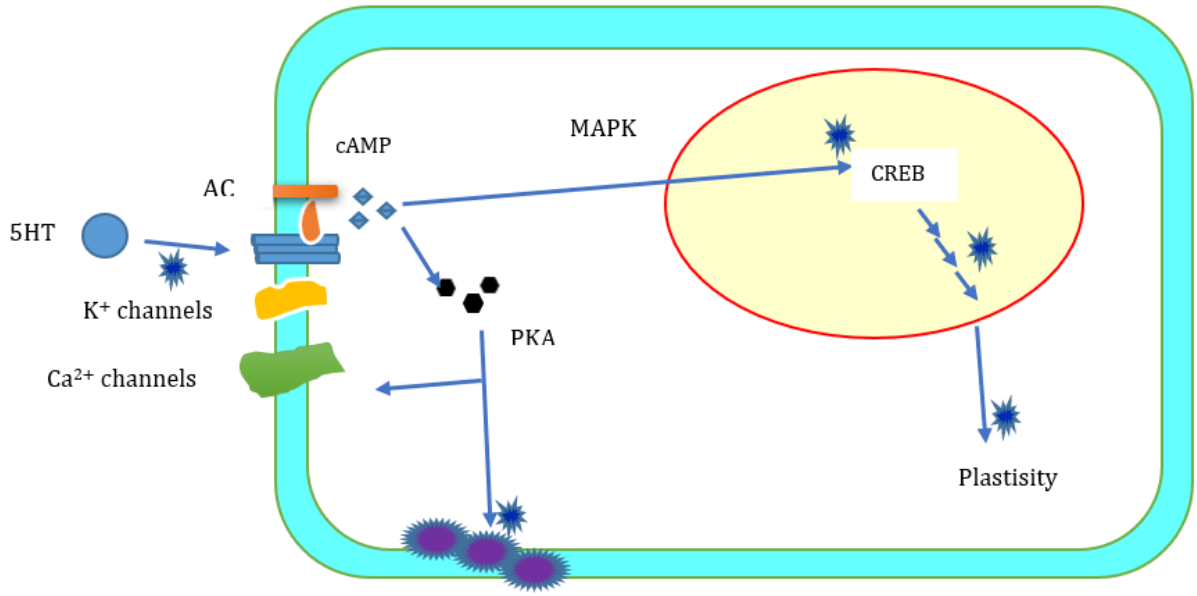

Figure 2. Possible effects of omega 3 PUFA in short term and long term memory: in short term sensitization a transient release of serotonin leads to modification of pre-existing proteins. The serotonin acts on a transmembrane serotonin receptor to activate the enzyme adenylyl cyclase (AC), which converts ATP the second messenger cyclic AMP. In turn cyclic AMP recruits cAMP-dependent protein kinase A(PKA), then phosphorylate substrates (channel and exocytosis machinery) in the presynaptic terminals, leading to enhanced transmitter availability and release. In long term sensitization, repeated stimulation causes the level of cAMP to rise and persist for several minutes. The catalytic subunits can then translocate to the nucleus, and recruit the mitogen activating protein kinase (MAPK). In the nucleus, PKA and MAPK phosphorylate and activate the cAMP response element-binding (CREB) protein activating several immediate-response genes, and leading to different forms of plasticity. Omega 3 PUFAs increase the availability of neurotransmitters, receptors, membrane fusion for exocytosis, signalling molecules indicated by the blue star.

4. Evidence of omega 3 fatty acids as therapeutic agents

Clinical trials mainly focused on the treatment of dementia, supplementation in healthy adults and developing children. In elderly omega 3 fatty acid supplementation for cognitive decline and dementia have promising advantages, omega-3 supplementation reduces verbal episodic memory deteriorations [116], n-3 PUFAs integrated into phosphatidylcholine, activate cognitive function in the elderly [117]. In elderly with memory complaint without dementia, DHA improves cognitive performance [118].

The beneficial effect of n-3 PUFAs in the elderly at risk of dementia is recognized [119]. Increased consumption of DHA and EPA helped mental conditions in older people by reducing the risk of progressing to dementia [120], long chain omega 3-FA enhance memory functions in healthy older adults [121]. On the other hand, 90 days of DHA supplementation showed no significant effects on cognitive functioning in healthy aging population [122], and Polyunsaturated fatty acids, on cognitive decline over 3 years in elderly people with memory complaints in another study [123].

Results from PUFA levels and cognitive performance measures in children also indicated omega 3 supplementation, and decrease the consumption of ω-6 fatty acids are important for cognitive function [124,125].

Following the EPA-rich supplementation, of young adults, neurocognitive functioning was enhanced after a 30-day of supplementation in the same group of individuals than prior to supplementation [126].
The accumulated knowledge indicates that healthy populations may have preventive benefits from omega 3 PUFA intake, and older adults with memory complaints or mild cognitive impairment, and maybe subgroups of patients with mild/moderate Alzheimer's disease may also show such benefits [127]. Also, consumption of DHA at a dosage of 300 mg/day for 15 weeks or 100 mg/day for 30 weeks is recommended for non-demented elderly as safe, well tolerated, and without negative effects [128].
Table 1: recent trials of omega 3 PUFA supplimentation and cognitive function

No	Study	Subjects	Sample size	Supplimentation	Duration	Parameters measured	Response	Citation
1	Jaremka et al., 2014	Healthy, overweight and sedentary adults	138	Omega 3 PUFA	4 months	Verbal episodic memory	Attenuated	[116]
2	Konagai et al., 2013	Males aged 61-72 years	45	Krill oil or sardine oil (n-3 PUFA)	12 weeks	working memory task, changes in oxyhemoglobin concentrations	Significantly greater than controls	[117]
3	Vakhapova et al., 2010	50-90 years non-demented, with memory complaints	157	Phosphatidylserine Containing ω–3 Fatty Acids	15 weeks	The Rey Auditory Verbal Learn-ing Test, Rey Complex Figure Test, and a computerized cognitive battery.	Improved	[118]
4	Sinn et al., 2012	>65 years with MCI	50	EPA, DHA	6 months	Verbal fluency Rey Auditory Verbal Learning Test and others	Improved No change	[120]
5	Külzow et al., 2016	50–75 years	44	Omega 3 PUFA	26 weeks	object-location memory	Significantly better	[121]
6	Stough et al., 2012	Healthy, 45-77 years	74	DHA	90 day	Congnitive function	No significant effects	[122]
7	Andrieu et al., 2017	non-demented, aged 70 years or older, with memory complaint	1680	EPA, DHA	3 years	Selective Reminding test, Mini-Mental State Examination orientation items, Digit Symbol Substitution Test, and Category Naming Test	No effect	[123]
8	Kirby et al., 2010	Children 8-10 years	450	EPA, DHA	16 weeks	Cognitive assessments	Significantly higher for many of the parameteres	[125]

5. Conclusions

As a component of neuronal cell membrane, omega 3 fatty acids stabilize membrane fluidity, increasing the availability of receptors for neurotransmitter binding: by increasing syntaxin for SNARE complex formation, an increase in SNARE complex availability at the plasma membrane, expose a hidden site on Munc18a for SNARE complex binding, and/or bring a conformational change in Syntaxin1a potentiates Ca^{2+} dependent exocytosis. Omega 3 PUFAs increase neurotransmitter concentration by inhibiting neurotransmitter uptake, increase

availability of receptors for binding, act on several signaling molecules to enhance LTP and affect gene expression including neurotrophic factors. Thereby improving the memory of both demented and healthy animals. The accumulated knowledge indicates that healthy populations including school children and adults may have cognitive benefits from omega 3 PUFAs intake, and older adults with memory complaints or mild cognitive impairment, as well as subgroups of patients with Alzheimer's disease, may

Abbreviations
AA: Arachidonic acid, BDNF: brain-derived neurotrophic factor, CaMKII: Ca2+/calmodulin-dependent protein kinase II, cAMP: cyclic adenosine monophosphate, CREB: cAMP response element binding protein, DA: dopamine, DHA: Docosahexaenoic acid, EPA: Eicosapentaenoic acid, LTD: long-term depression, LTP: long term potentiation, MAPK: mitogen-activated protein kinase, mGluRs: Metabotropic glutamate receptors, NMDA: N-methyl-D-aspartate, NPY: neuropeptide Y, PKA: protein kinase A, PUFA: Omega-3 polyunsaturated fatty acids, SNARE: Soluble NSF Attachment Protein Receptor, tPA: tissue plasminogen activator, Vglut: vesicular glutamate transporter

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The authors declare that they have no competing interests.

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AA prepared the primary draft, MB and WR revised the draft and amended by AA. All authors critically reviewed the manuscript. After all authors gave final approval of the paper to be published, AA; the corresponding author have the responsibility to submit the manuscript for publication.

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