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Review

Omega-3 polyunsaturated fatty acids and brain health: Preclinical evidence for the prevention of neurodegenerative diseases

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ABSTRACT

Background: As the prevalence of neurodegenerative diseases increases steadily, the need to develop new treatment approaches intensifies and the possibility of targeting risk and protective factors to delay onset of these diseases is attracting more interest. Dietary habits stand as one of the most promising modifiable risk factors for both Alzheimer's (AD) and Parkinson's (PD) diseases.

Scope and approach: Over the last 30 years, several groups have generated data indicating that concentrations of specific brain lipids highly depend on dietary intake. Preclinical results show that treatments with omega-3 polyunsaturated fatty acids (n-3 PUFA) improve cognition, provide neuroprotection (and even neurorestoration), reduce neuroinflammation and influence neuronal function, while high-fat diets exert deleterious effects. Preclinical experiments have been conducted in well-recognized animal models of AD, PD, and ischemic stroke.

Key findings and conclusions: These studies have shown that dietary n-3 PUFA treatments consistently improve cognitive performance in animal models and may also exert disease-modifying actions. N-3 PUFA also provide protection to dopaminergic neurons in animal models of PD and possibly recovery after lesion. Furthermore, some of these effects might depend on specific diet formulations to protect long-chain fatty acids from oxidation or synergies with other nutrients. More generally, this review aims at providing evidence that adjustments in the consumption of dietary lipids alone or combined with other nutrients may be a cost-effective intervention to optimize brain function and prevent AD or PD.

1. Introduction

Neurodegenerative diseases (NDD) stand between us and the hope of successful aging. More than 40 million people worldwide are living with Alzheimer's disease (AD) or related dementia, a number expected to double by 2031 (Hebert, Weuve, Scherr, & Evans, 2013; Lambert et al., 2014). The rise in life expectancy has also increased the prevalence of Parkinson's disease (PD), which now affects more than 10 million people worldwide (Pringsheim, Jette, Frolkis, & Steeves, 2014). For both diseases, but particularly for AD due to the weaker efficacy of treatment, it is of prime importance for patients, their loved ones and the society as a whole, that we rapidly develop new therapeutic strategies. In the AD field, the majority of preclinical and clinical studies have focused on the two neuropathological markers: amyloid plaques (Aβ peptide) and neurofibrillary tangles (tau) (Gauthier et al., 2016; Katsuno, Tanaka, & Sobue, 2012; Scheltens et al., 2016). However, since 2004, despite marked research efforts, no new drug has yet been marketed. The failure of recent AD clinical trials can be attributed in part to the complexity of the disease, but also to the reliance on compounds, such as large biopharmaceuticals, with poor central nervous system (CNS) bioavailability (Katsuno et al., 2012; St-Amour et al., 2014, St-Amour, Cicchetti, & Calon, 2016; Yu & Watts, 2013).

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An additional challenge to the management of NDD comes from the fact that when the diagnosis is made based on symptoms, the disease has progressed to a phase in which it is difficult to treat, and obviously too late to prevent (Calon, 2011; Cummings, Doody, & Clark, 2007; Emery, 2011; Kivipelto & Mangialasche, 2014; Scheltens et al., 2016). Our health systems in the Western world have been built to react to clinical symptoms, when the severity of symptoms has forced patients to consult a health professional. At least for brain diseases, symptomatic treatment is the norm rather than the exception (Cummings et al., 2007; Fox et al., 2011; Herrmann, Lanctôt, & Hogan, 2013). However, in the case of neurodegenerative diseases, there is a growing understanding that the irreversible nature of their pathophysiology may not fit so well this traditional way of responding to a health problem (Katsuno et al., 2012). Indeed, it is becoming increasingly clear that key events in AD or PD pathogenesis occur many years before symptoms. When symptoms are evident, real therapeutic opportunities may just be long gone.

Including preventive approaches will thus probably impose itself as an inescapable principle of the medical care of NDD (Hickman, Faustin, & Wisniewski, 2016; Katsuno et al., 2012; Kivipelto & Mangialasche, 2014; Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). A valuable strategy for prevention is to identify modifiable risk factors and use this knowledge to act early to reduce the incidence of NDD (Barnes & Yaffe, 2011; Kivipelto & Mangialasche, 2014; Norton et al., 2014; St-Amour et al., 2016). There is hope that modulating environmental factors as early as possible could curb disease progression and extend quality of life before severe symptoms appear (Exalto et al., 2014; Kivipelto & Mangialasche, 2014; Ngandu et al., 2015; St-Amour et al., 2016). To address this issue there is thus a need to develop preventive tools, to intervene much earlier, using secondary or even primary prevention paradigms (Barnes & Yaffe, 2011; Kivipelto & Mangialasche, 2014; Norton et al., 2014; Scheltens et al., 2016; St-Amour et al., 2016). However, patients subjected to preventive treatments show a lower acceptance of adverse effects, higher rate of nocebo affect and, consequently, at risk of poor adherence to treatment (Barsky, Saintfort, Rogers, & Borus, 2002; Stathis, Smpiliris, Konitsiotis, & Mitsikostas, 2013; Zis & Mitsikostas, 2015). Opposition to vaccine offers a vivid example as many people are reluctant to be vaccinated against severe diseases, even despite the well-known benefit/risk balance for individuals and for the whole society (Bean, 2011). Therefore, the development of inexpensive and safe interventions, which can be used on large scale, should continue to receive growing interest from public funding agencies.

Nutrition is often considered as one of the most promising modifiable risk factors for both AD and PD, a contention fully appreciated in ongoing or published multidomain intervention studies (Gillette-Guyonnet, Secher, & Vellas, 2013; Ngandu et al., 2015; Solomon et al., 2014; Vellas et al., 2014). As a result, many groups worldwide have been interested in the development of nutraceuticals strategies against these diseases, especially using omega-3 polyunsaturated fatty acids (n-3 PUFA). (Calon & Cole, 2007; Calon, 2011; Joffre, Nadjar, Lebbadi, Calon, & Laye, 2014).

2. Omega-3 polyunsaturated fatty acids (n-3 PUFA): how do they reach the brain?

In the pharmaceutical world, bioavailability is determinant in the ultimate clinical efficacy of drugs and can, at least in part, be ascertained at the preclinical level. A similar approach can be taken with nutraceuticals. However, CNS diseases offer an additional challenge compared to peripheral diseases: the blood-brain barrier (BBB). The BBB is formed of tightly attached endothelial cells surrounding every microvessel feeding the brain, in close interaction with other brain cells such as pericytes, astrocytes and neurons (Cornford & Hyman, 2005; Daneman & Prat, 2015; Oldendorf, Cornford, & Brown, 1977; Weiss, Miller, Cazaubon, & Couraud, 2009). The BBB offers protection to cerebral tissue with the consequence that most endogenous and exogenous molecules circulating in the blood cannot reach the central nervous system to exert neuroactivity. In the field of neuropharmacology, cerebral bioavailability remains one of the steepest obstacles to the development of new drugs (Henderson & Piquette-Miller, 2015; Kesselheim, Hwang, & Franklin, 2015).

To exert a rapid effect on the brain, nutrients must also cross the BBB. Evidence suggests that dietary lipids are particularly bioavailable for cerebral tissue. Work largely done between 1970 and 1990 has shown that brain lipid levels are highly dependent on their intake, implying a notable exchange between the periphery and the brain. Seminal work aiming at studying the effect of deficiencies have pointed out alterations in the fatty acid (FA) composition of various subcellular fractions from the brain of rodents (Alling, Bruce, Karlsson, & Svennerholm, 1974; Bourre et al., 1984; Galli, White, & Paoletti, 1971; Sun, 1972). Later studies progressively worked on more specific FA, mostly using vegetable oils, evidencing for instance opposite effects between n-6 PUFA and n-3 PUFA (Bourre et al., 1984; Lamptey & Walker, 1976). Direct respective effects on brain concentrations of dietary long-chain PUFA such as docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) or arachidonic acid (ARA) have also been shown in rodents or non-human primates (Arsenault, Julien, & Calon, 2012; Calon et al., 2005; Diau et al., 2005; Joffre et al., 2014; Salem, Litman, Kim, & Gawrisch, 2001, Salem, Vandal, & Calon, 2015). Other similar diet/brain relations have been shown for other classes of FA such as mono-unsaturated fatty acids (MUFA) (Arsenault, Julien, Chen, Bazinet, & Calon, 2012; Greenwood & Winocur, 1996) or *trans*-fat (Cook, 1978; Phivilay et al., 2009). This sensitivity (or vulnerability) of brain tissue to dietary intake may seem surprising since it implies that a deficiency of a given FA could affect its function. From an evolutionary point of view, it suggests that the first human beings lived in an environment with sufficient supply in n-3 PUFA essential to brain function (Crawford et al., 2000; Cunnane, Plourde, Stewart, & Crawford, 2007).

To the eyes of a neuropharmacologist, the chemical structure of FA suggests free diffusion across the BBB(Hamilton & Brunaldi, 2007). A relatively small molecular size, very few potential hydrogen bonds and highly lipophilic moieties are all key characteristics of brain penetrant molecules (Chikhale, Ng, Burton, & Borchardt, 1994; Pardridge, 2012). Recent studies in animal models have confirmed the importance of diffusion of plasma non-esterified DHA to supply the brain (Chen et al., 2015) through a non-saturable uptake mechanism across the BBB(Calon, 2011; Ouellet et al., 2009). However, it is also clear that most DHA in the blood is bound to carriers such as albumin and/or in various esterified forms (Chen et al., 2015). An analogy can be made with cholesterol, which also has the physicochemical characteristics of a BBB permeable compound (Cattelotte et al., 2008; Do et al., 2011). Due to the binding of cholesterol to blood-borne carriers and its affinity to efflux transporters, it is well known that no significant direct exchange of cholesterol exists between the blood and the brain (Bjorkhem, 2004). Thus, it is important to consider that DHA binding to carriers like lysophosphatidylcholine (LPC) or albumin also influences the uptake into brain tissue (Hachem et al., 2016; Lemaitre-Delaunay et al., 1999; Ouellet et al., 2009). In addition, BBB transporters such as FABP5 (fatty acid binding protein 5) or Mfsd2a (Major facilitator superfamily domain-containing protein 2) have been shown to impact cerebral concentrations of DHA (Nguyen et al., 2014; Pan et al., 2015b), perhaps by affecting its

uptake through the BBB (Pan, Khalil, & Nicolazzo, 2015; Pan et al., 2015). Overall, the current data suggest that, while plasma non-esterified FA are probably the most readily available form of DHA for the brain, it remains likely that exchanges of PUFA between the blood and the brain might be regulated by (lipo)proteins either located in the BBB or circulating in the blood.

One of these potential regulators is apolipoprotein E, which exists in 3 polymorphic alleles in humans. The carriage of ApoE4 has been shown to reduce the uptake of DHA in the CNS based on studies in animal models (Vandal et al., 2014) or human cerebrospinal fluid (CSF) data (Yassine, Rawat, et al., 2016). On the other hand, a slightly higher brain DHA uptake coefficient was recently reported in a small group APOE4 carriers of various age (Yassine et al., 2017), suggesting a complex interaction between APOE carriage and DHA distribution and metabolism. In addition, reduced uptake of DHA has been reported in mice previously exposed for months to a high-DHA diet (Ouellet et al., 2009) and in a mouse model of AD (Calon, 2011), further supporting the existence of mechanism controlling the influx of PUFA at the BBB.

3. Omega-3 fatty acids and Alzheimer's disease: cognition

The association between AD and cognition has been mostly investigated by correlative epidemiological studies, which overall suggest that a high consumption in food rich in n-3 PUFA is associated with better performance and possibly the prevention of age-related cognitive impairment or AD. Most longitudinal or case-control studies show an association between n-3 PUFA consumption or blood levels with lower risks of dementia or AD (reviewed in (Barberger-Gateau, Samieri, Feart, & Plourde, 2011; Morris, 2016; Yassine, Feng, et al., 2016)). Recently, higher serum concentrations of long-chain n-3 PUFA have been associated with better performance on neuropsychological tests, as reported in a cross-sectional study in a Finnish cohort (D'Ascoli et al., 2016). Other recent results, presented at the Alzheimer's Association International Conference in Toronto, indicate that blood DHA levels are significantly associated with superior cognitive ability in two large population-based studies, totaling more than 5000 individuals (Van Duijn et al., 2016).

Results from clinical intervention studies with n-3 PUFA suggest no significant effect after the clinical diagnosis of AD, but still confer limited support to a potential preventive effect (Joffre et al., 2014; Quinn et al., 2010; Salem et al., 2015; Yurko-Mauro, Alexander, & Van Elswyk, 2015). Indeed, larger randomized controlled trials in individuals with age-related cognitive decline report no change or improvement in memory-related endpoints (reviewed in (Joffre et al., 2014; Quinn et al., 2010; Salem et al., 2015; Yurko-Mauro, Alexander, et al., 2015)). Four small clinical trials in MCI (mild cognitive impairment) reported possible cognitive-enhancing effects (reviewed in (Joffre et al., 2014; Quinn et al., 2010; Salem et al., 2015; Yurko-Mauro, Alexander, et al., 2015). However, randomized controlled trials with high-DHA formulations in patients diagnosed with AD have been negative (Freund-Levi et al., 2006; Quinn et al., 2010). Recently published data from the MAPT trial (Multidomain Alzheimer Preventive Trial) reported no significant cognitive benefit in old participants who received 800 mg/d of DHA supplementation over 3 years (Andrieu et al., 2017). Nevertheless, a posteriori analysis highlights a dose-response association between n-3 PUFA plasma levels and preservation of cognitive performance (Eriksdotter et al., 2015). Finally, preclinical studies with controlled diet very consistently show that increasing DHA concentrations in the brain improves rodent performance in a wealth of different memory tests (Catalan et al., 2002; Joffre et al., 2014). This has been confirmed in various animal models of AD-like neuropathology (Tables 1 and 2) (Arsenault, et al., 2011; Calon et al., 2004; Casali et al., 2015; Hashimoto et al., 2011; Hooijmans et al., 2009; Joffre et al., 2014; Oksman et al., 2006).

4. Omega-3 fatty acids and Alzheimer's disease: neuropathology

DHA-induced decreases in amyloid, tau or synaptic neuropathologies have been reported in animal models of AD over the years (Tables 1 and 2) (Arsenault et al., 2011; Calon et al., 2004; Calon et al., 2005; Casali et al., 2015; Green et al., 2007; Hooijmans et al., 2009; Joffre et al., 2014; Lebbadi et al., 2011; Lim et al., 2005; Oksman et al., 2006; Perez et al., 2010; Teng et al., 2015). More specifically, lower brain Aβ levels after a high DHA intake have been reported by at least 4 groups in amyloid protein precursor (APP)transgenic mice (Hooijmans et al., 2009; Lim et al., 2005; Oksman et al., 2006; Perez et al., 2010) and, to a lesser extent, in the tri-transgenic (3xTg-AD) model (Tables 1 and 2) (Arsenault et al., 2011; Green et al., 2007). Other series of evidence suggest that DHA may also act more directly on neuronal function by progressively integrating cell membranes, without necessarily targeting AD neuropathology per se (Arsenault et al., 2011, Arsenault, Julien, & Calon, 2012; Arsenault, Julien, Chen, et al., 2012; Bruno, Koeppe, & Andersen, 2007). A reduction of markers of neuroinflammation has also been observed following n-3 PUFA intake, which could contribute to a therapeutic effect in NDD (Bazinet & Layé, 2014; Hopperton, Trépanier, Giuliano, & Bazinet, 2016; Lalancette-Hebert et al., 2011; Trépanier, Hopperton, Orr, & Bazinet, 2016). On the other hand, very limited evidence in humans support the contention that n-3 PUFA improves AD neuropathology. One small intervention study has reported a decreased loss of gray matter volume after treatment with a DHA/EPA combo (Witte et al., 2014) and Yassine, Feng, et al. (2016); Yassine, Rawat, et al. (2016) showed significant associations between low serum docosahexaenoic acid (DHA) concentrations with: (i) brain amyloid load (PiB PET), (ii) smaller brain volume (MRI) and (iii) impaired nonverbal memory, in volunteers with no or mild cognitive impairment (Yassine, Feng, et al., 2016). Finally, one must keep in mind that most clinicopathological studies do not detect lower levels of DHA in the brain of AD or PD patients, in part due to the difficulty in assessing lipid levels post-mortem (Cunnane et al., 2009, Cunnane, Chouinard-Watkins, Castellano, & Barberger-Gateau, 2013; Julien et al., 2006; Tremblay, St-Amour, Schneider, Bennett, & Calon, 2011). Overall, preclinical investigations have provided mechanistic data for a potential disease-modifying effect of n-3 PUFA in the prevention of NDD (Calon & Cole, 2007; Cole & Frautschy, 2010; Joffre et al., 2014; Salem et al., 2015).

5. Other fatty acids can influence AD pathogenesis

High adherence to a Mediterranean diet consisting of olive oil, nuts, unrefined cereals, fruits and vegetables has been associated with lower risk of cognitive decline using various epidemiological study paradigms (Feart, Samieri, & Barberger-Gateau, 2010; Panza et al., 2010; Solfrizzi et al., 1999, 2010). The Mediterranean diet is rich in MUFA, which are known to be reduced in AD CSF (Fonteh, Cipolla, Chiang, Arakaki, & Harrington, 2014) and to exert direct effects on the physiology of neurons within the entorhinal cortex-hippocampus loop, which is involved in learning and memory (Arsenault, Julien, Chen, et al., 2012). Oleic acid has been reported to reduce amyloid burden in transgenic APP mice (Amtul, Westaway, Cechetto, & Rozmahel, 2011) and more recently to be a component of abnormal oil droplets found in 3xTg-AD (triple-transgenic) mice and AD brain (Hamilton et al., 2015). Finally, studies in animal models suggest that a high saturated fat intake, included in 'westernized' diets, contribute to significantly impair memory-

Table 1
Effects of omega-3 fatty acids on cognition in animal models of Alzheimer's disease.

Rodent species and age	Treatment and duration *Model*	Outcomes	Study
Rats, 20 weeks	DHA 300 mg/kg/day 7 weeks *Aβ infused rats*	↓reference memory error	Hashimoto, Hossain, et al. (2005) and Hashimoto, Tanabe, et al. (2005)
Rats, 20 weeks	DHA 300 mg/kg/day 12 weeks *Aβ infused rats*	↓reference and working memory errors	Hashimoto, Hossain, et al. (2005) and Hashimoto, Tanabe, et al. (2005)
Mice, 17 months	DHA 0.6% 103 ± 5 days *Tg2576*	↑spatial memory	Calon et al (2004)
Mice, 8 months and 15 months	DHA 3.5 g/Kg diet 6 or 13 months *APP/PS1*	↑spatial memory in 15-month-old mice	Hooijmans et al. (2009)
Mice, 6 months	DHA 0.4% 3-4 months *APP/PS1*	↑exploration activity No change in spatial learning in Morris water maze	Oksman et al. (2006)
Mice, 12–14 months	DHA 0.6 g/Kg/day 8 to 10 months *3xTg-AD*	↑object recognition	Arsenault et al. (2011)
Rats, 17–18 months	DHA 0.6% 4 months *APP/PS1*	↑spatial memory	Teng et al (2015)

Aβ, amyloid beta; APP, amyloid protein precursor; DHA, docosahexaenoic acid.

related behavior and increase astrogliosis as well as signs of AD neuropathology, such as Aβ burden or, perhaps less consistently, tau phosphorylation (Barron, Rosario, Elteriefi, & Pike, 2013; Gratuze et al., 2016; Ho et al., 2004; Julien et al., 2010; Leboucher et al., 2013; Martin, Jameson, Allan, & Lawrence, 2014; Refolo et al., 2000).

6. Omega-3 fatty acids and Parkinson's disease: neuroprotection and neurorestoration

A clear distinction can be made in the clinical care of PD compared to AD because of the availability of very efficient symptomatic treatments for the former NDD. Pharmaceutical or surgical approaches can at least partially relieve motor symptoms of nigrostriatal dopaminergic denervation in most patients (Fox et al., 2011). However, no treatment yet can alter the progression of the neurodegenerative processes underlying PD (Meissner et al., 2011; Schapira, Olanow, Greenamyre, & Bezard, 2014). Neuroprotection, neurorescue, neurorecovery and neurorestoration are all words dear to the heart of PD 'semanticologists'. While the former can be attributed to treatment before the occurrence of nigral cell death, the 3 latter refer to disease-modifying intervention after the diagnosis. The holy grail of PD research is to develop approaches that not only stop neurodegeneration, but also actually reverse it (Meissner et al., 2011; Schapira et al., 2014).

In the last 10 years, we accumulated data in support of the neuroprotective effects of n-3 PUFA dietary intake against toxicity induced by a neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Bousquet et al., 2008, 2009, 2010, 2011, 2012; Bousquet, Calon, & Cicchetti, 2011; Calon & Cicchetti, 2008). While MPTP administration induced a 30% neurodegeneration of dopaminergic nigral cells in C57BL/6 mice fed a "control" high n-6 PUFA diet, no signs of cell death along with higher dopamine (DA) concentrations in the striatum were seen in mice fed a high n-3 PUFA diet (Bousquet et al., 2008). We have also noticed that several key dopaminergic markers correlated with DHA concentrations in the brain of MPTP-treated Fat-1 mice (Bousquet et al., 2011b). Increased brain-derived neurotrophic factor (BDNF) secretion may contribute to the beneficial effect of n-3 PUFA against MPTP neurotoxicity (Bousquet et al., 2009). More recently, we have shown that DHA induces a recovery of the dopaminergic system after an extensive lesion in animal models of PD (Coulombe et al., 2016). After 6-hydroxy-dopamine-induced dopaminergic denervation, a high intake in DHA led to (i) higher dopamine levels in the striatum, (ii) more numerous TH-positive dopaminergic terminals to the striatum, and (iii) larger soma perimeter and area of dopamine neurons (Coulombe et al., 2016). Although cell count remained unchanged, such an enhancement of key components of the dopaminergic system suggests that DHA-triggered compensatory mechanisms may contribute to functional recovery (Coulombe et al., 2016). Therefore, these data suggest that DHA induced neurorecovery and could be used after the diagnosis of PD.

7. Role of n-3 PUFA in neuroinflammatory pathways, a putative protective mechanism in neurodegenerative diseases

A compelling body of evidence has accumulated in the last 10 years linking neurodegenerative diseases with the brain innate immune system (Heneka et al., 2015; Perry, Nicoll, & Holmes, 2010; St-Amour et al., 2016; Wes, Sayed, Bard, & Gan, 2016). More attention has been paid to the role of microglia, the main innate immune system cells in the brain, in the etiology of AD. It is now well accepted that these cells are not only involved in protecting the brain against infection or damage (Ransohoff & Perry, 2009), but they also modulate synaptic functions in the healthy brain (Hanisch & Kettenmann, 2007). An intriguing role in synaptic pruning has been recently demonstrated during brain development and at adulthood, shedding light on the role of microglia and the complement system in the phagocytosis of unnecessary synapses and brain wiring (Kettenmann, Kirchhoff, & Verkhratsky, 2013; Tremblay, Stevens, et al., 2011b). This has led to the concept that microglia/complement dysregulation, occurring during aging or a neurodegenerative process, participates to synaptic loss, not only in diseases such as AD or multiple sclerosis (Hong, Dissing-Olesen, & Stevens, 2016) but also as a consequence to stress (Delpech, Madore, Nadjar, et al., 2015) or dietary lipid unbalance (Madore et al., 2016; Nadjar, Leyrolle, Joffre, & Laye, 2017). In addition,

Table 2
Effects of omega-3 fatty acids on neuropathology in animal models of Alzheimer's disease and Parkinson's disease.

Rodent species and age	Treatment and duration *Model*	Brain regions	Outcomes	Study
Alzheimer's disease				
Rats, 20 weeks	DHA 300 mg/kg/day 7 weeks *Aβ infused rats*	Cx	↓Aβ ↓cholesterol ↓reference memory error	Hashimoto, Hossain, et al. (2005) and Hashimoto, Tanabe, et al. (2005)
Mice, 17 months	DHA 0.6% 103 ± 5 days *APP/Tg2576*	FrCx, Cx and hemi brain	↑drebrin ↓oxidation ↓caspase-cleaved actin ↑antiapoptotic BAD phosphorylation	Calon et al (2004)
Mice, 8 months and 15 months	DHA 3.5 g/Kg diet 6 or 13 months *APP/PS1*	FrCx, Cx, Hip, Acg	No change in rCBV in 8 months old mice ↓Aβ in 15 months old mice ↑rCBV in 15 months old mice	Hooijmans et al. (2009)
Mice, 6 months	DHA 0.4% 3-4 months *APP/PS1*	Hip, FrCx, Cx,Cer	↓Aβ ↓activated microglia	Oksman et al. (2006)
Mice, 12–14 months	DHA 0.6 g/Kg/day 8 to 10 months *3xTg-AD*	ECx neurons, FrCx, Cx	↑DHA and ↓AA ↓seizure-like akinetic episodes ↑cell capacitance ↓firing rate versus injected current	Arsenault et al. (2011)
Mice, 17 and 19 months	DHA 0.6% *APP/Tg2576*	Cx, Hip, parietal Cx	↓Aβ40 and Aβ42 ↓Aβ plaques ↓α- and β-APP *C*-terminal fragments	Lim et al. (2005)
Mice, 3 months	*APPswe/PS1 Delta E9*	Cx, HipV, Str, Hip, liver	↑DHA and ↓AA ↓Aβ plaques ↑drebrin	Perez et al. (2010)
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 *3xTg-AD*	Whole brain	↓intraneuronal Aβ and Tau ↓PS1	Green et al. (2007)
Mice, 12 and 20 months	n-6/n-3 = 25 (4.6Kcalories/g diet) *fat-1* transgene Whole life *fat-1 x 3x-TgAD*	Cx, FrCx	↑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. (2011)
Mice, 17 months	DHA 0.6% 3-5 months *3xTg-AD*	Cx, Hip	↑NMDA receptor subunit (NR2A and NR2B) ↑CaMKII ↓caspase/calpain activity	Calon et al. (2005)
Rats, 17–18 months	DHA 0.6% 4 months *APP/PS1*	Cx, Hip	↓Aβ plaque ↑soluble fibrillar Aβ oligomers	Teng et al (2015)
Parkinson's disease				
Mice, 2 months	DHA/EPA:425/90 mg/kg 10 months *MPTP*	SN, Str	↑TH + nigral cells ↑Nurr1 mRNA ↑DAT mRNA ↑DA in striatum	Bousquet et al. (2008)
Mice, 2 months	DHA/EPA:425/90 mg/kg 10 months *MPTP*	Str	↑BDNF mRNA ↑TrkB mRNA	Bousquet et al. (2009)
Mice, 6 months	n-6/n-3 ratio: 101.79 (3.9 kcal/g diet) Whole life *MPTP repeated injections in fat 1 mice*	Str	Correlation between DHA levels and: ↑TH + nigral cells ↑Nurr1 mRNA ↑DAT mRNA	Bousquet et al. (2011)
Mice, 9 weeks	DHA 0.5–1.0 g/kg/day Week 3 to week 9 after 6-OHDA lesion *6-OHDA*	SN, Str	↑TH + terminals in Str ↑perimeter of DAergic neurons in SN ↑areas of DAergic neuron cell bodies in SN ↑DA turnover in Str	Coulombe et al. (2016)
Rats	Fish oil 4.0 mg/kg of (DHA/EPA:180/120 mg) 21-90 days of life *6-OHDA*	Str	↑DA turnover ↓apomorphine-induced rotational behavior	Delattre et al. (2010)
Cynomolgus female monkey	DHA (100 mg/kg SC or 200 mg/kg PO) before or after the initiation of L-DOPA treatment. *MPTP*	na	↓L-DOPA induced dyskinesias	Samadi et al. (2006)

3xTgAD, triple transgenic model of Alzheimer's disease; 6-OHDA: 6-hydroxydopamine; Aβ, amyloid beta; Acg, anterior cingulate gyrus; APP, amyloid protein precursor; BDNF, Brain-derived neurotrophic factor; CaMKII, calcium/calmodulin-dependent protein kinase II; Cer, cerebellum; Cx, cortex; FrCx, frontal cortex; DA, dopamine; DAT, dopamine transporter; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; ECx, enthorinal cortex; EPA, eicosopentaenoic acid; Hip, hippocampus; HipV, ventral hippocampus; GFAP, glial fibrillary acidic protein; L-DOPA, levodopa; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; na, not applicable; NMDA, *N*-methyl-D-aspartate; PO, *per* os; PS1, presenilin 1; rCBV, relative cerebral blood volume; SC, subcutaneous; SN, substantia nigra; Str, striatum; TrkB, tropomyosine receptor kinase B.

aging and neurodegenerative diseases are accompanied by increased production of proinflammatory factors, components of complement pathways and reactive oxygen species (ROS), which have been largely shown in animal models to be involved in neuronal death and neuropathological processes (Ransohoff, 2016; St-Amour et al., 2016). In addition to microglia senescence, microglia priming, a phenomenon linked to insult, aging, psychological or nutritional stress, is incriminated in the persisting production of proinflammatory factors (Perry & Holmes, 2014). This long-lasting proinflammatory cytokine production in turn activates neuropathological processes of neurodegenerative diseases and promotes cognitive deficit. Recent genetic studies in AD patients have identified variants of genes involved in microglia function as risk factors of AD (TREM-2 [Triggering receptor expressed on myeloid cells 2], CR1 [complement receptor 1], CD33, IL-1RAP [Interleukin-1 receptor accessory protein]), leading to the idea that the corresponding proteins could be targeted to treat AD (Colonna & Wang, 2016; Wes et al., 2016). Of note, TREM2 is of particular interest as this receptor binds lipids to control microglia activity and promote phagocytosis of Aβ(Colonna & Wang, 2016; St-Amour et al., 2016). Altogether, these data place microglia as a targetable cell to prevent and/or treat neurodegenerative diseases.

In this context, the immunomodulatory potency of long-chain n-3 PUFA (DHA and EPA) may be put to use in brain disorders that have an inflammatory component, including AD and PD (Bazinet & Layé, 2014; Joffre et al., 2014; Trépanier, Hopperton, Orr, et al., 2016). For example, n-3 PUFA anti-inflammatory and pro-resolving properties may exert a control on microglia activity and associated neuroinflammatory processes (Bazinet & Layé, 2014; Joffre et al., 2014; Layé, 2010). It has been reported that cerebral expression of proinflammatory cytokines in animal models after endotoxin administration (Delpech, Madore, Joffre, et al., 2015a, Delpech, Thomazeau, et al., 2015c), aging (Labrousse et al., 2012), ischemic stroke (Lalancette-Hebert et al., 2011) or increased Aβ (Hopperton et al., 2016) are reduced in rodents with higher levels of brain DHA. This anti-inflammatory effect could be due to a direct action of DHA on microglia as suggested by in vitro and in vivo data (De Smedt-Peyrusse et al., 2008; Madore et al., 2014). However, whether n-3-PUFA supplementation generates a favorable inflammatory marker profile to prevent NDD is still an open question, as it remains unclear which immune-related abnormality is a potential therapeutic target in these diseases (St-Amour et al., 2016; Yates, Calder, & Ed Rainger, 2014). Mitigated results of fish oil supplementation on peripheral inflammatory markers in AD patients have been reported (Freund-Levi, Vedin, Cederholm, & et al., 2014a; Freund-Levi, Vedin, Hjorth, & et al., 2014b), although DHA levels were negatively correlated to inflammatory markers and phosphorylated tau in the CSF (Freund-Levi et al., 2014a,b). Recently, postmortem changes in n-3 PUFA derived pro-resolving mediators (SPM), known to regulate microglia activity (Hopperton et al., 2016; Rey et al., 2016; Trépanier, Hopperton, Mizrahi, Mechawar, & Bazinet, 2016), have been reported in the brain of AD patients (Wang et al., 2015; Zhu et al., 2016). However, the role of n-3 PUFA in the promotion of a protective microglia phenotype in neurodegenerative diseases remains to be evaluated.

8. Intake, source and formulation of omega-3 fatty acids: conservation, bioavailability and sustainability

From a public health perspective, compared to synthetic drugs, it is an advantage that long-chain n-3 PUFA can readily be obtained from dietary sources. There is no consensus on the recommended dietary intake of EPA and DHA. The World Health Organization recommends that n-3 PUFA intake should represent 1–2% of energy/day while the European Food Safety Authority recommends 250 mg EPA + DHA/day (Aranceta & Pérez-Rodrigo, 2012; Nishida, Uauy, Kumanyika, & Shetty, 2004; Vannice & Rasmussen, 2014). In the US, no clear dietary intake recommendations has been delivered for n-3 PUFA, although in 2002 the Institute of Medicine estimated an adequate intake of 1.6 g or 1.1 g a day of n-3 PUFA (total) for healthy adult men or women, respectively (Trumbo, Schlicker, Yates, Poos, & Food and Nutrition Board of the Institute of Medicine T. N. A., 2002; Vannice & Rasmussen, 2014). Doses of 500 mg or up to 1 g of DHA/EPA per day have been suggested by the International Society for the Study of Fatty Acids and Lipids (ISSFAL) and American Heart Association, particularly based on cardiovascular health (improvement of blood lipid profiles or treatment of coronary artery disease) (Harris et al., 2009; Lee, 2013; Meyer, 2011; Vannice & Rasmussen, 2014). However, most evidence suggests that n-3-PUFA consumption remains lower than abovementioned doses in most countries (Lucas et al., 2010; Meyer, 2011; Papanikolaou, Brooks, Reider, & Fulgoni, 2014; Vannice & Rasmussen, 2014; Yurko-Mauro et al., 2015).

It is also difficult to determine a minimum effective dose of EPA and DHA, at which PUFAs would exert brain benefits. Background levels of EPA and DHA in clinical trial participants are key confounding variables (Calon, 2011; Jernerén et al., 2015). They can result from differences in nutritional intake of EPA and DHA as well as α-linolenic acid (ALA), an essential fatty acid, which is converted into DHA and EPA at varying degrees among individuals (Barceló-Coblijn & Murphy, 2009; Domenichiello, Kitson, & Bazinet, 2015), but also from inter-individual genetic variation in PUFA distribution and metabolism. Most studies in humans are correlative and based on declarative information, evaluated by questionnaire about food habits, or based on blood levels, which do not convey information on the exact dietary intake. Even in animal models, different doses and varying formulations have been utilized and no clear dose-response curves have been established. Therefore, more studies in animals and in humans are necessary to propose a solid recommendation for dietary n-3 PUFA intake as well as to determine a minimum effective dose, particularly when aiming at maintaining brain health.

It is increasingly recognized that marine sources of n-3 PUFA cannot fulfill global human needs in a sustainable manner (Jenkins et al., 2009; Newton & McManus, 2011). One alternative to consider is the use of the metabolic precursor of DHA, ALA, which also increases DHA concentrations in the brain (Barceló-Coblijn & Murphy, 2009; Domenichiello et al., 2015). Various plant seeds contain significant amounts of ALA and represent sustainable sources (Vannice & Rasmussen, 2014). Bioengineered plants could also produce n-3 PUFA-enriched vegetable oils, by improving synthesis of the desired PUFA (Petrie et al., 2012; Qi et al., 2004). Microalgae and biotechnology based on microalgae are also a very promising alternative to produce n-3 PUFA in a sustainable way (Adarme-Vega et al., 2012; Arterburn et al., 2007). As opposed to fish oil, canola and camelina oils extracted from seeds are very versatile because of their stability and heat resistance and are already used extensively in the food industry. Other promising sources include flaxseed/linseed or chia oils, which contains elevated levels of ALA (Vannice & Rasmussen, 2014; Vuksan et al., 2017).

Beside nutritional intake, growing evidence behind the benefits of n-3 PUFA brings a strong incentive to develop formulations to be used as supplements. Some studies suggest that specific types of formulations may provide enhanced bioavailability while others do not (Ghasemifard, Hermon, Turchini, & Sinclair, 2015; Sanguansri et al., 2015; Yurko-Mauro et al., 2015). Since the expected benefits of LC n-3-PUFA likely require chronic consumption, it is unclear how slight differences in initial bioavailability parameters may have significant effects on long-term health outcomes.

Nonetheless, one thing certain is that LC n-3 PUFA are sensitive to oxidation due to the presence of several double bonds in their chemical structures (Arab-Tehrany et al., 2012, pp. 24–33; Shahidi & Zhong, 2010). Therefore, the use of formulations that effectively preserve n-3 PUFA bioactivity is likely to be critical. In preclinical studies, protecting DHA molecules from oxidation can be achieved by using microencapsulated n-3 PUFA formulations, like those developed by DSM Nutritional Products. Microencapsulated DHA can then be incorporated in a pelleted rodent diets. The microencapsulation process into gelatin beads is intended to allow incorporation of DHA into ordinary food such as milk or bread and has been designed to preserve DHA for months (Hogan, O'Riordan, & O'Sullivan, 2003; Kolanowski, Laufenberg, & Kunz, 2004). It is also crucial in n-3 PUFA nutritional supplements for humans to prevent oxidation. Indeed, LC-FA oxidation leads to the apparition of primary lipid hydroperoxides and secondary oxidation products (Albert, Cameron-Smith, Hofman, & Cutfield, 2013; Arab-Tehrany et al., 2012, pp. 24–33; Shahidi & Zhong, 2010). It has been shown in animals that lipid peroxidation could contribute to the pathophysiology of inflammation-associated diseases, including NDD (Grimm et al., 2016; Maruyama et al., 2014; Pamplona et al., 2005; Yakubenko & Byzova, 2017). Formulation excipients can be useful for preservation purposes and phenolic compounds have been widely shown to be efficient to delay oxidation of n-3 PUFA (Crauste, Rosell, Durand, & Vercauteren, 2016; Hasiewicz-Derkacz et al., 2015). However, these synthetic components have been criticized and the use of natural antioxidants often favored both by consumers and public health authorities. In a very recent study, Guitard, Paul, Nardello-Rataj, and Aubry (2016), have shown that natural antioxidants such as myricetin, rosmarinic and carnosic acids are more effective to prevent oxidation in n-3 PUFA oils than α-tocopherol (fat-soluble antioxidants that function as scavengers of lipid peroxyl radicals) and synthetic antioxidants (Guitard et al., 2016).

9. Conclusion

Scientists, health professionals and the lay public increasingly recognize the potential benefit of nutrition in the prevention of CNS-related diseases. A steep rise in reported consumption of n-3 PUFA supplements was recently reported between 1999 and 2012 (Kantor, Rehm, Du, White, & Giovannucci, 2016). However, since the diagnosis of NDD is made a long time after disease onset, we may wonder if it is not too late to intervene. Manipulating dietary intake of fatty acids could be a relevant strategy to postpone the appearance of the more severe symptoms of NDD. Animal, epidemiology and non-AD clinical data all suggest cognitive benefits of n-3 PUFA, while animal studies may highlight evidence of disease modifications. Clinical evidence however remains limited to possible benefits in prodromal stages. It could also be interesting to combine n-3 PUFA with other nutrients such as polyphenols, which may also have cognitive benefits. Indeed, with the Neurophenols Consortium, our group has just reported the cognitive benefits of polyphenol extracts in the 3xTg-AD animal model of AD, without clear impact on canonical neuropathological markers (Dal-Pan et al., 2017). It will still be difficult to adopt the best omega-3 PUFA supplementation strategy, as we need a better understanding of mechanisms of NDD. That includes pharmacodynamic and pharmacokinetic studies. A more precise knowledge of AD pathogenesis and PUFA metabolism could lead to the constitution of different subgroups of patients more likely to take benefit of omega-3 PUFA supplementation. Furthermore, larger clinical trials on prevention should be made in order to understand the real impact of omega-3 PUFA on neuroprotection in the population. In summary, literature shows that many nutrients (n-3 PUFA, polyphenols, antioxidants …) have a potential benefit in the prevention of diseases and especially those related to the CNS through direct effect on brain function and not necessarily related to classical pathophysiological cascades. As NDD prevalence will continue to rise in the next decades, prevention strategies based on nutrition needs to be thoroughly investigated now, in the hope of defining an optimal diet for the aging brain.

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References

Adarme-Vega, T. C., Lim, D. K. Y., Timmins, M., Vernen, F., Li, Y., & Schenk, P. M. (2012). Microalgal biofactories: A promising approach towards sustainable omega-3 fatty acid production. *Microbial Cell Factories, 11*, 96. http://doi.org/10.1186/1475-2859-11-96.

Albert, B. B., Cameron-Smith, D., Hofman, P. L., & Cutfield, W. S. (2013). Oxidation of marine omega-3 supplements and human health. *BioMed Research International, 2013*(343), 464921–464928. http://doi.org/10.1155/2013/464921.

Alling, C., Bruce, A., Karlsson, I., & Svennerholm, L. (1974). The effect of different dietary levels of essential fatty acids on lipids of rat cerebrum during maturation. *Journal of Neurochemistry, 23*(6), 1263–1270.

Amtul, Z., Westaway, D., Cechetto, D. F., & Rozmahel, R. F. (2011). Oleic acid ameliorates amyloidosis in cellular and mouse models of Alzheimer's disease. *Brain Pathology (Zurich, Switzerland), 21*(3), 321–329. http://doi.org/10.1111/j.1750-3639.2010.00449.x.

Andrieu, S., Guyonnet, S., Coley, N., Cantet, C., Bonnefoy, M., Bordes, S., et al. (2017). Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *The Lancet Neurology, 16*(5), 377–389. http://doi.org/10.1016/S1474-4422(17)30040-6.

Arab-Tehrany, E., Jacquot, M., Gaiani, C., Imran, M., Desobry, A., & Linder, M. (2014). Beneficial effects and oxidative stability of omega-3 long-chain polyunsaturated fatty acids. *Trends in Food Science, 25*(1), 24–33.

Aranceta, J., & Pérez-Rodrigo, C. (2012). Recommended dietary reference intakes, nutritional goals and dietary guidelines for fat and fatty acids: A systematic review. *The British Journal of Nutrition, 107*(S2), S8–S22. http://doi.org/10.1017/S0007114512001444.

Arsenault, D., Julien, C., & Calon, F. (2012). Chronic dietary intake of α-linolenic acid does not replicate the effects of DHA on passive properties of entorhinal cortex neurons. *The British Journal of Nutrition, 107*(8), 1099–1111. http://doi.org/10.1017/S0007114511004089.

Arsenault, D., Julien, C., Chen, C. T., Bazinet, R. P., & Calon, F. (2012). Dietary intake of unsaturated fatty acids modulates physiological properties of entorhinal cortex neurons in mice. *Journal of Neurochemistry, 122*(2), 427–443. http://doi.org/10.1111/j.1471-4159.2012.07772.x.

Arsenault, D., Julien, C., Tremblay, C., & Calon, F. (2011). DHA improves cognition and prevents dysfunction of entorhinal cortex neurons in 3xTg-AD mice. *PLoS ONE, 6*(2), e17397. http://doi.org/10.1371/journal.pone.0017397.

Arterburn, L. M., Oken, H. A., Hoffman, J. P., Bailey-Hall, E., Chung, G., Rom, D., et al. (2007). Bioequivalence of Docosahexaenoic acid from different algal oils in capsules and in a DHA-fortified food. *Lipids, 42*(11), 1011–1024. http://doi.org/10.1007/s11745-007-3098-5.

Barberger-Gateau, P., Samieri, C., Feart, C., & Plourde, M. (2011). Dietary omega 3 polyunsaturated fatty acids and Alzheimer's disease: Interaction with apolipoprotein E genotype. *Current Alzheimer Research, 8*(5), 479–491.

Barceló-Coblijn, G., & Murphy, E. J. (2009). Alpha-linolenic acid and its conversion to longer chain n-3 fatty acids: Benefits for human health and a role in maintaining tissue n-3 fatty acid levels. *Progress in Lipid Research, 48*(6), 355–374. http://doi.org/10.1016/j.plipres.2009.07.002.

Barnes, D. E., & Yaffe, K. (2011). The projected effect of risk factor reduction on Alzheimer's disease prevalence. *The Lancet Neurology, 10*(9), 819–828. http://doi.org/10.1016/S1474-4422(11)70072-2.

Barron, A. M., Rosario, E. R., Elteriefi, R., & Pike, C. J. (2013). Sex-specific effects of high fat diet on indices of metabolic syndrome in 3xTg-AD Mice: Implications for Alzheimer's disease. *PLoS ONE, 8*(10), e78554. http://doi.org/10.1371/journal.pone.0078554.

Barsky, A. J., Saintfort, R., Rogers, M. P., & Borus, J. F. (2002). Nonspecific medication

side effects and the nocebo phenomenon. *JAMA, 287*(5), 622–627.
Bazinet, R. P., & Layé, S. (2014). Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nature Reviews Neuroscience, 15*(12), 771–785. http://doi.org/10.1038/nrn3820.
Bean, S. J. (2011). Emerging and continuing trends in vaccine opposition website content. *Vaccine, 29*(10), 1874–1880. http://doi.org/10.1016/j.vaccine.2011.01.003.
Bjorkhem, I. (2004). Brain cholesterol: Long secret life behind a barrier. *Arteriosclerosis, Thrombosis, and Vascular Biology, 24*(5), 806–815. http://doi.org/10.1161/01.ATV.0000120374.59826.1b.
Bourre, J. M., Pascal, G., Durand, G., Masson, M., Dumont, O., & Piciotti, M. (1984). Alterations in the fatty acid composition of rat brain cells (neurons, astrocytes, and oligodendrocytes) and of subcellular fractions (myelin and synaptosomes) induced by a diet devoid of n-3 fatty acids. *Journal of Neurochemistry, 43*(2), 342–348.
Bousquet, M., Calon, F., & Cicchetti, F. (2011). Impact of ω-3 fatty acids in Parkinson's disease. *Ageing Research Reviews, 10*(4), 453–463. http://doi.org/10.1016/j.arr.2011.03.001.
Bousquet, M., Gibrat, C., Ouellet, M., Rouillard, C., Calon, F., & Cicchetti, F. (2010). Cystamine metabolism and brain transport properties: Clinical implications for neurodegenerative diseases. *Journal of Neurochemistry, 114*(6), 1651–1658. http://doi.org/10.1111/j.1471-4159.2010.06874.x.
Bousquet, M., Gibrat, C., Saint-Pierre, M., Julien, C., Calon, F., & Cicchetti, F. (2009). Modulation of brain-derived neurotrophic factor as a potential neuroprotective mechanism of action of omega-3 fatty acids in a parkinsonian animal model. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33*(8), 1401–1408. http://doi.org/10.1016/j.pnpbp.2009.07.018.
Bousquet, M., Gue, K., Emond, V., Julien, P., Kang, J. X., Cicchetti, F., et al. (2011). Transgenic conversion of omega-6 into omega-3 fatty acids in a mouse model of Parkinson's disease. *Journal of Lipid Research, 52*(2), 263–271. http://doi.org/10.1194/jlr.M011692.
Bousquet, M., Saint-Pierre, M., Julien, C., Salem, N. J., Cicchetti, F., & Calon, F. (2008). Beneficial effects of dietary omega-3 polyunsaturated fatty acid on toxin-induced neuronal degeneration in an animal model of Parkinson's disease. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology, 22*(4), 1213–1225. http://doi.org/10.1096/fj.07-9677com.
Bousquet, M., St-Amour, I., Vandal, M., Julien, P., Cicchetti, F., & Calon, F. (2012). High-fat diet exacerbates MPTP-induced dopaminergic degeneration in mice. *Neurobiology of Disease, 45*(1), 529–538. http://doi.org/10.1016/j.nbd.2011.09.009.
Bruno, M. J., Koeppe, R. E., & Andersen, O. S. (2007). Docosahexaenoic acid alters bilayer elastic properties. *Proceedings of the National Academy of Sciences, 104*(23), 9638–9643. http://doi.org/10.1073/pnas.0701015104.
Calon, F. (2011). Omega-3 polyunsaturated fatty acids in Alzheimer's Disease: Key questions and partial answers. *Current Alzheimer Research, 8*(5), 470–478.
Calon, F., & Cicchetti, F. (2008). Can we prevent Parkinson's disease with n-3 polyunsaturated fatty acids? *Future Lipidology, 3*(2), 133–137. http://doi.org/10.2217/17460875.3.2.133.
Calon, F., & Cole, G. (2007). Neuroprotective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: Evidence from animal studies. *Prostaglandins, Leukotrienes and Essential Fatty Acids, 77*(5-6), 287–293. http://doi.org/10.1016/j.plefa.2007.10.019.
Calon, F., Lim, G. P., Morihara, T., Yang, F., Ubeda, O., Salem, N. J., et al. (2005). Dietary n-3 polyunsaturated fatty acid depletion activates caspases and decreases NMDA receptors in the brain of a transgenic mouse model of Alzheimer's disease. *The European Journal of Neuroscience, 22*(3), 617–626. http://doi.org/10.1111/j.1460-9568.2005.04253.x.
Calon, F., Lim, G. P., Yang, F., Morihara, T., Teter, B., Ubeda, O., et al. (2004). Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. *Neuron, 43*(5), 633–645. http://doi.org/10.1016/j.neuron.2004.08.013.
Casali, B. T., Corona, A. W., Mariani, M. M., Karlo, J. C., Ghosal, K., & Landreth, G. E. (2015). Omega-3 fatty acids augment the actions of nuclear receptor agonists in a mouse model of Alzheimer's disease. *The Journal of Neuroscience : the Official Journal of the Society for Neuroscience, 35*(24), 9173–9181. http://doi.org/10.1523/JNEUROSCI.1000-15.2015.
Catalan, J., Moriguchi, T., Slotnick, B., Murthy, M., Greiner, R. S., & Salem, N., Jr. (2002). Cognitive deficits in docosahexaenoic acid-deficient rats. *Behavioral Neuroscience, 116*(6), 1022–1031.
Cattelotte, J., Andre, P., Ouellet, M., Bourasset, F., Scherrmann, J.-M., & Cisternino, S. (2008). In situ mouse carotid perfusion model: Glucose and cholesterol transport in the eye and brain. *Journal of Cerebral Blood Flow and Metabolism, 28*(8), 1449–1459. http://doi.org/10.1038/jcbfm.2008.34.
Chen, C. T., Kitson, A. P., Hopperton, K. E., Domenichiello, A. F., Trépanier, M.-O., Lin, L. E., et al. (2015). Plasma non-esterified docosahexaenoic acid is the major pool supplying the brain. *Scientific Reports, 5*(1), 15791. http://doi.org/10.1038/srep15791.
Chikhale, E. G., Ng, K. Y., Burton, P. S., & Borchardt, R. T. (1994). Hydrogen bonding potential as a determinant of the in vitro and in situ blood-brain barrier permeability of peptides. *Pharmaceutical Research, 11*(3), 412–419.
Cole, G. M., & Frautschy, S. A. (2010). DHA may prevent age-related dementia. *The Journal of Nutrition, 140*(4), 869–874. http://doi.org/10.3945/jn.109.113910.
Colonna, M., & Wang, Y. (2016). TREM2 variants: New keys to decipher alzheimer disease pathogenesis. *Nature Reviews Neuroscience, 17*(4), 201–207. http://doi.org/10.1038/nrn.2016.7.
Cook, H. W. (1978). Incorporation, metabolism and positional distribution of trans-unsaturated fatty acids in developing and mature brain. Comparison of elaidate and oleate administered intracerebrally. *Biochimica Et Biophysica Acta, 531*(3), 245–256.
Cornford, E. M., & Hyman, S. (2005). Localization of brain endothelial luminal and abluminal transporters with immunogold electron microscopy. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics, 2*(1), 27–43. http://doi.org/10.1602/neurorx.2.1.27.
Coulombe, K., Saint-Pierre, M., Cisbani, G., St-Amour, I., Gibrat, C., Giguère-Rancourt, A., et al. (2016). Partial neurorescue effects of DHA following a 6-OHDA lesion of the mouse dopaminergic system. *The Journal of Nutritional Biochemistry, 30*, 133–142. http://doi.org/10.1016/j.jnutbio.2015.11.014.
Crauste, C., Rosell, M., Durand, T., & Vercauteren, J. (2016). Omega-3 polyunsaturated lipophenols, how and why. *Biochimie, 120*, 62–74. http://doi.org/10.1016/j.biochi.2015.07.018.
Crawford, M. A., Bloom, M., Cunnane, S., Holmsen, H., Ghebremeskel, K., Parkington, J., et al. (2000). Docosahexaenoic acid and cerebral evolution. In *Fatty Acids and Lipids - New Findings* (vol. 88, pp. 6–17). Basel: KARGER. http://doi.org/10.1159/000059743.
Cummings, J. L., Doody, R., & Clark, C. (2007). Disease-modifying therapies for alzheimer disease: Challenges to early intervention. *Neurology, 69*(16), 1622–1634. http://doi.org/10.1212/01.wnl.0000295996.54210.69.
Cunnane, S. C., Chouinard-Watkins, R., Castellano, C. A., & Barberger-Gateau, P. (2013). Docosahexaenoic acid homeostasis, brain aging and Alzheimer's disease: Can we reconcile the evidence? *Prostaglandins, Leukotrienes and Essential Fatty Acids, 88*(1), 61–70. http://doi.org/10.1016/j.plefa.2012.04.006.
Cunnane, S. C., Plourde, M., Pifferi, F., Begin, M., Feart, C., & Barberger-Gateau, P. (2009). Fish, docosahexaenoic acid and Alzheimer's disease. *Progress in Lipid Research, 48*(5), 239–256. http://doi.org/10.1016/j.plipres.2009.04.001.
Cunnane, S. C., Plourde, M., Stewart, K., & Crawford, M. A. (2007). Docosahexaenoic acid and shore-based diets in hominin encephalization: A rebuttal. *American Journal of Human Biology : The Official Journal of the Human Biology Council, 19*(4), 578–581. http://doi.org/10.1002/ajhb.20673.
D'Ascoli, T. A., Mursu, J., Voutilainen, S., Kauhanen, J., Tuomainen, T. P., & Virtanen, J. K. (2016). Association between serum long-chain omega-3 polyunsaturated fatty acids and cognitive performance in elderly men and women: The Kuopio Ischaemic Heart Disease Risk Factor Study. *European Journal of Clinical Nutrition, 70*(8), 970–975. http://doi.org/10.1038/ejcn.2016.59.
Dal-Pan, A., Dudonné, S., Bourassa, P., Bourdoulous, M., Tremblay, C., Desjardins, Y., et al. (2017). Cognitive-enhancing effects of a polyphenols-rich extract from fruits without changes in neuropathology in an animal model of Alzheimer's disease. *Journal of Alzheimer's Disease: JAD, 55*(1), 115–135. http://doi.org/10.3233/JAD-160281.
Daneman, R., & Prat, A. (2015). The blood-brain barrier. *Cold Spring Harbor Perspectives in Biology, 7*(1), a020412. http://doi.org/10.1101/cshperspect.a020412.
De Smedt-Peyrusse, V., Sargueil, F., Moranis, A., Harizi, H., Mongrand, S., & Layé, S. (2008). Docosahexaenoic acid prevents lipopolysaccharide-induced cytokine production in microglial cells by inhibiting lipopolysaccharide receptor presentation but not its membrane subdomain localization. *Journal of Neurochemistry, 105*(2), 296–307. http://doi.org/10.1111/j.1471-4159.2007.05129.x.
Delattre, A. M., Kiss, A., Szawka, R. E., Anselmo-Franci, J. A., Bagatini, P. B., Xavier, L. L., et al. (2010). Evaluation of chronic omega-3 fatty acids supplementation on behavioral and neurochemical alterations in 6-hydroxydopamine-lesion model of Parkinson's disease. *Neuroscience Research, 66*(3), 256–264.
Delpech, J.-C., Madore, C., Joffre, C., Aubert, A., Kang, J. X., Nadjar, A., et al. (2015). Transgenic increase in n-3/n-6 fatty acid ratio protects against cognitive deficits induced by an immune challenge through decrease of neuroinflammation. *Neuropsychopharmacology, 40*(3), 525–536. http://doi.org/10.1038/npp.2014.196.
Delpech, J.-C., Madore, C., Nadjar, A., Joffre, C., Wohleb, E. S., & Layé, S. (2015). Microglia in neuronal plasticity: Influence of stress. *Neuropharmacology, 96*(Pt A), 19–28. http://doi.org/10.1016/j.neuropharm.2014.12.034.
Delpech, J.-C., Thomazeau, A., Madore, C., Bosch-Bouju, C., Larrieu, T., Lacabanne, C., et al. (2015). Dietary n-3 PUFAs deficiency increases vulnerability to inflammation-induced spatial memory impairment. *Neuropsychopharmacology, 40*(12), 2774–2787. http://doi.org/10.1038/npp.2015.127.
Diau, G.-Y., Hsieh, A. T., Sarkadi-Nagy, E. A., Wijendran, V., Nathanielsz, P. W., & Brenna, J. T. (2005). The influence of long chain polyunsaturate supplementation on docosahexaenoic acid and arachidonic acid in baboon neonate central nervous system. *BMC Medicine, 3*(1), 11. http://doi.org/10.1186/1741-7015-3-11.
Do, T. M., Ouellet, M., Calon, F., Chimini, G., Chacun, H., Farinotti, R., et al. (2011). Direct evidence of abca1-mediated efflux of cholesterol at the mouse blood-brain barrier. *Molecular and Cellular Biochemistry, 357*(1-2), 397–404. http://doi.org/10.1007/s11010-011-0910-6.
Domenichiello, A. F., Kitson, A. P., & Bazinet, R. P. (2015). Is docosahexaenoic acid synthesis from α-linolenic acid sufficient to supply the adult brain? *Progress in Lipid Research, 59*, 54–66. http://doi.org/10.1016/j.plipres.2015.04.002.
Emery, V. O. B. (2011). Alzheimer disease: Are we intervening too late? Pro. *Journal of Neural Transmission (Vienna, Austria: 1996), 118*(9), 1361–1378. http://doi.org/10.1007/s00702-011-0663-0.
Eriksdotter, M., Vedin, I., Falahati, F., Freund-Levi, Y., Hjorth, E., Faxen-Irving, G., et al. (2015). Plasma fatty acid profiles in relation to cognition and gender in Alzheimer's disease patients during oral Omega-3 fatty acid Supplementation: The OmegAD study. *Journal of Alzheimer's Disease: JAD, 48*(3), 805–812. http://

doi.org/10.3233/JAD-150102.
Exalto, L. G., Quesenberry, C. P., Barnes, D., Kivipelto, M., Biessels, G. J., & Whitmer, R. A. (2014). Midlife risk score for the prediction of dementia four decades later. *Alzheimer's & Dementia: the Journal of the Alzheimer's Association, 10*(5), 562–570. http://doi.org/10.1016/j.jalz.2013.05.1772.
Feart, C., Samieri, C., & Barberger-Gateau, P. (2010). Mediterranean diet and cognitive function in older adults. *Current Opinion in Clinical Nutrition and Metabolic Care, 13*(1), 14–18. http://doi.org/10.1097/MCO.0b013e3283331fe4.
Fonteh, A. N., Cipolla, M., Chiang, J., Arakaki, X., & Harrington, M. G. (2014). Human cerebrospinal fluid fatty acid levels differ between supernatant fluid and brain-derived nanoparticle fractions, and are altered in Alzheimer's disease. *PLoS ONE, 9*(6), e100519. http://doi.org/10.1371/journal.pone.0100519.
Fox, S. H., Katzenschlager, R., Lim, S.-Y., Ravina, B., Seppi, K., Coelho, M., et al. (2011). The movement disorder society evidence-based medicine review Update: Treatments for the motor symptoms of Parkinson's disease. *Movement Disorders, 26*(Suppl 3), S2–S41. http://doi.org/10.1002/mds.23829.
Freund Levi, Y., Vedin, I., Cederholm, T., Basun, H., Faxén Irving, G., Eriksdotter, M., et al. (2014). Transfer of omega-3 fatty acids across the blood-brain barrier after dietary supplementation with a docosahexaenoic acid-rich omega-3 fatty acid preparation in patients with Alzheimer's disease: The OmegAD study. *Journal of Internal Medicine, 275*(4), 428–436. http://doi.org/10.1111/joim.12166.
Freund-Levi, Y., Eriksdotter-Jönhagen, M., Cederholm, T., Basun, H., Faxén-Irving, G., Garlind, A., et al. (2006). Omega-3 fatty acid treatment in 174 patients with mild to moderate alzheimer disease: OmegAD study: A randomized double-blind trial. *Archives of Neurology, 63*(10), 1402–1408. http://doi.org/10.1001/archneur.63.10.1402.
Freund-Levi, Y., Vedin, I., Hjorth, E., Basun, H., Faxen-Irving, G., Schultzberg, M., et al. (2014). Effects of supplementation with omega-3 fatty acids on oxidative stress and inflammation in patients with Alzheimer's disease: The OmegAD study. *Journal of Alzheimer's Disease: JAD, 42*(3), 823–831. http://doi.org/10.3233/JAD-132042.
Galli, C., White, H. B., & Paoletti, R. (1971). Lipid alterations and their reversion in the central nervous system of growing rats deficient in essential fatty acids. *Lipids, 6*(6), 378–387.
Gauthier, S., Albert, M., Fox, N., Goedert, M., Kivipelto, M., Mestre-Ferrandiz, J., et al. (2016). Why has therapy development for dementia failed in the last two decades? *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 12*(1), 60–64. http://doi.org/10.1016/j.jalz.2015.12.003.
Ghasemifard, S., Hermon, K., Turchini, G. M., & Sinclair, A. J. (2015). Metabolic fate (absorption, β-oxidation and deposition) of long-chain n-3 fatty acids is affected by sex and by the oil source (krill oil or fish oil) in the rat. *The British Journal of Nutrition, 114*(5), 684–692. http://doi.org/10.1017/S0007114515002457.
Gillette-Guyonnet, S., Secher, M., & Vellas, B. (2013). Nutrition and neurodegeneration: Epidemiological evidence and challenges for future research. *British Journal of Clinical Pharmacology, 75*(3), 738–755. http://doi.org/10.1111/bcp.12058.
Gratuze, M., Julien, J., Morin, F., Calon, F., Hébert, S. S., Marette, A., et al. (2016). High-fat, high-sugar, and high-cholesterol consumption does not impact tau pathogenesis in a mouse model of Alzheimer's disease-like tau pathology. *Neurobiology of Aging, 47*, 71–73. http://doi.org/10.1016/j.neurobiolaging.2016.07.016.
Green, K. N., Martinez-Coria, H., Khashwji, H., Hall, E. B., Yurko-Mauro, K. A., Ellis, L., et al. (2007). Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 27*(16), 4385–4395. http://doi.org/10.1523/JNEUROSCI.0055-07.2007.
Greenwood, C. E., & Winocur, G. (1996). Cognitive impairment in rats fed high-fat diets: A specific effect of saturated fatty-acid intake. *Behavioral Neuroscience, 110*(3), 451–459.
Grimm, M. O. W., Haupenthal, V. J., Mett, J., Stahlmann, C. P., Blümel, T., Mylonas, N. T., et al. (2016). Oxidized docosahexaenoic acid species and lipid peroxidation products increase amyloidogenic amyloid precursor protein processing. *Neuro-Degenerative Diseases, 16*(1-2), 44–54. http://doi.org/10.1159/000440839.
Guitard, R., Paul, J.-F., Nardello-Rataj, V., & Aubry, J.-M. (2016). Myricetin, rosmarinic and carnosic acids as superior natural antioxidant alternatives to α-tocopherol for the preservation of omega-3 oils. *Food Chemistry, 213*, 284–295. http://doi.org/10.1016/j.foodchem.2016.06.038.
Hachem, M., Géloën, A., Van, A. L., Foumaux, B., Fenart, L., Gosselet, F., et al. (2015). Efficient docosahexaenoic acid uptake by the brain from a structured phospholipid. *Molecular Neurobiology, 53*(5), 3205–3215. http://doi.org/10.1007/s12035-015-9228-9.
Hamilton, J. A., & Brunaldi, K. (2007). A model for fatty acid transport into the brain. *Journal of Molecular Neuroscience: MN, 33*(1), 12–17.
Hamilton, L. K., Dufresne, M., Joppé, S. E., Petryszyn, S., Aumont, A., Calon, F., et al. (2015). Aberrant lipid metabolism in the forebrain niche suppresses adult neural stem cell proliferation in an animal model of Alzheimer's disease. *Cell Stem Cell, 17*(4), 397–411. http://doi.org/10.1016/j.stem.2015.08.001.
Hanisch, U.-K., & Kettenmann, H. (2007). Microglia: Active sensor and versatile effector cells in the normal and pathologic brain. *Nature Neuroscience, 10*(11), 1387–1394. http://doi.org/10.1038/nn1997.
Harris, W. S., Mozaffarian, D., Lefevre, M., Toner, C. D., Colombo, J., Cunnane, S. C., et al. (2009). Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *The Journal of Nutrition, 139*(4), 804S–819S. http://doi.org/10.3945/jn.108.101329.
Hashimoto, M., Hossain, S., Agdul, H., & Shido, O. (2005). Docosahexaenoic acid-induced amelioration on impairment of memory learning in amyloid beta-infused rats relates to the decreases of amyloid beta and cholesterol levels in detergent-insoluble membrane fractions. *Biochimica et Biophysica Acta, 1738*(1–3), 91–98.
Hashimoto, M., Tanabe, Y., Fujii, Y., Kikuta, T., Shibata, H., & Shido, O. (2005). Chronic administration of docosahexaenoic acid ameliorates the impairment of spatial cognition learning ability in amyloid beta-infused rats. *Journal of Nutrition, 135*(3), 549–555.
Hashimoto, M., Tozawa, R., Katakura, M., Shahdat, H., Haque, A. M., Tanabe, Y., et al. (2011). Protective effects of prescription n-3 fatty acids against impairment of spatial cognitive learning ability in amyloid β-infused rats. *Food & Function, 2*(7), 386–394. http://doi.org/10.1039/c1fo00002k.
Hasiewicz-Derkacz, K., Kulma, A., Czuj, T., Prescha, A., Żuk, M., Grajzer, M., et al. (2015). Natural phenolics greatly increase flax (Linum usitatissimum) oil stability. *BMC Biotechnology, 15*(1), 62. http://doi.org/10.1186/s12896-015-0178-0.
Hebert, L. E., Weuve, J., Scherr, P. A., & Evans, D. A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. *Neurology, 80*(19), 1778–1783. http://doi.org/10.1212/WNL.0b013e31828726f5.
Henderson, J. T., & Piquette-Miller, M. (2015). Blood-brain barrier: An impediment to neuropharmaceuticals. *Clinical Pharmacology and Therapeutics, 97*(4), 308–313. http://doi.org/10.1002/cpt.77.
Heneka, M. T., Carson, M. J., Khoury El, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., et al. (2015). Neuroinflammation in Alzheimer's disease. *The Lancet Neurology, 14*(4), 388–405. http://doi.org/10.1016/S1474-4422(15)70016-5.
Herrmann, N., Lanctôt, K. L., & Hogan, D. B. (2013). Pharmacological recommendations for the symptomatic treatment of dementia: The Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. *Alzheimer's Research & Therapy, 5*(Suppl. 1), S5. http://doi.org/10.1186/alzrt201.
Hickman, R. A., Faustin, A., & Wisniewski, T. (2016). Alzheimer disease and its growing Epidemic: Risk factors, biomarkers, and the urgent need for therapeutics. *Neurologic Clinics, 34*(4), 941–953. http://doi.org/10.1016/j.ncl.2016.06.009.
Ho, L., Qin, W., Pompl, P. N., Xiang, Z., Wang, J., Zhao, Z., et al. (2004). Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 18*(7), 902–904. http://doi.org/10.1096/fj.03-0978fje.
Hogan, S. A., O'Riordan, E. D., & O'Sullivan, M. (2003). Microencapsulation and oxidative stability of spray-dried fish oil emulsions. *Journal of Microencapsulation, 20*(5), 675–688. http://doi.org/10.1080/0265204031000151974.
Hong, S., Dissing-Olesen, L., & Stevens, B. (2016). New insights on the role of microglia in synaptic pruning in health and disease. *Current Opinion in Neurobiology, 36*, 128–134. http://doi.org/10.1016/j.conb.2015.12.004.
Hooijmans, C. R., Van der Zee, C. E. E. M., Dederen, P. J., Brouwer, K. M., Reijmer, Y. D., van Groen, T., et al. (2009). DHA and cholesterol containing diets influence Alzheimer-like pathology, cognition and cerebral vasculature in APPswe/PS1dE9 mice. *Neurobiology of Disease, 33*(3), 482–498. http://doi.org/10.1016/j.nbd.2008.12.002.
Hopperton, K. E., Trépanier, M.-O., Giuliano, V., & Bazinet, R. P. (2016). Brain omega-3 polyunsaturated fatty acids modulate microglia cell number and morphology in response to intracerebroventricular amyloid-β 1-40 in mice. *Journal of Neuroinflammation, 13*(1), 257. http://doi.org/10.1186/s12974-016-0721-5.
Jenkins, D. J. A., Sievenpiper, J. L., Pauly, D., Sumaila, U. R., Kendall, C. W. C., & Mowat, F. M. (2009). Are dietary recommendations for the use of fish oils sustainable? *CMAJ: Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne, 180*(6), 633–637. http://doi.org/10.1503/cmaj.081274.
Jernerén, F., Elshorbagy, A. K., Oulhaj, A., Smith, S. M., Refsum, H., & Smith, A. D. (2015). Brain atrophy in cognitively impaired elderly: The importance of long-chain ω-3 fatty acids and B vitamin status in a randomized controlled trial. *The American Journal of Clinical Nutrition, 102*(1), 215–221. http://doi.org/10.3945/ajcn.114.103283.
Joffre, C., Nadjar, A., Lebbadi, M., Calon, F., & Laye, S. (2014). n-3 LCPUFA improves cognition: The young, the old and the sick. *Prostaglandins, Leukotrienes and Essential Fatty Acids, 91*(1-2), 1–20. http://doi.org/10.1016/j.plefa.2014.05.001.
Julien, C., Berthiaume, L., Hadj-Tahar, A., Rajput, A. H., Bedard, P. J., Di Paolo, T., et al. (2006). Postmortem brain fatty acid profile of levodopa-treated Parkinson disease patients and parkinsonian monkeys. *Neurochemistry International, 48*(5), 404–414. http://doi.org/10.1016/j.neuint.2005.12.002.
Julien, C., Tremblay, C., Phivilay, A., Berthiaume, L., Emond, V., Julien, P., et al. (2010). High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. *Neurobiology of Aging, 31*(9), 1516–1531. http://doi.org/10.1016/j.neurobiolaging.2008.08.022.
Kantor, E. D., Rehm, C. D., Du, M., White, E., & Giovannucci, E. L. (2016). Trends in dietary supplement use among US adults from 1999-2012. *Journal of the American Medical Association, 316*(14), 1464–1474. http://doi.org/10.1001/jama.2016.14403.
Katsuno, M., Tanaka, F., & Sobue, G. (2012). Perspectives on molecular targeted therapies and clinical trials for neurodegenerative diseases. *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(3), 329–335. http://doi.org/10.1136/jnnp-2011-301307.
Kesselheim, A. S., Hwang, T. J., & Franklin, J. M. (2015). Two decades of new drug development for central nervous system disorders. *Nature Reviews. Drug*

Discovery, 14(12), 815–816. http://doi.org/10.1038/nrd4793.
Kettenmann, H., Kirchhoff, F., & Verkhratsky, A. (2013). Microglia: New roles for the synaptic stripper. *Neuron, 77*(1), 10–18. http://doi.org/10.1016/j.neuron.2012.12.023.
Kivipelto, M., & Mangialasche, F. (2014). Alzheimer disease: To what extent can Alzheimer disease be prevented? *Nature Publishing Group, 10*(10), 552–553. http://doi.org/10.1038/nrneurol.2014.170.
Kolanowski, W., Laufenberg, G., & Kunz, B. (2004). Fish oil stabilisation by microencapsulation with modified cellulose. *International Journal of Food Sciences and Nutrition, 55*(4), 333–343. http://doi.org/10.1080/09637480410001725157.
Labrousse, V. F., Nadjar, A., Joffre, C., Costes, L., Aubert, A., Grégoire, S., et al. (2012). Short-term long chain omega3 diet protects from neuroinflammatory processes and memory impairment in aged mice. *PLoS ONE, 7*(5), e36861. http://doi.org/10.1371/journal.pone.0036861.
Lalancette-Hebert, M., Julien, C., Cordeau, P., Bohacek, I., Weng, Y.-C., Calon, F., & Kriz, J. (2011). Accumulation of dietary docosahexaenoic acid in the brain attenuates acute immune response and development of postischemic neuronal damage. *Stroke, 42*(10), 2903–2909. http://doi.org/10.1161/STROKEAHA.111.620856.
Lambert, M. A., Bickel, H., Prince, M., Fratiglioni, L., Strauss Von, E., Frydecka, D., et al. (2014). Estimating the burden of early onset dementia; systematic review of disease prevalence. *European Journal of Neurology, 21*(4), 563–569. http://doi.org/10.1111/ene.12325.
Lamptey, M. S., & Walker, B. L. (1976). A possible essential role for dietary linolenic acid in the development of the young rat. *The Journal of Nutrition, 106*(1), 86–93.
Layé, S. (2010). Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins, Leukotrienes and Essential Fatty Acids, 82*(4-6), 295–303. http://doi.org/10.1016/j.plefa.2010.02.006.
Lebbadi, M., Julien, C., Phivilay, A., Tremblay, C., Emond, V., et al. (2011). Endogenous conversion of omega-6 into omega-3 fatty acids improves neuropathology in an animal model of Alzheimer's disease. *Journal of Alzheimer's Disease: JAD, 27*(4), 853–869. http://doi.org/10.3233/JAD-2011-111010.
Leboucher, A., Laurent, C., Fernandez-Gomez, F.-J., Burnouf, S., Troquier, L., Eddarkaoui, S., et al. (2013). Detrimental effects of diet-induced obesity on τ pathology are independent of insulin resistance in τ transgenic mice. *Diabetes, 62*(5), 1681–1688. http://doi.org/10.2337/db12-0866.
Lee, J.-H. (2013). Polyunsaturated Fatty acids in children. *Pediatric Gastroenterology, Hepatology & Nutrition, 16*(3), 153–161. http://doi.org/10.5223/pghn.2013.16.3.153.
Lemaitre-Delaunay, D., Pachiaudi, C., Laville, M., Pousin, J., Armstrong, M., & Lagarde, M. (1999). Blood compartmental metabolism of docosahexaenoic acid (DHA) in humans after ingestion of a single dose of [(13)C]DHA in phosphatidylcholine. *Journal of Lipid Research, 40*(10), 1867–1874.
Lim, G. P., Calon, F., Morihara, T., Yang, F., Teter, B., Ubeda, O., et al. (2005). A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 25*(12), 3032–3040. http://doi.org/10.1523/JNEUROSCI.4225-04.2005.
Lucas, M., Asselin, G., Plourde, M., Cunnane, S. C., Dewailly, E., & Dodin, S. (2010). n-3 Fatty acid intake from marine food products among Quebecers: Comparison to worldwide recommendations. *Public Health Nutrition, 13*(1), 63–70. http://doi.org/10.1017/S1368980009005679.
Madore, C., Nadjar, A., Delpech, J.-C., Sere, A., Aubert, A., Portal, C., et al. (2014). Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain, Behavior, and Immunity, 41*, 22–31. http://doi.org/10.1016/j.bbi.2014.03.021.
Madore, C., Nadjar, A., Delpech, J.-C., Sere, A., Aubert, A., Portal, C., et al. (2014). Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain, Behavior, and Immunity, 41*, 22–31. http://doi.org/10.1016/j.bbi.2014.03.021.
Martin, S. A. L., Jameson, C. H., Allan, S. M., & Lawrence, C. B. (2014). Maternal high-fat diet worsens memory deficits in the triple-transgenic (3xTgAD) mouse model of Alzheimer's disease. *PLoS ONE, 9*(6), e99226. http://doi.org/10.1371/journal.pone.0099226.
Maruyama, W., Shaomoto-Nagai, M., Kato, Y., Hisaka, S., Osawa, T., & Naoi, M. (2014). Role of lipid peroxide in the neurodegenerative disorders. *Sub-Cellular Biochemistry, 77*(Chapter 11), 127–136. http://doi.org/10.1007/978-94-007-7920-4-11.
Meissner, W. G., Frasier, M., Gasser, T., Goetz, C. G., Lozano, A., Piccini, P., et al. (2011). Priorities in Parkinson's disease research. *Nature Reviews. Drug Discovery, 10*(5), 377–393. http://doi.org/10.1038/nrd3430.
Meyer, B. J. (2011). Are we consuming enough long chain omega-3 polyunsaturated fatty acids for optimal health? *Prostaglandins, Leukotrienes and Essential Fatty Acids, 85*(5), 275–280. http://doi.org/10.1016/j.plefa.2011.04.010.
Morris, M. C. (2016). Nutrition and risk of dementia: Overview and methodological issues. *Annals of the New York Academy of Sciences, 1367*(1), 31–37. http://doi.org/10.1111/nyas.13047.
Nadjar, A., Leyrolle, Q., Joffre, C., & Laye, S. (2017). Bioactive lipids as new class of microglial modulators: When nutrition meets neuroimunology. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 79*(Pt A), 19–26. http://doi.org/10.1016/j.pnpbp.2016.07.004.
Newton, W., & McManus, A. (2011). Consumption of fish and Alzheimer's disease. *The Journal of Nutrition, Health & Aging, 15*(7), 551–4552.
Ngandu, T., Lehtisalo, J., Solomon, A., Levälahti, E., Ahtiluoto, S., Antikainen, R., et al. (2015). A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. *Lancet (London, England), 385*(9984), 2255–2263. http://doi.org/10.1016/S0140-6736(15)60461-5.
Nguyen, L. N., Ma, D., Shui, G., Wong, P., Cazenave-Gassiot, A., Zhang, X., et al. (2014). Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. *Nature, 509*(7501), 503–506. http://doi.org/10.1038/nature13241.
Nishida, C., Uauy, R., Kumanyika, S., & Shetty, P. (2004). The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: Process, product and policy implications. *Public Health Nutrition, 7*, 245–250.
Norton, S., Matthews, F. E., Barnes, D. E., Yaffe, K., & Brayne, C. (2014). Potential for primary prevention of Alzheimer's disease: An analysis of population-based data. *The Lancet Neurology, 13*(8), 788–794. http://doi.org/10.1016/S1474-4422(14)70136-X.
Oksman, M., Iivonen, H., Hogyes, E., Amtul, Z., Penke, B., Leenders, I., et al. (2006). Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. *Neurobiology of Disease, 23*(3), 563–572. http://doi.org/10.1016/j.nbd.2006.04.013.
Oldendorf, W. H., Cornford, M. E., & Brown, W. J. (1977). The large apparent work capability of the blood-brain barrier: A study of the mitochondrial content of capillary endothelial cells in brain and other tissues of the rat. *Annals of Neurology, 1*(5), 409–417. http://doi.org/10.1002/ana.410010502.
Ouellet, M., Emond, V., Chen, C. T., Julien, C., Bourasset, F., Oddo, S., et al. (2009). Diffusion of docosahexaenoic and eicosapentaenoic acids through the blood-brain barrier: An in situ cerebral perfusion study. *Neurochemistry International, 55*(7), 476–482. http://doi.org/10.1016/j.neuint.2009.04.018.
Pamplona, R., Dalfó, E., Ayala, V., Bellmunt, M. J., Prat, J., Ferrer, I., et al. (2005). Proteins in human brain cortex are modified by oxidation, glycoxidation, and lipoxidation. Effects of Alzheimer disease and identification of lipoxidation targets. *The Journal of Biological Chemistry, 280*(22), 21522–21530. http://doi.org/10.1074/jbc.M502255200.
Pan, Y., Khalil, H., & Nicolazzo, J. A. (2015). The impact of docosahexaenoic acid on Alzheimer's Disease: Is there a role of the blood-brain barrier? *Current Clinical Pharmacology, 10*(3), 222–241.
Pan, Y., Scanlon, M. J., Owada, Y., Yamamoto, Y., Porter, C. J. H., & Nicolazzo, J. A. (2015). Fatty acid-binding protein 5 facilitates the blood-brain barrier transport of docosahexaenoic acid. *Molecular Pharmaceutics, 12*(12), 4375–4385. http://doi.org/10.1021/acs.molpharmaceut.5b00580.
Panza, F., Frisardi, V., Seripa, D., Imbimbo, B. P., Pilotto, A., & Solfrizzi, V. (2010). Dietary unsaturated fatty acids and risk of mild cognitive impairment. *Journal of Alzheimer's Disease: JAD, 21*(3), 867–870. http://doi.org/10.3233/JAD-2010-100777.
Papanikolaou, Y., Brooks, J., Reider, C., & Fulgoni, V. L. (2014). U.S. adults are not meeting recommended levels for fish and omega-3 fatty acid intake: Results of an analysis using observational data from NHANES 2003–2008. *Nutrition Journal, 13*, 31.
Pardridge, W. M. (2012). Drug transport across the blood-brain barrier. *Journal of Cerebral Blood Flow and Metabolism, 32*(11), 1959–1972. http://doi.org/10.1038/jcbfm.2012.126.
Perez, S. E., Berg, B. M., Moore, K. A., He, B., Counts, S. E., Fritz, J. J., et al. (2010). DHA diet reduces AD pathology in young APPswe/PS1 Delta E9 transgenic mice: Possible gender effects. *Journal of Neuroscience Research, 88*(5), 1026–1040. http://doi.org/10.1002/jnr.22266.
Perry, V. H., & Holmes, C. (2014). Microglial priming in neurodegenerative disease. *Nature Publishing Group, 10*(4), 217–224. http://doi.org/10.1038/nrneurol.2014.38.
Perry, V. H., Nicoll, J. A. R., & Holmes, C. (2010). Microglia in neurodegenerative disease. *Nature Publishing Group, 6*(4), 193–201. http://doi.org/10.1038/nrneurol.2010.17.
Petrie, J. R., Shrestha, P., Zhou, X.-R., Mansour, M. P., Liu, Q., Belide, S., et al. (2012). Metabolic engineering plant seeds with fish oil-like levels of DHA. *PLoS ONE, 7*(11), e49165. http://doi.org/10.1371/journal.pone.0049165.
Phivilay, A., Julien, C., Tremblay, C., Berthiaume, L., Julien, P., Giguère, Y., & Calon, F. (2009). High dietary consumption of trans fatty acids decreases brain docosahexaenoic acid but does not alter amyloid-beta and tau pathologies in the 3xTg-AD model of Alzheimer's disease. *Neuroscience, 159*(1), 296–307. http://doi.org/10.1016/j.neuroscience.2008.12.006.
Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Movement Disorders, 29*(13), 1583–1590. http://doi.org/10.1002/mds.25945.
Qi, B., Fraser, T., Mugford, S., Dobson, G., Sayanova, O., Butler, J., et al. (2004). Production of very long chain polyunsaturated omega-3 and omega-6 fatty acids in plants. *Nature Biotechnology, 22*(6), 739–745. http://doi.org/10.1038/nbt972.
Quinn, J. F., Raman, R., Thomas, R. G., Yurko-Mauro, K., Nelson, E. B., Van Dyck, C., et al. (2010). Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: A randomized trial. *Journal of the American Medical Association, 304*(17), 1903–1911. http://doi.org/10.1001/jama.2010.1510.
Ransohoff, R. M. (2016). How neuroinflammation contributes to neurodegeneration. *Science (New York, N.Y.), 353*(6301), 777–783. http://doi.org/10.1126/science.aag2590.
Ransohoff, R. M., & Perry, V. H. (2009). Microglial physiology: Unique stimuli, specialized responses. *Annual Review of Immunology, 27*(1), 119–145. http://doi.org/10.1146/annurev.immunol.021908.132528.

Refolo, L. M., Malester, B., LaFrancois, J., Bryant-Thomas, T., Wang, R., Tint, G. S., et al. (2000). Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiology of Disease, 7*(4), 321–331. http://doi.org/10.1006/nbdi.2000.0304.

Rey, C., Nadjar, A., Buaud, B., Vaysse, C., Aubert, A., Pallet, V., et al. (2016). Resolvin D1 and E1 promote resolution of inflammation in microglial cells in vitro. *Brain, Behavior, and Immunity, 55*, 249–259. http://doi.org/10.1016/j.bbi.2015.12.013.

Salem, N., Litman, B., Kim, H. Y., & Gawrisch, K. (2001). Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids, 36*(9), 945–959.

Salem, N., Vandal, M., & Calon, F. (2015). The benefit of docosahexaenoic acid for the adult brain in aging and dementia. *Prostaglandins, Leukotrienes and Essential Fatty Acids, 92*, 15–22. http://doi.org/10.1016/j.plefa.2014.10.003.

Samadi, P., Grégoire, L., Rouillard, C., Bédard, P. J., Di Paolo, T., et al. (2006). Docosahexaenoic acid reduces levodopa-induced dyskinesias in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine monkeys. *Annals of Neurology, 59*(2), 282–288.

Sanguansri, L., Augustin, M. A., Lockett, T. J., Abeywardena, M. Y., Royle, P. J., Mano, M. T., et al. (2015). Bioequivalence of n-3 fatty acids from microencapsulated fish oil formulations in human subjects. *The British Journal of Nutrition, 113*(5), 822–831. http://doi.org/10.1017/S000711451400436X.

Schapira, A. H. V., Olanow, C. W., Greenamyre, J. T., & Bezard, E. (2014). Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: Future therapeutic perspectives. *Lancet (London, England), 384*(9942), 545–555. http://doi.org/10.1016/S0140-6736(14)61010-2.

Scheltens, P., Blennow, K., Breteler, M. M. B., de Strooper, B., Frisoni, G. B., Salloway, S., et al. (2016). Alzheimer's disease. *Lancet (London, England), 388*(10043), 505–517. http://doi.org/10.1016/S0140-6736(15)01124-1.

Shahidi, F., & Zhong, Y. (2010). Lipid oxidation and improving the oxidative stability. *Chemical Society Reviews, 39*(11), 4067–4079. http://doi.org/10.1039/b922183m.

Solfrizzi, V., Frisardi, V., Seripa, D., Capurso, C., Vendemiale, G., Pilotto, A., et al. (2010). Dietary patterns and protection against Alzheimer disease and cognitive decline. *Archives of Neurology, 67*(10), 1285–6– author reply 1287–8 http://doi.org/10.1001/archneurol.2010.244.

Solfrizzi, V., Panza, F., Torres, F., Mastroianni, F., Del Parigi, A., Venezia, A., et al. (1999). High monounsaturated fatty acids intake protects against age-related cognitive decline. *Neurology, 52*(8), 1563–1569.

Solomon, A., Mangialasche, F., Richard, E., Andrieu, S., Bennett, D. A., Breteler, M., et al. (2014). Advances in the prevention of Alzheimer's disease and dementia. *Journal of Internal Medicine, 275*(3), 229–250. http://doi.org/10.1111/joim.12178.

St-Amour, I., Cicchetti, F., & Calon, F. (2016). Immunotherapies in Alzheimer's disease: Too much, too little, too late or off-target? *Acta Neuropathologica, 131*(4), 481–504. http://doi.org/10.1007/s00401-015-1518-9.

St-Amour, I., Pare, I., Tremblay, C., Coulombe, K., Bazin, R., & Calon, F. (2014). IVIg protects the 3xTg-AD mouse model of Alzheimer's disease from memory deficit and Aβ pathology. *Journal of Neuroinflammation, 11*(1), 54. http://doi.org/10.1186/1742-2094-11-54.

Stathis, P., Smpiliris, M., Konitsiotis, S., & Mitsikostas, D. D. (2013). Nocebo as a potential confounding factor in clinical trials for Parkinson's disease treatment: A meta-analysis. *European Journal of Neurology, 20*(3), 527–533. http://doi.org/10.1111/ene.12014.

Sun, G. Y. (1972). Effects of a fatty acid deficiency on lipids of whole brain, microsomes, and myelin in the rat. *Journal of Lipid Research, 13*(1), 56–62.

Teng, E., Taylor, K., Bilousova, T., Weiland, D., Pham, T., Zuo, X., et al. (2015). Dietary DHA supplementation in an APP/PS1 transgenic rat model of AD reduces behavioral and Aβ pathology and modulates Aβ oligomerization. *Neurobiology of Disease, 82*, 552–560. http://doi.org/10.1016/j.nbd.2015.09.002.

Tremblay, C., St-Amour, I., Schneider, J., Bennett, D. A., & Calon, F. (2011). Accumulation of transactive response DNA binding protein 43 in mild cognitive impairment and Alzheimer disease. *Journal of Neuropathology & Experimental Neurology, 70*(9), 788–798. http://doi.org/10.1097/NEN.0b013e31822c62cf.

Tremblay, M.-E., Stevens, B., Sierra, A., Wake, H., Bessis, A., & Nimmerjahn, A. (2011). The role of microglia in the healthy brain. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 31*(45), 16064–16069. http://doi.org/10.1523/JNEUROSCI.4158-11.2011.

Trépanier, M. O., Hopperton, K. E., Mizrahi, R., Mechawar, N., & Bazinet, R. P. (2016). Postmortem evidence of cerebral inflammation in schizophrenia: A systematic review. *Molecular Psychiatry, 21*(8), 1009–1026. http://doi.org/10.1038/mp.2016.90.

Trépanier, M.-O., Hopperton, K. E., Orr, S. K., & Bazinet, R. P. (2016). N-3 polyunsaturated fatty acids in animal models with neuroinflammation: An update. *European Journal of Pharmacology, 785*, 187–206. http://doi.org/10.1016/j.ejphar.2015.05.045.

Trumbo, P., Schlicker, S., Yates, A. A., & Poos, M. Food and Nutrition Board of the Institute of Medicine, The National Academies. (2002, November). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *Journal of the American Dietetic Association*.

Van Duijn, C. M., van der Lee, S. J., Ikram, M. A., Hofman, A., Hankemeier, T., Amin, N., et al. (2016). Metabolites associated with cognitive function in the Rotterdam study and Erasmus rucphen family study. *Alzheimer's & Dementia, 12*(7), P165. http://doi.org/10.1016/j.jalz.2016.06.277.

Vandal, M., Alata, W., Tremblay, C., Rioux-Perreault, C., Salem, N., Jr., Calon, F., et al. (2014). Reduction in DHA transport to the brain of mice expressing human APOE4compared to APOE2. *Journal of Neurochemistry, 129*(3), 516–526. http://doi.org/10.1111/jnc.12640.

Vannice, G., & Rasmussen, H. (2014). Position of the academy of nutrition and dietetics: Dietary fatty acids for healthy adults. *Journal of the Academy of Nutrition and Dietetics, 114*(1), 136–153. http://doi.org/10.1016/j.jand.2013.11.001.

Vellas, B., Carrie, I., Gillette-Guyonnet, S., Touchon, J., Dantoine, T., Dartigues, J. F., et al. (2014). MAPT study: A multidomain approach for preventing Alzheimer's disease: Design and baseline data. *The Journal of Prevention of Alzheimer's Disease, 1*(1), 13–22.

Vuksan, V., Choleva, L., Jovanovski, E., Jenkins, A. L., Au-Yeung, F., Dias, A. G., et al. (2017). Comparison of flax (Linum usitatissimum) and Salba-chia (Salvia hispanica L.) seeds on postprandial glycemia and satiety in healthy individuals: A randomized, controlled, crossover study. *European Journal of Clinical Nutrition, 71*(2), 234–238. http://doi.org/10.1038/ejcn.2016.148.

Wang, X., Zhu, M., Hjorth, E., Cortés-Toro, V., Eyjolfsdottir, H., Graff, C., et al. (2015). Resolution of inflammation is altered in Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 11*(1), 40–50. e1–2 http://doi.org/10.1016/j.jalz.2013.12.024.

Weiss, N., Miller, F., Cazaubon, S., & Couraud, P.-O. (2009). The blood-brain barrier in brain homeostasis and neurological diseases. *Biochimica Et Biophysica Acta, 1788*(4), 842–857. http://doi.org/10.1016/j.bbamem.2008.10.022.

Wes, P. D., Sayed, F. A., Bard, F., & Gan, L. (2016). Targeting microglia for the treatment of Alzheimer's Disease. *Glia, 64*(10), 1710–1732. http://doi.org/10.1002/glia.22988.

Witte, A. V., Kerti, L., Hermannstädter, H. M., Fiebach, J. B., Schreiber, S. J., Schuchardt, J. P., et al. (2014). Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cerebral Cortex (New York, N.Y.: 1991), 24*(11), 3059–3068. http://doi.org/10.1093/cercor/bht163.

Yakubenko, V. P., & Byzova, T. V. (2017). Biological and pathophysiological roles of end-products of DHA oxidation. *Biochimica Et Biophysica Acta, 1862*(4), 407–415. http://doi.org/10.1016/j.bbalip.2016.09.022.

Yassine, H. N., Croteau, E., Rawat, V., Hibbeln, J. R., Rapoport, S. I., Cunnane, S. C., et al. (2017). DHA brain uptake and APOE4 status: A PET study with [1-(11)C]-DHA. *Alzheimer's Research & Therapy, 9(1)*(23). http://doi.org/10.1186/s13195-017-0250-1.

Yassine, H. N., Feng, Q., Azizkhanian, I., Rawat, V., Castor, K., Fonteh, A. N., et al. (2016). Association of serum docosahexaenoic acid with cerebral amyloidosis. *JAMA Neurology, 73*(10), 1208–1216. http://doi.org/10.1001/jamaneurol.2016.1924.

Yassine, H. N., Rawat, V., Mack, W. J., Quinn, J. F., Yurko-Mauro, K., Bailey-Hall, E., et al. (2016). The effect of APOE genotype on the delivery of DHA to cerebrospinal fluid in Alzheimer's disease. *Alzheimer's Research & Therapy, 8*(1), 25. http://doi.org/10.1186/s13195-016-0194-x.

Yates, C. M., Calder, P. C., & Ed Rainger, G. (2014). Pharmacology and therapeutics of omega-3 polyunsaturated fatty acids in chronic inflammatory disease. *Pharmacology & Therapeutics, 141*(3), 272–282. http://doi.org/10.1016/j.pharmthera.2013.10.010.

Yu, Y. J., & Watts, R. J. (2013). Developing therapeutic antibodies for neurodegenerative disease. *Neurotherapeutics: The Journal of the American Society for Experimental NeuroTherapeutics, 10*(3), 459–472. http://doi.org/10.1007/s13311-013-0187-4.

Yurko-Mauro, K., Alexander, D. D., & Van Elswyk, M. E. (2015). Docosahexaenoic acid and adult memory: A systematic review and meta-analysis. *PLoS ONE, 10*(3), e0120391. http://doi.org/10.1371/journal.pone.0120391.

Yurko-Mauro, K., Kralovec, J., Bailey-Hall, E., Smeberg, V., Stark, J. G., & Salem, N. (2015). Similar eicosapentaenoic acid and docosahexaenoic acid plasma levels achieved with fish oil or krill oil in a randomized double-blind four-week bioavailability study. *Lipids in Health and Disease, 14*(1), 99. http://doi.org/10.1186/s12944-015-0109-z.

Zhu, M., Wang, X., Hjorth, E., Colas, R. A., Schroeder, L., Granholm, A.-C., et al. (2016). PPro-resolving lipid mediators improve neuronal survival and increase Aβ42 Phagocytosis. *Molecular Neurobiology, 53*(4), 2733–2749. http://doi.org/10.1007/s12035-015-9544-0.

Zis, P., & Mitsikostas, D.-D. (2015). Nocebo in Alzheimer's disease; meta-analysis of placebo-controlled clinical trials. *Journal of the Neurological Sciences, 355*(1-2), 94–100. http://doi.org/10.1016/j.jns.2015.05.029.