



Food for Mood: Relevance of Nutritional Omega-3 Fatty Acids for Depression and Anxiety

Thomas Larrieu*† and Sophie Layé*

UMR 1286, NutriNeuro: Laboratoire Nutrition et Neurobiologie Intégrée, Institut National de la Recherche Agronomique, Université de Bordeaux, Bordeaux, France

OPEN ACCESS

Edited by:

Céline Cruciani-Guglielmacci,
Paris Diderot University, France

Reviewed by:

Stephanie Fulton,
Université de Montréal, Canada
Ameer Taha,
University of California, Davis,
United States

*Correspondence:

Thomas Larrieu
larrieu.thomas@gmail.com
Sophie Layé
sophie.laye@inra.fr

† Present address:

Thomas Larrieu,
Center for Psychiatric Neurosciences,
Lausanne University Hospital,
Lausanne, Switzerland

Specialty section:

This article was submitted to
Integrative Physiology,
a section of the journal
Frontiers in Physiology

Received: 08 February 2018

Accepted: 13 July 2018

Published: 06 August 2018

Citation:

Larrieu T and Layé S (2018) Food
for Mood: Relevance of Nutritional
Omega-3 Fatty Acids for Depression
and Anxiety. *Front. Physiol.* 9:1047.
doi: 10.3389/fphys.2018.01047

The central nervous system (CNS) has the highest concentration of lipids in the organism after adipose tissue. Among these lipids, the brain is particularly enriched with polyunsaturated fatty acids (PUFAs) represented by the omega-6 ($\omega 6$) and omega-3 ($\omega 3$) series. These PUFAs include arachidonic acid (AA) and docosahexaenoic acid (DHA), respectively. PUFAs have received substantial attention as being relevant to many brain diseases, including anxiety and depression. This review addresses an important question in the area of nutritional neuroscience regarding the importance of $\omega 3$ PUFAs in the prevention and/or treatment of neuropsychiatric diseases, mainly depression and anxiety. In particular, it focuses on clinical and experimental data linking dietary intake of $\omega 3$ PUFAs and depression or anxiety. In particular, we will discuss recent experimental data highlighting how $\omega 3$ PUFAs can modulate neurobiological processes involved in the pathophysiology of anxiety and depression. Potential mechanisms involved in the neuroprotective and corrective activity of $\omega 3$ PUFAs in the brain are discussed, in particular the sensing activity of free fatty acid receptors and the activity of the PUFAs-derived endocannabinoid system and the hypothalamic–pituitary–adrenal axis.

Keywords: omega-3 fatty acid, endocannabinoids, HPA axis, nutrient sensing, mood disorders, anxiety, depression, DHA

INTRODUCTION

Since the discovery of omega-3 ($\omega 3$) PUFAs in 1929 by George Burr and Mildred Burr (Burr and Burr, 1929; Spector and Kim, 2015), research on $\omega 3$ PUFAs became an appealing topic ranging from their role in cardiovascular risk to more recently neuropsychiatric pathologies such as depression and anxiety, cognitive decline or neurodegenerative diseases (Bazinet and Layé, 2014; Joffre et al., 2014; Coulombe et al., 2017). The relevance of lipids in brain function is illustrated by the fact that the CNS has the highest concentration of lipids in the organism after the

Abbreviations: 2-AG, 2-arachidonoylglycerol; AA, arachidonic acid; AC, adenylyl cyclase; AEA, ethanolamides anandamide; ALA, alpha-linolenic acid; CA1, cornu ammonis 1; cAMP, cyclic adenosine monophosphate; CB1R, cannabinoid receptor 1; CNS, central nervous system; COX, cyclooxygenase; CRH, corticotrophin-releasing hormone; CSDS, chronic social defeat stress; CYP450, cytochrome P450; DHA, docosahexaenoic acid; DHEA, docosahexaenoyl ethanolamide; DPA, docosapentaenoic acid; eCB, endocannabinoid; EPA, eicosapentaenoic acid; FADS, fatty acid desaturases; FFAR, free fatty acid receptors; FST, forced swimming test; GABA, gamma-aminobutyric acid; GPCR, G-protein-coupled receptor; GPR120, G-protein-coupled receptor 120; GPR40, G-protein-coupled receptor 40; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; LA, linoleic acid; LC, long chain; LOX, lipoxygenases; LPS, lipopolysaccharide; NAc, nucleus accumbens; PFC, prefrontal cortex; PPAR, peroxisome proliferator-activated receptor; PTSD, post-traumatic stress disorders; PUFAs, polyunsaturated fatty acids; RXR, retinoid X receptor; SPMs, specialized pro-resolving lipid mediators; SSRI, selective serotonin reuptake inhibitor; TNF α , tumor necrosis factor α ; WHO, World Health Organization.

adipose tissue (50–60% of the dry weight of the brain; Sastry, 1985). Among these lipids, the brain is particularly greedy for PUFAs from the $\omega 6$ and $\omega 3$ PUFAs families, in particular the LC PUFA (AA, 20:4n-6) and (DHA, 22:6n-3), respectively (Sastry, 1985). In the Human brain, DHA accounts for 10 to 15% of the total fatty acids (saturated, monounsaturated and PUFAs) in both males and females (McNamara et al., 2007, 2008b). This makes PUFAs indispensable to the normal development and function of the CNS (Makrides and Gibson, 2000; Innis, 2007; Bazinet and Layé, 2014). One hypothesis explaining this abundance in brain tissue is that *Homo sapiens* in Paleolithic settled around the lakes and seas where access to foods rich in $\omega 3$ PUFAs is easy (Bradbury, 2011). It is generally considered that humans evolved on a diet with a ratio of $\omega 6$ to $\omega 3$ PUFAs equal approximately to 1. During the industrial era, the rapid expansion of Western countries has been associated with drastic changes in the $\omega 6/\omega 3$ PUFAs content of the diet. This is reflected in large quantities of $\omega 6$ PUFA-containing foods and smaller amounts of $\omega 3$ PUFA-rich foods leading to Western diet being typically poor in $\omega 3$ PUFAs. In addition, the intake of saturated fats from lard and butter has been replaced by plant-based PUFAs based on recommendations from health agencies (Gibson et al., 2011). As a result, the use of oils such as sunflower oil which are mostly high in (LA, the precursor of AA) and low in α -linolenic acid (ALA, the precursor of DHA) leads to a marked increase in LA intake. In mammals, LA and ALA cannot be synthesized *de novo* and need to be provided through the diet (Simopoulos, 1991; Gibson and Makrides, 2001). These essential PUFAs are metabolized into LC PUFAs using the same enzymatic pathway, meaning that LA and ALA are in competition for endogenous conversion to their respective LC forms AA, and DHA (Figure 1) but also for their entry into the brain (Bazinet and Layé, 2014). Of importance, ALA bioconversion into DHA through several cycles of elongation (ELOVLs) and desaturation ($\Delta 5$ and $\Delta 6$ desaturases) is in the range of 0.05% (Burdge et al., 2003) to 4% (Emken et al., 1994) and might not be sufficient to cover brain needs. This led to the recommendation of dietary intake of oily fish rich in the LC $\omega 3$ PUFAs DHA and EPA (Tejera et al., 2016). Overall, western diets which are rich in LA (coming from vegetable oils rich in LA) and poor in ALA and DHA (coming from fat fish, sea food or certain algae) have created “a conditional essentiality for $\omega 3$ PUFAs” as previously described by Cunnane (2003) and Gibson et al. (2011). Indeed, the amount of LC $\omega 3$

PUFAs needed to compensate this lack in western diet is likely to increase, which is not sustainable in the actual context of fish stock decline (Fernandes and Cook, 2013).

The reduced dietary supply of $\omega 3$ PUFAs to the brain is associated with many brain diseases, including depression and anxiety disorders (see review from Müller et al., 2015). Epidemiological studies have linked low $\omega 3$ PUFAs dietary intake with the prevalence of depression in the general population (Hibbeln, 1998). Clinical studies further revealed that subjects diagnosed with depression or anxiety display significant lower levels of $\omega 3$ PUFAs and higher ratio of $\omega 6$ to $\omega 3$ PUFAs in the blood and in the brain (Green et al., 2006; McNamara and Liu, 2011; Parletta et al., 2016). Supporting clinical observations, preclinical studies conducted in rodents showed that $\omega 3$ PUFA deficient diet consumption induces depressive- and anxiety-like symptoms as well as abnormal social behavior in adult offspring (Lafourcade et al., 2011; Larrieu et al., 2012, 2014, 2015; Bondi et al., 2014). Importantly, the use of dietary animal models has been crucial to study the neurobiological mechanisms underlying the alteration of emotional behaviors following decreased bioavailability of $\omega 3$ PUFAs in the brain. In this review, we first discuss clinical and pre-clinical evidence of the importance of $\omega 3$ PUFAs in anxiety and depressive disorders as well as the rationale for evaluating baseline levels of $\omega 3$ PUFAs prior to starting nutritional intervention studies. Then we describe mechanisms linking $\omega 3$ PUFAs and emotional behaviors disturbance, especially the sensing activity of FFAR, the eCB system, glucocorticoids as well as neuroinflammatory pathways.

THE ROLE OF $\omega 3$ PUFAs IN DEPRESSION AND ANXIETY DISORDERS

Clinical and Epidemiological Evidence Linking $\omega 3$ PUFAs, Depression and Anxiety

Several clinical and epidemiological studies highlighted the link between mood disorders and blood and/or cellular membrane PUFAs content (reviewed in Müller et al., 2015). These observations led to the “phospholipids hypothesis” according to which PUFAs are possible aetiological factors in the development

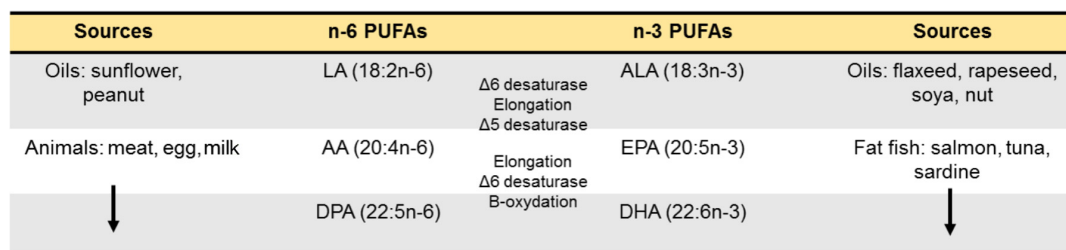


FIGURE 1 | Long-chain PUFAs synthesis. Essential fatty acids precursors of n-6 and n-3 PUFAs are provided by food. Once in the livers, they are metabolized into long-chain PUFAs using a series of desaturations and elongation machinery. The newly synthesized long-chain n-6 PUFAs are AA (20:4n-6) and DPA (22:5n-6) and the long-chain n-3 PUFAs are DHA (22:6n-3) and DPA (22:5n-3).

of depressive disorders (Hibbeln and Salem, 1995). Indeed, subjects diagnosed for anxiety and depressive disorders show lower ω 3 PUFAs and higher ratio of ω 6 to ω 3 PUFAs in their blood and brains compared to healthy subjects matching for age and sex (Adams et al., 1996; Maes et al., 1996; Edwards et al., 1998a,b; Tiemeier et al., 2003; Frasure-Smith et al., 2004; Green et al., 2006; McNamara et al., 2007; McNamara and Liu, 2011; Parletta et al., 2016). EPA (20:5 n-3) concentration (Adams et al., 1996; Green et al., 2006; Liu et al., 2013) as well as DHA concentration (Edwards et al., 1998a; Frasure-Smith et al., 2004; Green et al., 2006; McNamara and Liu, 2011; Liu et al., 2013; Otoki et al., 2017) are decreased in the membrane of erythrocytes and in the plasma of patients suffering from unipolar depression, seasonal winter affective disorder or social anxiety disorders (Adams et al., 1996; Green et al., 2006). A recent study showed that the AA:EPA ratio in the blood is positively correlated with illness duration in patients diagnosed with major depression (Scola et al., 2018). A meta-analysis work from Lin et al. (2010) supports these observations by showing significant low levels of EPA, DHA, and total ω 3 PUFAs among 3,318 depressed patients. In some of these studies, the severity of the depressive and anxious symptoms is negatively correlated with the concentration of the total ω 3 PUFA levels in the blood (Adams et al., 1996; Maes et al., 1996; Edwards et al., 1998a; Green et al., 2006; Liu et al., 2013). Post-mortem studies report reduced levels of DHA in the PFC of patients diagnosed with major depression, bipolar disorders or committing suicide (McNamara et al., 2007, 2008a, 2013). In pregnant women, for whom the risk of ω 3 PUFAs deficiency is relatively high as they provide DHA to the fetus, nearly 10% experience post-partum depression (Markhus et al., 2013). Yet, no clear consensus exist as to whether low ω 3 PUFAs and high ω 6 PUFA levels in the blood are linked to the development of post-partum depression (Hibbeln, 2002; Parker et al., 2015). These observations are not limited to depression as decreased ω 3 PUFAs (DHA) levels in erythrocytes and PFC have also been found in patients suffering from PTSD (de Vries et al., 2016). As decreased ω 3 PUFAs status is associated with several forms of depression and stress disorders, the understanding of the origin (dietary or genetic) of the decreased bioavailability of DHA or EPA is of high interest.

The rationale for identifying baseline nutritional ω 3 PUFAs status comes from one hypothesis advanced by researchers that weak food supply in ω 3 PUFAs might be a risk factor of the development of depression. As fish is the main source of LC ω 3 PUFAs, several epidemiological studies investigating putative associations between major depressive disorder and fish consumption were conducted in various countries (Finland, New Zealand, France, Northern Ireland, Norway or Netherlands) (Tanskanen et al., 2001; Silvers and Scott, 2002; Timonen et al., 2004; Barberger-Gateau et al., 2005; Kamphuis et al., 2006; Appleton et al., 2007; Raeder et al., 2007; Colangelo et al., 2009). Subjects having low fish consumption (lower than once per week, including seafood) present high scores of depression (Timonen et al., 2004; Barberger-Gateau et al., 2005). A transnational ecological study conducted on a large cohort including individuals from different countries highlighted a strong negative correlation between fish consumption and

the prevalence of depression (Hibbeln, 1998). Indeed, this epidemiological study of great width (170,000 individuals) revealed that individuals from Asian countries like Japan, Korea, and Taiwan, who are the biggest fish consumers, suffer relatively little from major depression. This observation can appear counterintuitive as Japan experiences a high rate of suicide while the depression rate is thought very low (WHO, 2015). Such a high rate of suicide has been associated to cultural factors (idealization of suicide, acceptability, etc.) including aging society (Saito et al., 2013), divorce and unemployment (Yamauchi et al., 2013). On the contrary, Western countries like New Zealand, Canada, United States, Germany, or France are part of the countries that consume less fish with high prevalence to develop depression. These data suggest that fish consumption is conversely correlated with the development of depression.

To PUFA dietary intake consideration in decreasing ω 3 PUFAs bioavailability in depression, one must add the genetic variation of the FADS, an enzyme which converts PUFA precursors into LC-PUFAs (EPA, DHA, and AA) (Koletzko et al., 2011; Mathias et al., 2014; Park et al., 2015). Indeed, inter-individual variability in red blood cells DHA and AA levels is explained by FADS polygenes (71 and 53%, respectively) (Lemaitre et al., 2008). FADS genotypes influence DHA amounts in red blood cells of pregnant women independently of dietary effects (Koletzko et al., 2011). Children carrying FADS minor allele have lower DHA levels in erythrocyte, with no behavioral outcomes (Jensen et al., 2014). However, the link between FADS haplotype and the risk of developing neuropsychiatric disorders (schizophrenia or depression) is weak (Fallin et al., 2004; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011). A study conducted in patients with major depression found no association between FADS single nucleotide polymorphisms and major depression (Sublette et al., 2016). Recently, a study suggested that genetic variation in the FADS gene influences the ω 6/ ω 3 PUFAs ratio which appears to be associated with major depression (Cribb et al., 2017). To our knowledge, no study has so far linked brain DHA level to FADS genotype. Overall, in addition to dietary composition of PUFAs, FADS genetic variation should be considered in the LC-PUFAs status and the pathophysiology of depression and stress.

Taken together, these clinical observations raise a crucial question: Is there a causal link between the contents of ω 3 PUFAs in the blood/brain and depressive/anxiety disorders? If so, are the low levels of ω 3 PUFAs the cause or the consequence of these affective disorders? These relations of causalities were approached by nutritional interventions in Humans which are the object of the following section, first in depression, then in PTSD and stress disorders.

Dietary ω 3 PUFAs Supplementation, Depression, and PTSD in Humans

The results from LC ω 3 PUFA nutritional interventions carried out among patients with depressive disorders are heterogeneous as recently reviewed elsewhere (Bozzatello et al., 2016; Saunders et al., 2016). Some studies conducted on patients suffering from major depression without an antidepressant treatment

do not show significant effects of ω 3 PUFAs supplementation (Marangell et al., 2003; Freeman et al., 2008; Rees et al., 2008; Mischoulon et al., 2015), whereas others reveal a beneficial effect (Su et al., 2003; Nemets et al., 2006; Jazayeri et al., 2008). A 16-week dietary supplementation with EPA + DHA did not prevent maternal depressive symptoms (Vaz et al., 2017). These discrepancies are reflected by meta-analysis. Indeed, some found that EPA and DHA can reduce depressive symptoms (Kraguljac et al., 2009; Appleton et al., 2010; Sublette et al., 2011; Grosso et al., 2014) while other found no effect (Appleton et al., 2015). Mixed results of clinical trials could be attributed not only to the heterogeneity in clinical trials and design, but also to the quantity and quality of the PUFA used, including the EPA:DHA ratio, trial duration, the type of placebo (PUFA or other fatty acids) and to the concomitant use of medication and baseline symptom severity. Recently, EPA, rather than DHA, has been suggested to mediate the beneficial effect of ω 3 PUFAs supplementation in patients diagnosed with major depression DHA (Martins, 2009; Martins et al., 2012; Grosso et al., 2014; Hallahan et al., 2016). Indeed, several studies using ethyl-EPA (from 1 to 2 g/day) reported a beneficial effect in patients with major depression and resistant to anti-depressant (Peet and Horrobin, 2002) or recurrent unipolar depression (Nemets et al., 2002). In addition, EPA-rich formulation with no DHA is more effective than DHA-rich supplements in major depression (Sublette et al., 2011). A meta-analysis aiming at investigating the beneficial role of EPA or DHA supplementation in major depressive disorder found that EPA is more effective than DHA (Grosso et al., 2014). The beneficial effect of EPA has been recently corroborated by a new meta-analysis (Mocking et al., 2016). EPA efficiency could be linked to its conversion into DHA by elongase leading to increased DHA brain bioavailability and decreased LC ω 6 PUFAs production (Ganança et al., 2017). Indeed, as the conversion of EPA into DHA compete with the production of n-6 DPA from AA by using the same enzymatic pathway (i.e., FADS and elongases), the supplementation of EPA can simultaneously lead to an increase in DHA and a decrease in n-6 DPA levels that can subsequently improve mood. However, further studies with larger and more homogeneous samples are required to confirm these effects.

In addition, it has been suggested that depressive patients who display low levels of ω 3 PUFAs may rather benefit of the LC ω 3 PUFAs supplementation (Carney et al., 2016; Messamore and McNamara, 2016). Despite recent advances in understanding the pathophysiology of major depression, approximately 30% of patients remain refractory to multistep antidepressant treatments (Rush et al., 2006a,b). One explanation of this finding could come from individual differences in baseline levels of ω 3 PUFAs. To support this idea, a study recently showed that high baseline levels of EPA and DHA in red blood cells of depressive patients predict favorable depression outcomes in patients receiving ω 3 PUFAs supplements (Carney et al., 2016). In addition, among patients treated but resistant to antidepressants such as the (SSRI; e.g., Fluoxetine, Paroxetine), the severity of the symptoms of depression decreased in the group supplemented in ω 3 PUFAs (Nemets et al., 2002; Peet and Horrobin, 2002; Su et al., 2003; Jazayeri et al., 2008; Gertsik et al., 2012; Zimmer et al., 2013;

McNamara et al., 2014; Mocking et al., 2016). This strategy can be highly relevant as resistance to treatment is observed in a large proportion of patients (40%) (Brunoni et al., 2009; Shelton et al., 2010) and it suggests that dietary ω 3 PUFA intake may improve antidepressant response.

ω 3 PUFAs dietary supplementation has also been used in stress disorders. Stress is a well-known major risk factor for the development of depression or PTSD. One study aimed at investigating the effect of ω 3 PUFAs supplementation in chronically work-stressed individuals and found no significant treatment effect for EPA after 12 weeks of supplementation on the Perceived Stress Scale scores (Bradbury et al., 2017). On the contrary, a placebo-controlled trial of ω 3 PUFAs supplements in patients suffering from PTSD revealed that EPA but not DHA (Matsuoka et al., 2015) levels were inversely correlated with PTSD severity suggesting the potential efficacy of EPA rather than DHA for minimizing PTSD symptoms (Matsuoka et al., 2016). Regarding ω 3 PUFAs supplementation in the prevention of anxiety, a study conducted by Yehuda et al. (2005) has investigated whether administration of a cocktail of ω 3 PUFAs (90 mg of ALA/day) and ω 6 PUFAs (360 mg of LA/day) over 3 weeks in students could improve anxiety induced by the university examinations. These authors highlighted an improvement of several symptoms (appetite, mood, concentration, and fatigue) compared to the placebo group. These improvements are associated with a decreased level of salivary cortisol (Yehuda et al., 2005). Despite the low dose of ALA used in this study (90 mg/day) as compared to nutritional intake in the general population (1–2 g/day), this 10% increase was sufficient to improve symptoms. In addition, ALA conversion in EPA is determined by the amount of ALA in the diet (i.e., higher in the plasma phospholipid pool when ALA is low) (Goyens et al., 2006). Thus, the effectiveness of ALA in Yehuda et al.'s (2005) study could be linked to EPA. Moreover, students having received a supplementation with DHA and EPA during 12 weeks present a reduction of 20% of anxiety symptoms compared to the students treated with a placebo (Kiecolt-Glaser et al., 2011). In students treated with ω 3 PUFAs supplementation, an increase in plasma concentration of DHA and EPA were observed as of the third week of treatment. Lastly, the increase in DHA and EPA was negatively correlated with a reduction in anxiety symptoms.

In conclusion, these observations further support the role of PUFAs metabolism as an important mechanism in depression and anxiety disorders treatment. This brings new insight to personalized PUFAs formulation as a novel adjunctive treatment for patients with mood and anxiety disorders.

Pre-clinical Studies Linking ω 3 PUFAs and Emotional Behavior

To better understand whether the modifications of nutritional ω 6/ ω 3 PUFA ratio could affect brain function and behavior, studies have been carried out in animals (rodents, monkeys, and pigs) subjected to diets in which PUFAs contents are controlled during one or several generations (de la Presa Owens and Innis, 1999; Clouard et al., 2015). Numerous studies have shown that in

animal models of nutritional ω 3 PUFA deprivation, brain DHA levels were decreased while AA levels were increased in several brain areas leading to an imbalance between ω 6 and ω 3 PUFAs in the ω 3 PUFAs deficient mouse brain (Delion et al., 1994; Francès et al., 1995; Favrelière et al., 1998; Carrié et al., 2000b; McNamara and Carlson, 2006; Lafourcade et al., 2011; Larrieu et al., 2012). Nutritional ω 3 PUFAs deficiency-induced reduction of brain DHA levels has been associated with the development of depression-like behavior (Carrié et al., 2000a; Takeuchi et al., 2003; DeMar et al., 2006; Fedorova and Salem, 2006; Lafourcade et al., 2011; Larrieu et al., 2012, 2014, 2015; Bondi et al., 2014; Morgese et al., 2016; Manduca et al., 2017). By submitting mice to one generation dietary ω 3 PUFAs deficiency, we found that ω 3 PUFAs deficient diet alone disturbed social behavior as well as increased anxiety- and depression-related behavior in an open-field and FSTs, respectively (Lafourcade et al., 2011; Larrieu et al., 2012, 2014, 2015). Some studies conducted in rats indicate that the time of immobility in the FST was increased by ω 3 PUFAs deficiency (DeMar et al., 2006; Morgese et al., 2016) and reduced by ω 3 PUFAs supplementation with fish oil (Naliwaiko et al., 2004; Carlezon et al., 2005; Huang et al., 2008). In addition, the level of DHA in rat whole brains is negatively correlated with the time spent immobile during the FST, a behavioral test used for evaluating the efficacy of compounds rendering or preventing depressive-like states. Interestingly, similar behavioral impairments (e.g., anxiety-like behavior and social interaction) occur in mice after exposure to CSDS, a well-characterized preclinical model of anxiety and depression (Golden et al., 2011; Bosch-Bouju et al., 2016; Larrieu et al., 2017). This model presents strong face validity, as social defeat (e.g., bullying) is a major risk factor to developing depression in humans. One cardinal feature of CSDS is that mice experiencing this chronic stress develop a long-lasting (more than 1 month) aversion to social interaction as well as anhedonia, which can be normalized after chronic (28 days post-CSDS), but not acute administration of antidepressant (Berton et al., 2006; Krishnan et al., 2007) as observed in humans. By comparing the effects of dietary ω 3 PUFAs deficiency to those of CSDS on emotional behavior, we found that mice fed with a diet deficient in ω 3 PUFAs exhibited behavioral changes and neuronal atrophy profile that resemble those of mice exposed to CSDS (Larrieu et al., 2014). Interestingly, behavioral alterations can be reversed after chronic ω 3 PUFAs supplementation. As such, increased anxiety- and depressive-like behavior after chronic stress is normalized after ω 3 PUFAs supplementation (Ferraz et al., 2011; Larrieu et al., 2014).

RELEVANT MECHANISMS FOR NUTRITIONAL ω 3 PUFA-INDUCED MOOD-RELATED BEHAVIORAL DEFICITS

Numerous epidemiological, clinical, and preclinical studies demonstrated the key role of nutritional ω 3 PUFAs in depression and anxiety disorders. In recent years, emphasis was made

on identifying molecular and cellular mechanisms by which ω 3 PUFAs modulate brain function. ω 3 PUFAs and their metabolites are well known to play an important role as signaling molecules that regulate inflammation (Serhan, 2014) and neuroinflammation (recently reviewed in Layé et al., 2018). They also contribute to signal transduction between neurons or neurons and glial cells. Here, we will focus on DHA, the most aggregated fatty acid in the brain while EPA is rapidly β -oxidized and poorly accumulated (Chen and Bazinet, 2015). As DHA is poorly synthesized *de novo*, its brain levels depend on both the dietary supply and blood level bioavailability (Bazinet and Layé, 2014; Lacombe et al., 2018). Once free DHA has entered the brain, it is esterified at membrane phospholipids (both in neurons and glial cells). However, upon neuronal stimulation, injury or stress, DHA is released from phospholipids and can either activate specific receptors or be metabolized into specific derivatives, such as eCBs or oxylipins which regulate specific pathways important to neurotransmission or neuroinflammation (Bazinet and Layé, 2014; Bosch-bouju and Layé, 2016; Layé et al., 2018). In the following section, we first describe the receptors which have been reported to mediate DHA effect in the brain. Then, we focus on the regulation of the eCB system and the HPA axis as recent data show that they could mediate the neuroprotective effect of ω 3 PUFAs as both are thought to be involved in depression.

Direct Effect of DHA on Specific Receptors

While free fatty receptors have been widely described to mediate some of the effects of DHA at the periphery, few reports highlight a direct effect of DHA through signaling activity in the brain. In 2000, DHA has been shown to be a ligand of the RXR, the receptor of retinoic acid (a vitamin A metabolite), which heterodimerizes with other nuclear receptors such as retinoic acid receptor, vitamin D receptor, thyroid hormone receptor or PPAR (Lengqvist et al., 2004). DHA effect on neurogenesis does not involve RXR, as its effect *in vitro* does not activate RXR (Calderon and Kim, 2007). However, DHA potentiates retinoic acid effect and improves cognitive symptoms in a rodent model of Alzheimer disease (Casali et al., 2015) and aged rodents (Létondor et al., 2016). Interestingly, the loss of RXR signaling leads to altered emotional and cognitive behavior in mice (Krzyszosiak et al., 2010; Wietrzyk-Schindler et al., 2011). Importantly, DHA antidepressant effect is absent in RXR knock-out mice (Wietrzyk-Schindler et al., 2011), further highlighting the role of this receptor and its ligand (possibly DHA and retinoic acid) in emotional behavior. FFAR, members of the “rhodopsin-like” GPCR family, namely GPR40 (FFAR1) and GPR120 (FFAR4), have been recently highlighted as potentially mediating LC FFAs signal from pancreatic beta-cells as well as the intestines (Itoh et al., 2003; Hirasawa et al., 2005). These lipid receptors were also reported to be present in the brain (Ma et al., 2007; Dragano et al., 2017). Memory-induced progenitor cell proliferation and DHA-induced neurogenesis in the hypothalamus are mediated by GPR40 (Ma et al., 2008; Yamashima, 2008; Nascimento et al., 2016). In addition, DHA-induced GPR40 signaling pathway activates β -endorphin release in the hypothalamus of rodents

(Nakamoto et al., 2015). Importantly, the chronic activation of GPR40 signaling in the brain reduces depressive-like behavior (Nishinaka et al., 2014). In addition, anxiety-like behavior and sucrose preference, a behavioral sign of anhedonia, are reduced in GPR40 knock-out mice further highlighting the role of GPR40 signaling in the pathophysiology of mood disorders (Aizawa et al., 2016). GPR120, another GPR which signals DHA activity, is highly expressed in the arcuate nucleus of the hypothalamus and the NAc, a structure involved in emotional behavior (Auguste et al., 2016). Interestingly, GPR120 activation by a specific agonist reduces obesity-induced emotional behavior alteration (Auguste et al., 2016). Taken together, these data suggest that several receptors could mediate a direct effect of DHA on neurons to control emotional behavior, opening new avenues in drug development targeting these receptors. However, additional studies are needed to determine whether DHA acts through these receptors to protect from depression and anxiety disorders in humans.

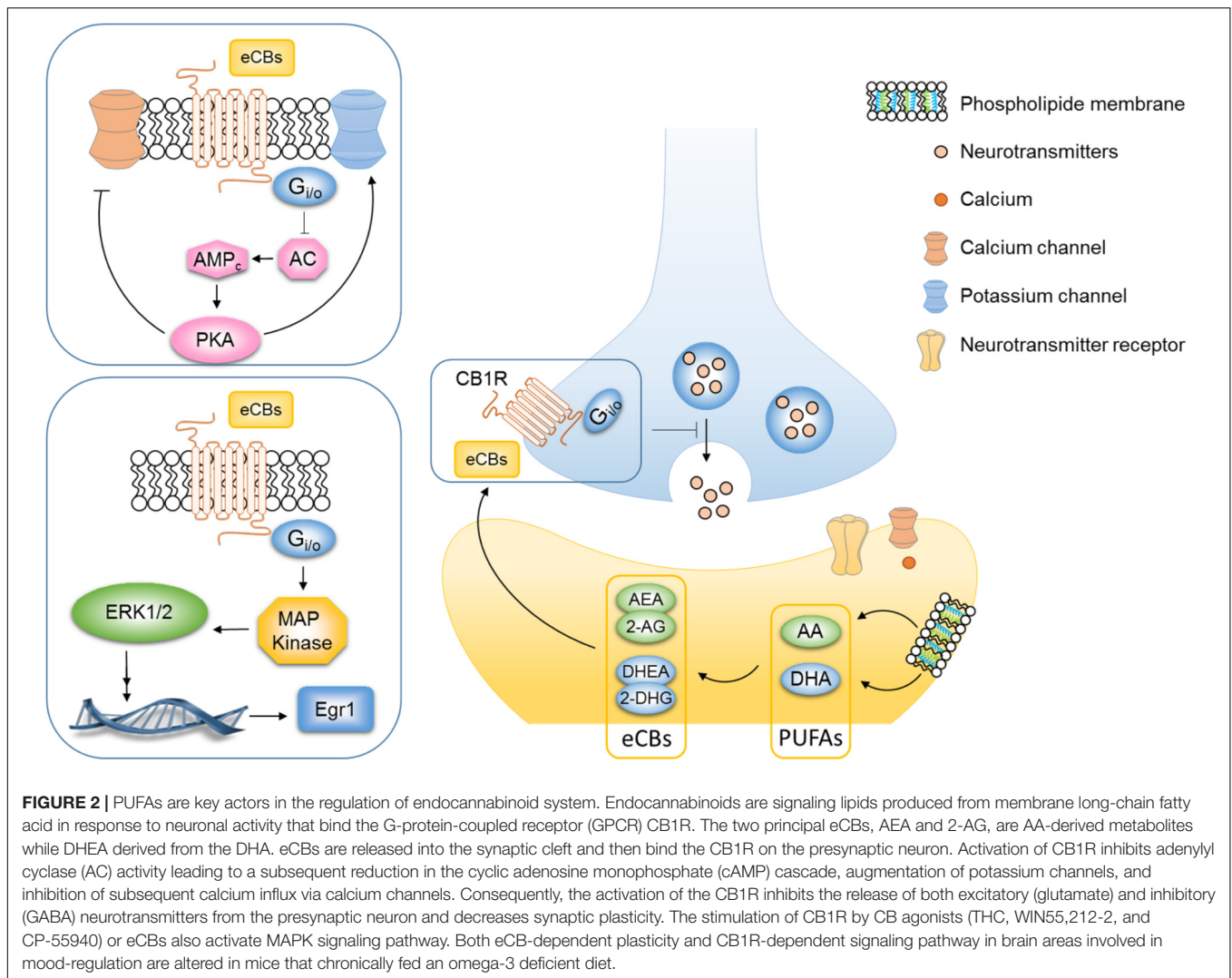
Endocannabinoid System

Regulation of the eCB system could mediate the neuroprotective effect of ω 3 PUFAs as both are thought to be involved in depression. The eCB system is in a unique position to link food lipids, neuroplasticity and behavior (Bazinnet and Layé, 2014; Bosch-bouju and Layé, 2016; Chianese et al., 2017). eCBs are signaling lipids produced from membrane LC fatty acid in response to neuronal activity and they bind the GPCR CB1R (Mackie, 2008) (**Figure 2**). eCBs are produced on-demand and are rapidly degraded, back into PUFAs or oxidized into active metabolites (Bosch-bouju and Layé, 2016). eCBs include the fatty acid AEA, DHEA, oleylethanolamide and palmitoylethanolamide, as well as 2-AG (Piomelli and Sasso, 2014). The two principal eCBs, AEA and 2-AG, are AA-derived metabolites, while DHEA is derived from the DHA and oleylethanolamide and palmitoylethanolamide is derived from EPA. The most well-studied eCBs are the ω 6 PUFA-derived AEA (Devane et al., 1992) and the 2-AG (Sugiura et al., 1995) as compared to the ω 3 PUFA-derived eCBs. Activation of CB1 receptors inhibits AC activity leading to a subsequent reduction in the cAMP cascade, augmentation of potassium channels, and inhibition of subsequent calcium influx via calcium channels (**Figure 2**) (Howlett and Fleming, 1984; Howlett, 2002). Consequently, the activation of the CB1R inhibits the release of both excitatory (glutamate) and inhibitory GABA neurotransmitters from presynaptic neurons (Wilson and Nicoll, 2001, 2002; Freund et al., 2003) (**Figure 2**). Finally, numerous important studies have unraveled the key role of eCB system in mood regulation (Morena et al., 2015; Hill and Lee, 2016). As eCBs are derived from ω 6 and ω 3 PUFA precursors, we hypothesized that the effects of PUFAs on mood-related behavior might be mediated, at least partly, through the eCB system (Lafourcade et al., 2011; Bosch-Bouju et al., 2016; Manduca et al., 2017). As such, inadequate PUFAs ratio during critical time window, i.e., gestation or lactation can lead to changes in eCBs contents in the brain. Newborn piglets that were fed with a diet containing ALA, AA and DHA during the first 18 days of life showed an expected increase of AA and DHA levels

in the brain but also of AEA and DHEA metabolites (Berger et al., 2001). Watanabe et al. reported that nutritional ω 3 PUFAs deficiency for 2 generations elevates the levels of 2-AG in the mouse brain while ω 3 PUFAs supplementation reduces them. In this study, DHA brain levels were affected by dietary ω 3 PUFAs deficiency, but not AA the precursor of 2-AG which remained unchanged as compared to the control diet group (Watanabe et al., 2003). It is now well documented that AA levels are barely impacted by PUFAs content of the diet while DHA brain levels are more sensitive to dietary ω 6/ ω 3 PUFAs. Whether increased 2-AG and AEA after exposure to a diet rich in ω 6 PUFAs is a compensatory effect to buffer AA concentrations remains to be determined. Lastly a 2-week-supplementation in DHA increased the DHEA and decreased the AEA in brain homogenates in both rats and mice (Wood et al., 2010). One *in vitro* study also demonstrated that unesterified free DHA could directly regulate CB1 gene expression in hippocampal neurons (Pan et al., 2011). Collectively, these reports support the hypothesis proposing that nutritional PUFAs intake is tightly linked to brain eCB levels. By regulating levels of eCBs in the brain, PUFAs have been shown to impact hippocampal synaptic plasticity (Thomazeau et al., 2017) and eCB-dependent plasticity (Lafourcade et al., 2011; Manduca et al., 2017) as well as CB1-associated signaling pathways (Larrieu et al., 2012) in the PFC and NAc. In mice, perinatal exposure to dietary ω 3 PUFA deficiency, which leads to low DHA levels in the PFC and the NAc, abolished the eCB-long-term depression in these brain structures. Specifically, this alteration is mediated by an uncoupling from CB1R to its G protein (Lafourcade et al., 2011). Moreover, the effect of the CB1 agonist WIN55,212-2 in anxiety-like behavior was abolished and the CB receptor signaling pathways were altered in the PFC and hypothalamus of ω 3 PUFA-deficient mice (Larrieu et al., 2012). A recent study has involved the 2-AG in these aforementioned alterations. Our recent work highlighted that the inhibition of 2-AG degradation normalized emotional behavior deficits and eCB-dependent synaptic plasticity alteration observed in ω 3 PUFA-deficient adult mice (Manduca et al., 2017). These observations are the first synaptic and molecular evidence that malnutrition related to ω 6/ ω 3 PUFAs ratio can have detrimental effect on eCB system, subsequently leading to impaired behavior.

Hypothalamic–Pituitary–Adrenal Axis

Stress and high trait anxiety are a major risk factor for neuropsychiatric diseases, particularly major depression and anxiety disorders, and are etiologically causal in PTSD (Sandi and Richter-Levin, 2009). Interestingly, although several mechanisms underlying the effects of dietary ω 3 PUFA deficiency on emotional behavior have been described (e.g., eCB system), those specifically related to HPA axis function remain poorly understood. Nevertheless, clinical data reported that low plasma DHA levels correlate with higher cerebrospinal fluid CRH levels (Hibbeln et al., 2004) and with higher cortisol in plasma (Nieminen et al., 2006; Mocking et al., 2013). Healthy men receiving supplementation for 3 weeks with dietary fish oil display a blunted cortisol response after an acute mental stress (Delarue et al., 2003). Mood-related deficits observed in



deficient mice or rats were recently linked to disrupted GR-mediated signaling pathway, HPA axis hyperactivity as well as eCB system impairment, all involved in mood regulation (Ferraz et al., 2011; Lafourcade et al., 2011; Larrieu et al., 2014, 2015; Bosch-Bouju et al., 2016). Rats that were fed with a ω 3 PUFA deficient diet display HPA axis hyper-reactivity after stress exposure reflected by increased levels of plasma corticosterone compared to control diet group (Levant et al., 2008). Conversely, corticosterone hypersecretion induced by a chronic stress and IL-1 β exposure is dampened in ω 3 PUFA supplemented rats (Song et al., 2003; Ferraz et al., 2011). In Morgese et al. (2016), increased hypothalamic CRF release as well as increased plasmatic corticosterone levels has been shown in ω 3 PUFA deficient rats, further demonstrating the link between HPA axis hyperactivity and dietary ω 3 PUFAs. In a recent study, we demonstrated that anxiety- and depressive-related behaviors as well as neuronal atrophy in the medial PFC observed in mice fed with a diet deficient in ω 3 PUFAs are both mediated by HPA axis hyperactivity (Larrieu et al., 2014). ω 3 PUFAs supplementation beyond weaning prevents chronic

stress-induced increases in plasma corticosterone levels (Ferraz et al., 2011; Larrieu et al., 2014; Meneses et al., 2017), PFC neuronal shrinkage (Larrieu et al., 2014) as well as anxiety- and depressive-like behaviors (Ferraz et al., 2011; Larrieu et al., 2014). In another study, we confirmed and followed up on their initial observations by demonstrating that GR signaling pathway is compromised in the PFC of ω 3 PUFA-deficient mice along with dendritic arborization atrophy (Larrieu et al., 2015). The modulation of neuronal morphology by ω 3 PUFAs might be not a generalized phenomenon since neuronal arborization atrophy is only observable in the PFC but not the CA1 of the hippocampus of ω 3 PUFA-deficient mice (Delpech et al., 2015b; Larrieu et al., 2015). To further establish the link between dietary ω 3 PUFAs consumption and neuronal morphology, *in vitro* studies were conducted showing that PUFAs activate neurites formation and growth in hippocampal (Calderon and Kim, 2004; Cao et al., 2009) and cortical neurons (Cao et al., 2005) in primary culture. Moreover, in these same cultures, a decrease of DHA leads to the reduction of the size of neurites (Ikemoto et al., 1997; Furuya et al., 2002; Calderon and Kim, 2004; Cao et al., 2009).

The accretion of DHA in the brain considerably facilitates the formation of the dendritic spines in the hippocampus of Gerbils that were fed with a diet supplemented in DHA (Sakamoto et al., 2007). Interestingly, genetically modified Fat-1 mice that are able to catalyze the conversion of $\omega 6$ into $\omega 3$ PUFAs display a higher density of spines in the hippocampus compared to WT mice (Kang et al., 2004; He et al., 2009). Moreover, increased spine density in the hippocampus of Fat-1 mice is associated with better cognitive performances assessed in Morris water maze along with increased adult neurogenesis (He et al., 2009). The protective effect of LC $\omega 3$ PUFAs could be linked to hippocampal neurogenesis (recently reviewed in (Zainuddin and Thuret, 2012)). As such, changes in hippocampal neurogenesis and cell survival in the dentate gyrus have been correlated with depressive-like behavior. A recent study demonstrated that clamping glucocorticoid levels prevent CSDS-induced decreases in neurogenesis and depressive-like behavior in wild type mice, but not in mice with a genetic ablation of neurogenesis (Lehmann et al., 2013). This is particularly relevant knowing that LC $\omega 3$ PUFAs supplementation prevents CSDS-induced HPA axis dysregulation (Larrieu et al., 2014). However, whether the beneficial effect of $\omega 3$ PUFAs on glucocorticoids and mood is dependent on neurogenesis remains to be evaluated. Finally, an elegant study showed that EPA but not DHA increases neural stem cell proliferation reflected by an increased number of neurospheres bulk via CB1R activity (Dyall et al., 2016). The findings that $\omega 3$ PUFAs alone modulate neuronal arborization as well as adult neurogenesis highlight the role of PUFAs as a potent modulator of brain health. Taken together, these studies provide strong validity of nutritional $\omega 3$ PUFA-deficient diet as one of the many faces of stress that deeply affects GR-dependent HPA axis function and neuronal morphology plasticity in brain areas associated with emotional behavior.

Neuroinflammatory Pathways

Inflammation is a key mechanism in the pathophysiology of mood disorders, including major depression, post-partum depression and bipolar disorder (Dantzer et al., 2008; Capuron and Miller, 2011). Increased levels of inflammatory factors, such as proinflammatory cytokines and chemokines, are found in a subset of depressed patients and may contribute to their symptoms through a direct effect in the brain (Raison and Miller, 2011). The mechanisms underlying inflammation and depression have been thoroughly reviewed elsewhere (Capuron and Castanon, 2017). Enhanced peripheral inflammation has also been reported in PTSD (Gill et al., 2008; Newton et al., 2014; Passos et al., 2015; Lerman et al., 2016) and bipolar disorder (Goldstein et al., 2009; Fiedorowicz et al., 2015; Kalelioglu et al., 2015; Uyanik et al., 2015). Importantly, inflammation has been proposed to be key in stress vulnerability and the pathogenesis of major depression (Ménard et al., 2017).

Long chain $\omega 3$ PUFAs, DHA, and EPA and their derivatives, so-called SPMs, are well-known regulators of the inflammatory response (Serhan, 2014, 2017). More recently, DHA, EPA, and their derivatives have been shown to also regulate neuroinflammatory processes (Kavanagh et al., 2004; Li et al., 2015; Rey et al., 2016; Dong et al., 2017; Fourrier et al., 2017;

Shi et al., 2017; recently reviewed in Layé et al., 2018). Briefly, the expression of the pro-inflammatory cytokine TNF α , IL-6, and IL-1 β in the brain (triggered by peripheral or intracerebral administration of LPS, the Gram-negative bacteria endotoxin, amyloid beta administration or associated to aging) is decreased by DHA and EPA dietary supplementation (Labrousse et al., 2012; Orr et al., 2013; Dehkordi et al., 2015; Hopperton et al., 2016). Importantly, in regards to the protective effect of EPA in depression, a dietary supplementation with this fatty acid decreased TNF α expression in the hippocampus following IL-1 β central injection (Dong et al., 2017). *In vitro*, DHA, and EPA directly target microglia, the brain innate immune cell (De Smedt-Peyrusse et al., 2008; Antonietta Ajmone-Cat et al., 2012; Pettit et al., 2013; Chang et al., 2015; Fourrier et al., 2017), however, a direct effect of these fatty acids on microglia *in vivo* has not been studied yet. In a model of multiple sclerosis induced by cuprizone, DHA/EPA promote the shift of microglia polarization toward a repair non-inflammatory phenotype (Chen et al., 2014). We have found that the brain content of $\omega 3$ PUFA, either increased through the diet or by genetic means, influences microglia and the related neuroinflammatory response to LPS (Mingam et al., 2008; Madore et al., 2014; Delpech et al., 2015a,b; Diné et al., 2016). In rodent models of neuroinflammation triggered by the intracerebral administration of amyloid- β or cuprizone, brain DHA decreases the number of activated microglia, but not of astrocytes (Hopperton et al., 2016), and promotes an anti-inflammatory phenotype of microglia (Chen et al., 2014). An acute intravenous administration of DHA reduces LPS-induced cytokine production in the hippocampus (Fourrier et al., 2017), but no significant effect of intravenously administered DHA was shown on microglia activation (measured by the upregulation of translocator protein TSPO by Positron-emission tomography) in the injured spinal cord of rat (Tremoleda et al., 2016). DHA and EPA effect on neuroinflammatory pathways could be either direct or indirect. Indeed, LC-PUFAs are converted by COX, LOX, and CYP450 into SPMs, which display pro or anti-inflammatory activities (Chiang and Serhan, 2017), including in the brain (Orr et al., 2013; Rey et al., 2016; Layé et al., 2018). Eicosanoids, resolvins, protectin and maresin derived from DHA and EPA have anti-inflammatory and pro-resolving activities (Bazan, 2009; Serhan et al., 2011). On the opposite, SPMs derived from LA and AA (prostaglandins, leukotrienes or thromboxanes) are mostly pro-inflammatory (Calder, 2006). *In vitro*, DHA derivatives display anti-inflammatory activities in microglia (Marcheselli et al., 2003; Lukiw et al., 2005; Orr et al., 2013; Rey et al., 2016). Brain inflammation triggered by the administration of LPS activates $\omega 6$ PUFA derived-prostaglandins production in the brain (Rosenberger et al., 2004; Taha et al., 2017), together with the expression of the enzymes involved in the synthesis of SPMs (Rosenberger et al., 2004; Taha et al., 2017). However, recent work showed that amyloid- β brain infusion, which is proinflammatory, did not increase brain SPMs production (Hopperton et al., 2018). Importantly, PUFAs dietary intervention can modulate cellular levels of both PUFAs and SPMs, with dietary $\omega 6$ PUFAs supplementation increasing AA-derived and decreasing EPA-derived SPMs (Taha et al., 2016).

Conversely, LC ω 3 PUFAs supplementation increasing EPA and DHA-derived SPMs (Balvers et al., 2012; Hashimoto et al., 2015) have not been consistently demonstrated (Hopperton et al., 2018). These observations reinforce the need for more studies to link nutritional interventions and SPMs production in specific brain regions.

As previously described, clinical trials using DHA and/or EPA showed mixed results on depressive symptoms. However, based on meta-analysis, EPA has been suggested as a predictor of mood disorder treatment efficiency (Martins, 2009; Sublette et al., 2011; Mocking et al., 2016). Such a positive effect of EPA could be linked to its anti-inflammatory activity. Indeed, in depressed patients, high EPA supplementation is more effective in those with inflammation (Rapaport et al., 2016). In particular, patients with high IL-1 receptor antagonist and C-reactive protein blood levels have greater improvement in mood symptoms in response to EPA, but not DHA enriched dietary supplement. Additional studies with a higher number of patients are warranted to confirm this interesting first study. In addition, whether the higher efficiency of high EPA rather of DHA dietary supplementation is linked to its specific effect on inflammation through specific SPMs remains to be investigated.

CONCLUSION AND FUTURE DIRECTIONS

As indicated above, the summarized literature indicate that low ω 3 PUFAs intake may predispose certain individuals to depression and anxiety and that dietary supplementation with LC ω 3 PUFAs represents an interesting strategy for preventing or treating depression and anxiety disorders in certain individuals. However, several important issues remain to be determined. One of those is the discordant results regarding outcomes in clinical nutritional interventions to investigate the effectiveness of ω 3 PUFA supplementation on mood. The unmatched results seem to be partly due to the lack of standardization regarding important parameters such as (i) the inclusion criteria used,

(ii) the PUFA composition of the fish oil as well as (iii) the nutritional baseline status of subjects, and (iv) the methods of diagnosis used. We are now beginning to understand how PUFAs affect our brain through a direct sensing effect or an indirect one. This review highlights that ω 3 PUFAs, in particular DHA, act onto the brain through a direct effect on FFAR or other indirect mechanisms. We also discussed an indirect effect of ω 3 PUFAs on eCB and the HPA axis systems as relevant mechanisms by which dietary ω 3 PUFAs modulate mood-related behaviors. Although recent work suggest a causal relationship between nutritional ω 3 PUFAs deficiency and alterations of these two systems, major questions remain unanswered, such as how dietary ω 3 PUFA maintains HPA axis function to prevent emotional impairment. In this review, we highlighted how powerful dietary PUFAs are in the modulation of the eCB system, which is known to be intimately involved in the regulation of the HPA axis (McLaughlin et al., 2014). As to whether these two mechanisms are interconnected in the effects of ω 3 PUFA deficiency-induced depression is yet to be determined. In conclusion, this review reinforces the idea of the usefulness of the dietary ω 3 PUFAs as an interesting tool for the design and testing of new non-pharmacological strategies in the treatment of neuropsychiatric disorders such as mood-related disease.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

FUNDING

This work was supported by ANR, INRA, Fondation pour la Recherche Médicale (FRM), and Nouvelle Région Aquitaine. TL was the recipient of Société Française de Nutrition (SFN) and Labex BRAIN awards.

REFERENCES

- Adams, P. B., Lawson, S., Sanigorski, A., and Sinclair, A. J. (1996). Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 31, S157–S161. doi: 10.1007/BF02637069
- Aizawa, F., Nishinaka, T., Yamashita, T., Nakamoto, K., Kurihara, T., Hirasawa, A., et al. (2016). GPR40/FFAR1 deficient mice increase noradrenaline levels in the brain and exhibit abnormal behavior. *J. Pharmacol. Sci.* 132, 249–254. doi: 10.1016/j.jphs.2016.09.007
- Antonietta Ajmone-Cat, M., Lavinia Salvatori, M., De Simone, R., Mancini, M., Biagioni, S., Bernardo, A., et al. (2012). Docosahexaenoic acid modulates inflammatory and antineurogenic functions of activated microglial cells. *J. Neurosci. Res.* 90, 575–587. doi: 10.1002/jnr.22783
- Appleton, K. M., Peters, T. J., Hayward, R. C., Heatherley, S. V., McNaughton, S. A., Rogers, P. J., et al. (2007). Depressed mood and n-3 polyunsaturated fatty acid intake from fish: non-linear or confounded association? *Soc. Psychiatry Psychiatr. Epidemiol.* 42, 100–104. doi: 10.1007/s00127-006-0142-3
- Appleton, K. M., Rogers, P. J., and Ness, A. R. (2010). Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am. J. Clin. Nutr.* 91, 757–770. doi: 10.3945/ajcn.2009.28313
- Appleton, K. M., Sallis, H. M., Perry, R., Ness, A. R., and Churchill, R. (2015). Omega-3 fatty acids for depression in adults. *Cochrane Database Syst. Rev.* 5:CD004692. doi: 10.1002/14651858.CD004692.pub4
- Auguste, S., Fiset, A., Fernandes, M. F., Hryhorczuk, C., Poirout, V., Alquier, T., et al. (2016). Central agonism of gpr120 acutely inhibits food intake and food reward and chronically suppresses anxiety-like behavior in mice. *Int. J. Neuropsychopharmacol.* 19:pyw014. doi: 10.1093/ijnp/pyw014
- Balvers, M. G. J., Verhoeckx, K. C. M., Bijlsma, S., Rubingh, C. M., Meijerink, J., Wortelboer, H. M., et al. (2012). Fish oil and inflammatory status alter the n-3 to n-6 balance of the endocannabinoid and oxylipin metabolomes in mouse plasma and tissues. *Metabolomics* 8, 1130–1147. doi: 10.1007/s11306-012-0421-9
- Barberger-Gateau, P., Jutand, M. A., Letenneur, L., Larrieu, S., Tavernier, B., and Berr, C. (2005). Correlates of regular fish consumption in French elderly community dwellers: data from the three-City study. *Eur. J. Clin. Nutr.* 59, 817–825. doi: 10.1038/sj.ejcn.1602145
- Bazan, N. G. (2009). Neuroprotectin D1-mediated anti-inflammatory and survival signaling in stroke, retinal degenerations, and Alzheimer's disease. *J. Lipid Res.* 50(Suppl.), S400–S405. doi: 10.1194/jlr.R800068-JLR200

- Bazinet, R. P., and Layé, S. (2014). Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat. Rev. Neurosci.* 15, 771–785. doi: 10.1038/nrn3820
- Berger, A., Crozier, G., Bisogno, T., Cavaliere, P., Innis, S., and Di Marzo, V. (2001). Anandamide and diet: inclusion of dietary arachidonate and docosahexaenoate leads to increased brain levels of the corresponding N-acyl ethanolamines in piglets. *Proc. Natl. Acad. Sci. U.S.A.* 98, 6402–6406. doi: 10.1073/pnas.101119098
- Berton, O., McClung, C. A., Dileone, R. J., Krishnan, V., Renthal, W., Russo, S. J., et al. (2006). Essential role of BDNF in the mesolimbic dopamine pathway in social defeat stress. *Science* 311, 864–868. doi: 10.1126/science.1120972
- Bondi, C. O., Taha, A. Y., Tock, J. L., Totah, N. K. B., Cheon, Y., Torres, G. E., et al. (2014). Adolescent behavior and dopamine availability are uniquely sensitive to dietary omega-3 fatty acid deficiency. *Biol. Psychiatry* 75, 38–46. doi: 10.1016/j.biopsych.2013.06.007
- Bosch-Bouju, C., Larrieu, T., Linders, L., Manzoni, O. J., and Layé, S. (2016). Endocannabinoid-mediated plasticity in nucleus accumbens controls vulnerability to anxiety after social defeat stress. *Cell Rep.* 16, 1237–1242. doi: 10.1016/j.celrep.2016.06.082
- Bosch-bouju, C., and Layé, S. (2016). *Dietary Omega-6 / Omega-3 and Endocannabinoids: Implications for Brain Health and Diseases*. Osaka: InTech. doi: 10.5772/62498
- Bozzatello, P., Brignolo, E., De Grandi, E., and Bellino, S. (2016). Supplementation with omega-3 fatty acids in psychiatric disorders: a review of literature data. *J. Clin. Med.* 5:E67. doi: 10.3390/jcm5080067
- Bradbury, J. (2011). Docosahexaenoic acid (DHA): an ancient nutrient for the modern human brain. *Nutrients* 3, 529–554. doi: 10.3390/nu3050529
- Bradbury, J., Myers, S. P., Meyer, B., Brooks, L., Peake, J., Sinclair, A. J., et al. (2017). Chronic psychological stress was not ameliorated by omega-3 eicosapentaenoic acid (EPA). *Front. Pharmacol.* 8:551. doi: 10.3389/fphar.2017.00551
- Brunoni, A. R., Fraguas, R., and Fregni, F. (2009). Pharmacological and combined interventions for the acute depressive episode: focus on efficacy and tolerability. *Ther. Clin. Risk Manag.* 5, 897–910.
- Burdge, G. C., Finnegan, Y. E., Minihane, A. M., Williams, C. M., and Wootton, S. A. (2003). Effect of altered dietary n-3 fatty acid intake upon plasma lipid fatty acid composition, conversion of [13C]alpha-linolenic acid to longer-chain fatty acids and partitioning towards beta-oxidation in older men. *Br. J. Nutr.* 90, 311–321. doi: 10.1079/BJN2003901
- Burr, G. O., and Burr, M. M. (1929). A new deficiency disease produced by the rigid exclusion of fat from the diet. *J. Biol. Chem.* 82, 345–367.
- Calder, P. C. (2006). Polyunsaturated fatty acids and inflammation. *Prostaglandins Leukot. Essent. Fatty Acids* 75, 197–202. doi: 10.1016/j.plefa.2006.05.012
- Calderon, F., and Kim, H.-Y. (2004). Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *J. Neurochem.* 90, 979–988. doi: 10.1111/j.1471-4159.2004.02520.x
- Calderon, F., and Kim, H.-Y. (2007). Role of RXR in neurite outgrowth induced by docosahexaenoic acid. *Prostaglandins. Leukot. Essent. Fatty Acids* 77, 227–232. doi: 10.1016/j.plefa.2007.10.026
- Cao, D., Kevala, K., Kim, J., Moon, H.-S., Jun, S. B., Lovinger, D., et al. (2009). Docosahexaenoic acid promotes hippocampal neuronal development and synaptic function. *J. Neurochem.* 111, 510–521. doi: 10.1111/j.1471-4159.2009.06335.x
- Cao, D., Xue, R., Xu, J., and Liu, Z. (2005). Effects of docosahexaenoic acid on the survival and neurite outgrowth of rat cortical neurons in primary cultures. *J. Nutr. Biochem.* 16, 538–546. doi: 10.1016/j.jnutbio.2005.02.002
- Capuron, L., and Castanon, N. (2017). Role of inflammation in the development of neuropsychiatric symptom domains: evidence and mechanisms. *Curr. Top. Behav. Neurosci.* 31, 31–44. doi: 10.1007/7854_2016_14
- Capuron, L., and Miller, A. H. (2011). Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol. Ther.* 130, 226–238. doi: 10.1016/j.pharmthera.2011.01.014
- Carlezon, W. A., Mague, S. D., Parow, A. M., Stoll, A. L., Cohen, B. M., and Renshaw, P. F. (2005). Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. *Biol. Psychiatry* 57, 343–350. doi: 10.1016/j.biopsych.2004.11.038
- Carney, R. M., Steinmeyer, B. C., Freedland, K. E., Rubin, E. H., Rich, M. W., and Harris, W. S. (2016). Baseline blood levels of omega-3 and depression remission. *J. Clin. Psychiatry* 77, e138–e143. doi: 10.4088/JCP.14m09660
- Carrié, I., Clément, M., de Javel, D., Francès, H., and Bourre, J. M. (2000a). Phospholipid supplementation reverses behavioral and biochemical alterations induced by n-3 polyunsaturated fatty acid deficiency in mice. *J. Lipid Res.* 41, 473–480.
- Carrié, I., Clément, M., de Javel, D., Francès, H., and Bourre, J. M. (2000b). Specific phospholipid fatty acid composition of brain regions in mice. Effects of n-3 polyunsaturated fatty acid deficiency and phospholipid supplementation. *J. Lipid Res.* 41, 465–472.
- Casali, B. T., Corona, A. W., Mariani, M. M., Karlo, J. C., Ghosal, K., and Landreth, G. E. (2015). Omega-3 fatty acids augment the actions of nuclear receptor agonists in a mouse model of Alzheimer's Disease. *J. Neurosci.* 35, 9173–9181. doi: 10.1523/JNEUROSCI.1000-15.2015
- Chang, P. K.-Y., Khatchadourian, A., McKinney, R. A., and Maysinger, D. (2015). Docosahexaenoic acid (DHA): a modulator of microglia activity and dendritic spine morphology. *J. Neuroinflamm.* 12:34. doi: 10.1186/s12974-015-0244-245
- Chen, C. T., and Bazinet, R. P. (2015). β -oxidation and rapid metabolism, but not uptake regulate brain eicosapentaenoic acid levels. *Prostaglandins Leukot. Essent. Fatty Acids* 92, 33–40. doi: 10.1016/j.plefa.2014.05.007
- Chen, S., Zhang, H., Pu, H., Wang, G., Li, W., Leak, R. K., et al. (2014). n-3 PUFA supplementation benefits microglial responses to myelin pathology. *Sci. Rep.* 4:7458. doi: 10.1038/srep07458
- Chianese, R., Coccorello, R., Viggiano, A., Scafufo, M., Fiore, M., Coppola, G., et al. (2017). Impact of dietary fats on brain functions. *Curr. Neuropharmacol.* doi: 10.2174/1570159X15666171017102547 [Epub ahead of print].
- Chiang, N., and Serhan, C. N. (2017). Structural elucidation and physiologic functions of specialized pro-resolving mediators and their receptors. *Mol. Aspects Med.* 58, 114–129. doi: 10.1016/j.mam.2017.03.005
- Clouard, C., Souza, A. S., Gerrits, W. J., Hovenier, R., Lammers, A., and Bolhuis, J. E. (2015). Maternal fish oil supplementation affects the social behavior, brain fatty acid profile, and sickness response of piglets. *J. Nutr.* 145, 2176–2184. doi: 10.3945/jn.115.214650
- Colangelo, L. A., He, K., Whooley, M. A., Daviglius, M. L., and Liu, K. (2009). Higher dietary intake of long-chain omega-3 polyunsaturated fatty acids is inversely associated with depressive symptoms in women. *Nutrition* 25, 1011–1019. doi: 10.1016/j.nut.2008.12.008
- Coulombe, K., Kerdiles, O., Tremblay, C., Emond, V., Lebel, M., Boulianne, A.-S., et al. (2017). Impact of DHA intake in a mouse model of synucleinopathy. *Exp. Neurol.* 301, 39–49. doi: 10.1016/j.expneurol.2017.12.002
- Cribb, L., Murphy, J., Froud, A., Oliver, G., Bousman, C. A., Ng, C. H., et al. (2017). Erythrocyte polyunsaturated fatty acid composition is associated with depression and FADS genotype in Caucasians. *Nutr. Neurosci.* doi: 10.1080/1028415X.2017.1327685 [Epub ahead of print].
- Cunnane, S. C. (2003). Problems with essential fatty acids: time for a new paradigm? *Prog. Lipid Res.* 42, 544–568. doi: 10.1016/S0163-7827(03)00038-9
- Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., and Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9, 46–56. doi: 10.1038/nrn2297
- de la Presa Owens, S., and Innis, S. M. (1999). Docosahexaenoic and arachidonic acid prevent a decrease in dopaminergic and serotonergic neurotransmitters in frontal cortex caused by a linoleic and alpha-linolenic acid deficient diet in formula-fed piglets. *J. Nutr.* 129, 2088–2093. doi: 10.1093/jn/129.11.2088
- De Smedt-Peyrusse, V., Sargueil, F., Moranis, A., Harizi, H., Mongrand, S., and Layé, S. (2008). Docosahexaenoic acid prevents lipopolysaccharide-induced cytokine production in microglial cells by inhibiting lipopolysaccharide receptor presentation but not its membrane subdomain localization. *J. Neurochem.* 105, 296–307. doi: 10.1111/j.1471-4159.2007.05129.x
- de Vries, G.-J., Mocking, R., Lok, A., Assies, J., Schene, A., and Olf, M. (2016). Fatty acid concentrations in patients with posttraumatic stress disorder compared to healthy controls. *J. Affect. Disord.* 205, 351–359. doi: 10.1016/j.jad.2016.08.021
- Dehkordi, N. G., Noorbakhshnia, M., Ghaedi, K., Esmaili, A., and Dabaghi, M. (2015). Omega-3 fatty acids prevent LPS-induced passive avoidance learning and memory and CaMKII- α gene expression impairments in hippocampus of rat. *Pharmacol. Rep.* 67, 370–375. doi: 10.1016/j.pharep.2014.10.014
- Delarue, J., Matzinger, O., Binnert, C., Schneiter, P., Chioléro, R., and Tappy, L. (2003). Fish oil prevents the adrenal activation elicited by mental stress in healthy men. *Diabetes Metab.* 29, 289–295. doi: 10.1016/S1262-3636(07)70039-3

- Delion, S., Chalou, S., Héroult, J., Guilleoteau, D., Besnard, J. C., and Durand, G. (1994). Chronic dietary alpha-linolenic acid deficiency alters dopaminergic and serotonergic neurotransmission in rats. *J. Nutr.* 124, 2466–2476. doi: 10.1093/jn/124.12.2466
- Delpech, J.-C., Madore, C., Joffe, C., Aubert, A., Kang, J. X., Nadjar, A., et al. (2015a). 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, 525–536. doi: 10.1038/npp.2014.196
- Delpech, J.-C., Thomazeau, A., Madore, C., Bosch-Bouju, C., Larrieu, T., Lacabanne, C., et al. (2015b). Dietary n-3 PUFAs deficiency increases vulnerability to inflammation-induced spatial memory impairment. *Neuropsychopharmacology* 40, 2774–2787. doi: 10.1038/npp.2015.127
- DeMar, J. C., Ma, K., Bell, J. M., Igarashi, M., Greenstein, D., Rapoport, S. I., et al. (2006). One generation of n-3 polyunsaturated fatty acid deprivation increases depression and aggression test scores in rats. *J. Lipid Res.* 47, 172–180. doi: 10.1194/jlr.M500362-JLR200
- Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., et al. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 258, 1946–1949. doi: 10.1126/science.1470919
- Dinel, A. L., Rey, C., Baudry, C., Fressange-Mazda, C., Le Ruyet, P., Nadjar, A., et al. (2016). Enriched dairy fat matrix diet prevents early life lipopolysaccharide-induced spatial memory impairment at adulthood. *Prostaglandins Leukot. Essent. Fatty Acids* 113, 9–18. doi: 10.1016/j.plefa.2016.08.013
- Dong, Y., Xu, M., Kalueff, A. V., and Song, C. (2017). Dietary eicosapentaenoic acid normalizes hippocampal omega-3 and 6 polyunsaturated fatty acid profile, attenuates glial activation and regulates BDNF function in a rodent model of neuroinflammation induced by central interleukin-1 β administration. *Eur. J. Nutr.* 57, 1781–1791. doi: 10.1007/s00394-017-1462-7
- Dragano, N. R. V., Solon, C., Ramalho, A. F., de Moura, R. F., Razolli, D. S., Christiansen, E., et al. (2017). Polyunsaturated fatty acid receptors, GPR40 and GPR120, are expressed in the hypothalamus and control energy homeostasis and inflammation. *J. Neuroinflammation* 14:91. doi: 10.1186/s12974-017-0869-7
- Dyall, S. C., Mandhair, H. K., Fincham, R. E. A., Kerr, D. M., Roche, M., and Molina-Holgado, F. (2016). Distinctive effects of eicosapentaenoic and docosahexaenoic acids in regulating neural stem cell fate are mediated via endocannabinoid signalling pathways. *Neuropharmacology* 107, 387–395. doi: 10.1016/j.neuropharm.2016.03.055
- Edwards, R., Peet, M., Shay, J., and Horrobin, D. (1998a). Depletion of docosahexaenoic acid in red blood cell membranes of depressive patients. *Biochem. Soc. Trans.* 26:S142. doi: 10.1042/bst026s142
- Edwards, R., Peet, M., Shay, J., and Horrobin, D. (1998b). Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J. Affect. Disord.* 48, 149–155.
- Emken, E. A., Adlof, R. O., and Gulley, R. M. (1994). Dietary linoleic acid influences desaturation and acylation of deuterium-labeled linoleic and linolenic acids in young adult males. *Biochim. Biophys. Acta* 1213, 277–288. doi: 10.1016/0005-2760(94)00054-9
- Fallin, M. D., Lasseter, V. K., Wolyniec, P. S., McGrath, J. A., Nestadt, G., Valle, D., et al. (2004). Genomewide linkage scan for bipolar-disorder susceptibility loci among Ashkenazi Jewish families. *Am. J. Hum. Genet.* 75, 204–219. doi: 10.1086/422474
- Favrelière, S., Barrier, L., Durand, G., Chalou, S., and Tallineau, C. (1998). Chronic dietary n-3 polyunsaturated fatty acids deficiency affects the fatty acid composition of plasmalenyethanolamine and phosphatidylethanolamine differently in rat frontal cortex, striatum, and cerebellum. *Lipids* 33, 401–407. doi: 10.1007/s11745-998-0221-y
- Fedorova, I., and Salem, N. (2006). Omega-3 fatty acids and rodent behavior. *Prostaglandins Leukot. Essent. Fatty Acids* 75, 271–289. doi: 10.1016/j.plefa.2006.07.006
- Fernandes, P. G., and Cook, R. M. (2013). Reversal of fish stock decline in the Northeast Atlantic. *Curr. Biol.* 23, 1432–1437. doi: 10.1016/j.cub.2013.06.016
- Ferraz, A. C., Delattre, A. M., Almendra, R. G., Sonagli, M., Borges, C., Araujo, P., et al. (2011). Chronic n-3 fatty acids supplementation promotes beneficial effects on anxiety, cognitive and depressive-like behaviors in rats subjected to a restraint stress protocol. *Behav. Brain Res.* 219, 116–122. doi: 10.1016/j.bbr.2010.12.028
- Fiedorowicz, J. G., Prossin, A. R., Johnson, C. P., Christensen, G. E., Magnotta, V. A., and Wemmie, J. A. (2015). Peripheral inflammation during abnormal mood states in bipolar I disorder. *J. Affect. Disord.* 187, 172–178. doi: 10.1016/j.jad.2015.08.036
- Fourrier, C., Remus-Borel, J., Greenhalgh, A. D., Guichardant, M., Bernoud-Hubac, N., Lagarde, M., et al. (2017). Docosahexaenoic acid-containing choline phospholipid modulates LPS-induced neuroinflammation in vivo and in microglia in vitro. *J. Neuroinflammation* 14:170. doi: 10.1186/s12974-017-0939-x
- Francés, H., Monier, C., and Bourre, J. M. (1995). Effects of dietary alpha-linolenic acid deficiency on neuromuscular and cognitive functions in mice. *Life Sci.* 57, 1935–1947. doi: 10.1016/0024-3205(95)02180-Q
- Frasure-Smith, N., Lespérance, F., and Julien, P. (2004). Major depression is associated with lower omega-3 fatty acid levels in patients with recent acute coronary syndromes. *Biol. Psychiatry* 55, 891–896. doi: 10.1016/j.biopsych.2004.01.021
- Freeman, M. P., Davis, M., Sinha, P., Wisner, K. L., Hibbeln, J. R., and Gelenberg, A. J. (2008). Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *J. Affect. Disord.* 110, 142–148. doi: 10.1016/j.jad.2007.12.228
- Freund, T. F., Katona, I., and Piomelli, D. (2003). Role of endogenous cannabinoids in synaptic signaling. *Physiol. Rev.* 83, 1017–1066. doi: 10.1152/physrev.00004.2003
- Furuya, H., Watanabe, T., Sugioka, Y., Inagaki, Y., and Okazaki, I. (2002). Effect of ethanol and docosahexaenoic acid on nerve growth factor-induced neurite formation and neuron specific growth-associated protein gene expression in PC12 cells. *Nihon Arukoru Yakubutsu Igakkai Zasshi* 37, 513–522.
- Ganaça, L., Galfalvy, H. C., Oquendo, M. A., Hezghia, A., Cooper, T. B., Mann, J. J., et al. (2017). Lipid correlates of antidepressant response to omega-3 polyunsaturated fatty acid supplementation: a pilot study. *Prostaglandins Leukot. Essent. Fat. Acids* 119, 38–44. doi: 10.1016/j.plefa.2017.03.004
- Gertsik, L., Poland, R. E., Bresee, C., and Rapoport, M. H. (2012). Omega-3 fatty acid augmentation of citalopram treatment for patients with major depressive disorder. *J. Clin. Psychopharmacol.* 32, 61–64. doi: 10.1097/JCP.0b013e31823f3b5f
- Gibson, R. A., and Makrides, M. (2001). Long-chain polyunsaturated fatty acids in breast milk: are they essential? *Adv. Exp. Med. Biol.* 501, 375–383. doi: 10.1007/978-1-4615-1371-1_46
- Gibson, R. A., Muhlhauser, B., and Makrides, M. (2011). Conversion of linoleic acid and alpha-linolenic acid to long-chain polyunsaturated fatty acids (LCPUFAs), with a focus on pregnancy, lactation and the first 2 years of life. *Matern. Child Nutr.* 7(Suppl. 2), 17–26. doi: 10.1111/j.1740-8709.2011.00299.x
- Gill, J., Vythilingam, M., and Page, G. G. (2008). Low cortisol, high DHEA, and high levels of stimulated TNF-alpha, and IL-6 in women with PTSD. *J. Trauma. Stress* 21, 530–539. doi: 10.1002/jts.20372
- Golden, S. A., Covington, H. E., Berton, O., and Russo, S. J. (2011). A standardized protocol for repeated social defeat stress in mice. *Nat. Protoc.* 6, 1183–1191. doi: 10.1038/nprot.2011.361
- Goldstein, B. I., Kemp, D. E., Soczynska, J. K., and McIntyre, R. S. (2009). Inflammation and the phenomenology, pathophysiology, comorbidity, and treatment of bipolar disorder: a systematic review of the literature. *J. Clin. Psychiatry* 70, 1078–1090. doi: 10.4088/JCP.08r04505
- Goyens, P. L. L., Spilker, M. E., Zock, P. L., Katan, M. B., and Mensink, R. P. (2006). Conversion of alpha-linolenic acid in humans is influenced by the absolute amounts of alpha-linolenic acid and linoleic acid in the diet and not by their ratio. *Am. J. Clin. Nutr.* 84, 44–53. doi: 10.1093/ajcn/84.1.44
- Green, P., Hermesh, H., Monselise, A., Marom, S., Presburger, G., and Weizman, A. (2006). Red cell membrane omega-3 fatty acids are decreased in nondepressed patients with social anxiety disorder. *Eur. Neuropsychopharmacol.* 16, 107–113. doi: 10.1016/j.euroneuro.2005.07.005
- Grosso, G., Pajak, A., Marventano, S., Castellano, S., Galvano, F., Bucolo, C., et al. (2014). Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One* 9:e96905. doi: 10.1371/journal.pone.0096905
- Hallahan, B., Ryan, T., Hibbeln, J. R., Murray, I. T., Glynn, S., Ramsden, C. E., et al. (2016). Efficacy of omega-3 highly unsaturated fatty acids in the treatment of depression. *Br. J. Psychiatry* 209, 192–201. doi: 10.1192/bjp.bp.114.160242

- Hashimoto, M., Katakura, M., Tanabe, Y., Al Mamun, A., Inoue, T., Hossain, S., et al. (2015). n-3 fatty acids effectively improve the reference memory-related learning ability associated with increased brain docosahexaenoic acid-derived docosanoids in aged rats. *Biochim. Biophys. Acta* 1851, 203–209. doi: 10.1016/j.bbali.2014.10.009
- He, C., Qu, X., Cui, L., Wang, J., and Kang, J. X. (2009). Improved spatial learning performance of fat-1 mice is associated with enhanced neurogenesis and neurogenesis by docosahexaenoic acid. *Proc. Natl. Acad. Sci. U.S.A.* 106, 11370–11375. doi: 10.1073/pnas.0904835106
- Hibbeln, J. R. (1998). Fish consumption and major depression. *Lancet* 351:1213. doi: 10.1016/S0140-6736(05)79168-6
- Hibbeln, J. R. (2002). Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J. Affect. Disord.* 69, 15–29. doi: 10.1016/S0165-0327(01)00374-3
- Hibbeln, J. R., Bissette, G., Umhau, J. C., and George, D. T. (2004). Omega-3 status and cerebrospinal fluid corticotrophin releasing hormone in perpetrators of domestic violence. *Biol. Psychiatry* 56, 895–897. doi: 10.1016/j.biopsych.2004.08.021
- Hibbeln, J. R., and Salem, N. (1995). Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am. J. Clin. Nutr.* 62, 1–9. doi: 10.1093/ajcn/62.1.1
- Hill, M. N., and Lee, F. S. (2016). Endocannabinoids and stress resilience: is deficiency sufficient to promote vulnerability? *Biol. Psychiatry* 79, 792–793. doi: 10.1016/j.biopsych.2016.03.2099
- Hirasawa, A., Tsumaya, K., Awaji, T., Katsuma, S., Adachi, T., Yamada, M., et al. (2005). Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat. Med.* 11, 90–94. doi: 10.1038/nm1168
- Hopperton, K. E., Trépanier, M.-O., Giuliano, V., and 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. *J. Neuroinflammation* 13:257. doi: 10.1186/s12974-016-0721-5
- Hopperton, K. E., Trépanier, M.-O., James, N. C. E., Chouinard-Watkins, R., and Bazinet, R. P. (2018). Fish oil feeding attenuates neuroinflammatory gene expression without concomitant changes in brain eicosanoids and docosanoids in a mouse model of Alzheimer's disease. *Brain Behav. Immun.* 69, 74–90. doi: 10.1016/j.bbi.2017.11.002
- Howlett, A. C. (2002). The cannabinoid receptors. *Prostaglandins Other Lipid Mediat.* 68–69, 619–631. doi: 10.1016/S0090-6980(02)00060-6
- Howlett, A. C., and Fleming, R. M. (1984). Cannabinoid inhibition of adenylate cyclase. Pharmacology of the response in neuroblastoma cell membranes. *Mol. Pharmacol.* 26, 532–538.
- Huang, S.-Y., Yang, H.-T., Chiu, C.-C., Pariente, C. M., and Su, K.-P. (2008). Omega-3 fatty acids on the forced-swimming test. *J. Psychiatr. Res.* 42, 58–63. doi: 10.1016/j.jpsychires.2006.09.004
- Ikemoto, A., Kobayashi, T., Watanabe, S., and Okuyama, H. (1997). Membrane fatty acid modifications of PC12 cells by arachidonate or docosahexaenoate affect neurite outgrowth but not norepinephrine release. *Neurochem. Res.* 22, 671–678. doi: 10.1023/A:1027393724676
- Innis, S. M. (2007). Dietary (n-3) fatty acids and brain development. *J. Nutr.* 137, 855–859. doi: 10.1093/jn/137.4.855
- Itoh, Y., Kawamata, Y., Harada, M., Kobayashi, M., Fujii, R., Fukusumi, S., et al. (2003). Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* 422, 173–176. doi: 10.1038/nature01478
- Jazayeri, S., Tehrani-Doost, M., Keshavarz, S. A., Hosseini, M., Djazayeri, A., Amini, H., et al. (2008). Comparison of therapeutic effects of omega-3 fatty acid eicosapentaenoic acid and fluoxetine, separately and in combination, in major depressive disorder. *Aust. N. Z. J. Psychiatry* 42, 192–198. doi: 10.1080/00048670701827275
- Jensen, H. A. R., Harsløf, L. B. S., Nielsen, M. S., Christensen, L. B., Ritz, C., Michaelsen, K. F., et al. (2014). FADS single-nucleotide polymorphisms are associated with behavioral outcomes in children, and the effect varies between sexes and is dependent on PPAR genotype. *Am. J. Clin. Nutr.* 100, 826–832. doi: 10.3945/ajcn.114.087882
- Joffre, C., Nadjar, A., Lebbadi, M., Calon, F., and Laye, S. (2014). n-3 LCPUFA improves cognition: the young, the old and the sick. *Prostaglandins Leukot. Essent. Fatty Acids* 91, 1–20. doi: 10.1016/j.plefa.2014.05.001
- Kalelioglu, T., Akkus, M., Karamustafalioğlu, N., Genc, A., Genc, E. S., Cansiz, A., et al. (2015). Neutrophil-lymphocyte and platelet-lymphocyte ratios as inflammation markers for bipolar disorder. *Psychiatry Res.* 228, 925–927. doi: 10.1016/j.psychres.2015.05.110
- Kamphuis, M. H., Geerlings, M. I., Tijhuis, M. A. R., Kalmijn, S., Grobbee, D. E., and Kromhout, D. (2006). Depression and cardiovascular mortality: a role for n-3 fatty acids? *Am. J. Clin. Nutr.* 84, 1513–1517. doi: 10.1093/ajcn/84.6.1513
- Kang, J. X., Wang, J., Wu, L., and Kang, Z. B. (2004). Transgenic mice: fat-1 mice convert n-6 to n-3 fatty acids. *Nature* 427:504. doi: 10.1038/427504a
- Kavanagh, T., Lonergan, P. E., and Lynch, M. A. (2004). Eicosapentaenoic acid and gamma-linolenic acid increase hippocampal concentrations of IL-4 and IL-10 and abrogate lipopolysaccharide-induced inhibition of long-term potentiation. *Prostaglandins Leukot. Essent. Fatty Acids* 70, 391–397. doi: 10.1016/j.plefa.2003.12.014
- Kiecolt-Glaser, J. K., Belury, M. A., Andridge, R., Malarkey, W. B., and Glaser, R. (2011). Omega-3 supplementation lowers inflammation and anxiety in medical students: a randomized controlled trial. *Brain Behav. Immun.* 25, 1725–1734. doi: 10.1016/j.bbi.2011.07.229
- Koletzko, B., Lattka, E., Zeilinger, S., Illig, T., and Steer, C. (2011). Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. *Am. J. Clin. Nutr.* 93, 211–219. doi: 10.3945/ajcn.110.006189
- Kraguljac, N. V., Montori, V. M., Pavuluri, M., Chai, H. S., Wilson, B. S., and Unal, S. S. (2009). Efficacy of omega-3 fatty acids in mood disorders - a systematic review and metaanalysis. *Psychopharmacol. Bull.* 42, 39–54.
- Krishnan, V., Han, M.-H., Graham, D. L., Berton, O., Renthal, W., Russo, S. J., et al. (2007). Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* 131, 391–404. doi: 10.1016/j.cell.2007.09.018
- Krzyzosiak, A., Szyszka-Niagolov, M., Wietrzyk, M., Gobaille, S., Muramatsu, S., and Krezel, W. (2010). Retinoid x receptor gamma control of affective behaviors involves dopaminergic signaling in mice. *Neuron* 66, 908–920. doi: 10.1016/j.neuron.2010.05.004
- 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:e36861. doi: 10.1371/journal.pone.0036861
- Lacombe, R. J. S., Chouinard-Watkins, R., and Bazinet, R. P. (2018). Brain docosahexaenoic acid uptake and metabolism. *Mol. Aspects. Med.* doi: 10.1016/j.mam.2017.12.004 [Epub ahead of print].
- Lafourcade, M., Larrieu, T., Mato, S., Duffaud, A., Sepers, M., Matias, I., et al. (2011). Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. *Nat. Neurosci.* 14, 345–350. doi: 10.1038/nn.2736
- Larrieu, T., Cherix, A., Duque, A., Rodrigues, J., Lei, H., Gruetter, R., et al. (2017). Hierarchical status predicts behavioral vulnerability and nucleus accumbens metabolic profile following chronic social defeat stress. *Curr. Biol.* 27, 2202.e4–2210.e4. doi: 10.1016/j.cub.2017.06.027
- Larrieu, T., Hilal, M. L., Desmedt-peyrusse, V., Sans, N., and Layé, S. (2015). Nutritional omega-3 deficiency alters glucocorticoid receptor-signaling pathway and neuronal morphology in regionally distinct brain structures associated with emotional deficits. *Neural Plast.* 2016:8574830. doi: 10.1155/2016/8574830
- Larrieu, T., Hilal, M. L., Fourrier, C., Desmedt-Peyrusse, V., Sans, N., Capuron, L., et al. (2014). Nutritional omega-3 modulates neuronal morphology in the prefrontal cortex along with depression-related behaviour through corticosterone secretion. *Transl. Psychiatry* 4:e437. doi: 10.1038/tp.2014.77
- Larrieu, T., Madore, C., Joffre, C., and Layé, S. (2012). Nutritional n-3 polyunsaturated fatty acids deficiency alters cannabinoid receptor signaling pathway in the brain and associated anxiety-like behavior in mice. *J. Physiol. Biochem.* 68, 671–681. doi: 10.1007/s13105-012-0179-6
- Layé, S., Nadjar, A., Joffre, C., and Bazinet, R. P. (2018). Anti-inflammatory effects of omega-3 fatty acids in the brain: physiological mechanisms and relevance to pharmacology. *Pharmacol. Rev.* 70, 12–38. doi: 10.1124/pr.117.014092
- Lehmann, M. L., Brachman, R. A., Martinowich, K., Schloesser, R. J., and Herkenham, M. (2013). Glucocorticoids orchestrate divergent effects on mood through adult neurogenesis. *J. Neurosci.* 33, 2961–2972. doi: 10.1523/JNEUROSCI.3878-12.2013
- Lemaitre, R. N., Siscovick, D. S., Berry, E. M., Kark, J. D., and Friedlander, Y. (2008). Familial aggregation of red blood cell membrane fatty acid composition: the

- kibbutzim family study. *Metabolism* 57, 662–668. doi: 10.1016/j.metabol.2007.12.011
- Lengqvist, J., Mata De Urquiza, A., Bergman, A.-C., Willson, T. M., Sjövall, J., Perlmann, T., et al. (2004). Polyunsaturated fatty acids including docosahexaenoic and arachidonic acid bind to the retinoid X receptor alpha ligand-binding domain. *Mol. Cell. Proteomics* 3, 692–703. doi: 10.1074/mcp.M400003-MCP200
- Lerman, I., Davis, B. A., Bertram, T. M., Proudfoot, J., Hauger, R. L., Coe, C. L., et al. (2016). Posttraumatic stress disorder influences the nociceptive and intrathecal cytokine response to a painful stimulus in combat veterans. *Psychoneuroendocrinology* 73, 99–108. doi: 10.1016/j.psyneuen.2016.07.020
- Létondor, A., Buaud, B., Vaysse, C., Richard, E., Layé, S., Pallet, V., et al. (2016). EPA/DHA and vitamin A supplementation improves spatial memory and alleviates the age-related decrease in hippocampal rxry and kinase expression in rats. *Front. Aging Neurosci.* 8:103. doi: 10.3389/fnagi.2016.00103
- Levant, B., Ozias, M. K., Davis, P. F., Winter, M., Russell, K. L., Carlson, S. E., et al. (2008). Decreased brain docosahexaenoic acid content produces neurobiological effects associated with depression: interactions with reproductive status in female rats. *Psychoneuroendocrinology* 33, 1279–1292. doi: 10.1016/j.psyneuen.2008.06.012
- Li, Z., Ren, W., Han, X., Liu, X., Wang, G., Zhang, M., et al. (2015). ω -3 polyunsaturated fatty acids suppress lipoprotein-associated phospholipase A2 expression in macrophages and animal models. *Mol. Nutr. Food Res.* 59, 1771–1779. doi: 10.1002/mnfr.201500022
- Lin, P.-Y., Huang, S.-Y., and Su, K.-P. (2010). A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol. Psychiatry* 68, 140–147. doi: 10.1016/j.biopsych.2010.03.018
- Liu, J. J., Galfalvy, H. C., Cooper, T. B., Oquendo, M. A., Grunebaum, M. F., Mann, J. J., et al. (2013). Omega-3 polyunsaturated fatty acid (PUFA) status in major depressive disorder with comorbid anxiety disorders. *J. Clin. Psychiatry* 74, 732–738. doi: 10.4088/JCP.12m07970
- Lukiw, W. J., Cui, J.-G., Marcheselli, V. L., Bodker, M., Botkjaer, A., Gotlinger, K., et al. (2005). A role for docosahexaenoic acid-derived neuroprotectin D1 in neural cell survival and Alzheimer disease. *J. Clin. Invest.* 115, 2774–2783. doi: 10.1172/JCI25420
- Ma, D., Lu, L., Boneva, N. B., Warashina, S., Kaplamadzhiev, D. B., Mori, Y., et al. (2008). Expression of free fatty acid receptor GPR40 in the neurogenic niche of adult monkey hippocampus. *Hippocampus* 18, 326–333. doi: 10.1002/hipo.20393
- Ma, D., Tao, B., Warashina, S., Kotani, S., Lu, L., Kaplamadzhiev, D. B., et al. (2007). Expression of free fatty acid receptor GPR40 in the central nervous system of adult monkeys. *Neurosci. Res.* 58, 394–401. doi: 10.1016/j.neures.2007.05.001
- Mackie, K. (2008). Signaling via CNS cannabinoid receptors. *Mol. Cell. Endocrinol.* 286, S60–S65. doi: 10.1016/j.mce.2008.01.022
- Madore, C., Nadjar, A., Delpuch, 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 Behav. Immun.* 41, 22–31. doi: 10.1016/j.bbi.2014.03.021
- Maes, M., Smith, R., Christophe, A., Cosyns, P., Desnyder, R., and Meltzer, H. (1996). Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J. Affect. Disord.* 38, 35–46. doi: 10.1016/0165-0327(95)00092-5
- Makrides, M., and Gibson, R. A. (2000). Long-chain polyunsaturated fatty acid requirements during pregnancy and lactation. *Am. J. Clin. Nutr.* 71, 307S–311S. doi: 10.1093/ajcn/71.1.307S
- Manduca, A., Bara, A., Larrieu, T., Lassalle, O., Joffre, C., Layé, S., et al. (2017). Amplification of mGlu 5-endocannabinoid signaling rescues behavioral and synaptic deficits in a mouse model of adolescent and adult dietary polyunsaturated fatty acid imbalance. *J. Neurosci.* 37, 6851–6868. doi: 10.1523/JNEUROSCI.3516-16.2017
- Marangell, L. B., Martinez, J. M., Zboyan, H. A., Kertz, B., Kim, H. F. S., and Puryear, L. J. (2003). A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am. J. Psychiatry* 160, 996–998. doi: 10.1176/appi.ajp.160.5.996
- Marcheselli, V. L., Hong, S., Lukiw, W. J., Tian, X. H., Gronert, K., Musto, A., et al. (2003). Novel docosanoids inhibit brain ischemia-reperfusion-mediated leukocyte infiltration and pro-inflammatory gene expression. *J. Biol. Chem.* 278, 43807–43817. doi: 10.1074/jbc.M305841200
- Markhus, M. W., Skotheim, S., Graff, I. E., Froyland, L., Braarud, H. C., Stormark, K. M., et al. (2013). Low omega-3 index in pregnancy is a possible biological risk factor for postpartum depression. *PLoS One* 8:e67617. doi: 10.1371/journal.pone.0067617
- Martins, J. G. (2009). EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J. Am. Coll. Nutr.* 28, 525–542. doi: 10.1080/07315724.2009.10719785
- Martins, J. G., Bentsen, H., and Puri, B. K. (2012). Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: a critique of Bloch and Hannestad and updated meta-analysis. *Mol. Psychiatry* 17, 1144–1149. doi: 10.1038/mp.2012.25
- Mathias, R. A., Pani, V., and Chilton, F. H. (2014). Genetic variants in the fads gene: implications for dietary recommendations for Fatty Acid intake. *Curr. Nutr. Rep.* 3, 139–148. doi: 10.1007/s13668-014-0079-1
- Matsuoka, Y., Nishi, D., Hamazaki, K., Yonemoto, N., Matsumura, K., Noguchi, H., et al. (2015). Docosahexaenoic acid for selective prevention of posttraumatic stress disorder among severely injured patients: a randomized, placebo-controlled trial. *J. Clin. Psychiatry* 76, e1015–e1022. doi: 10.4088/JCP.14m09260
- Matsuoka, Y. J., Hamazaki, K., Nishi, D., and Hamazaki, T. (2016). Change in blood levels of eicosapentaenoic acid and posttraumatic stress symptom: a secondary analysis of data from a placebo-controlled trial of omega3 supplements. *J. Affect. Disord.* 205, 289–291. doi: 10.1016/j.jad.2016.08.005
- McLaughlin, R. J., Hill, M. N., and Gorzalka, B. B. (2014). A critical role for prefrontocortical endocannabinoid signaling in the regulation of stress and emotional behavior. *Neurosci. Biobehav. Rev.* 42, 116–131. doi: 10.1016/j.neubiorev.2014.02.006
- McNamara, R. K., and Carlson, S. E. (2006). Role of omega-3 fatty acids in brain development and function: potential implications for the pathogenesis and prevention of psychopathology. *Prostaglandins Leukot. Essent. Fatty Acids* 75, 329–349. doi: 10.1016/j.plefa.2006.07.010
- McNamara, R. K., Hahn, C.-G., Jandacek, R., Rider, T., Tso, P., Stanford, K. E., et al. (2007). Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biol. Psychiatry* 62, 17–24. doi: 10.1016/j.biopsych.2006.08.026
- McNamara, R. K., Jandacek, R., Rider, T., Tso, P., Stanford, K. E., Hahn, C.-G., et al. (2008a). Deficits in docosahexaenoic acid and associated elevations in the metabolism of arachidonic acid and saturated fatty acids in the postmortem orbitofrontal cortex of patients with bipolar disorder. *Psychiatry Res.* 160, 285–299. doi: 10.1016/j.psychres.2007.08.021
- McNamara, R. K., Liu, Y., Jandacek, R., Rider, T., and Tso, P. (2008b). The aging human orbitofrontal cortex: decreasing polyunsaturated fatty acid composition and associated increases in lipogenic gene expression and stearoyl-CoA desaturase activity. *Prostaglandins Leukot. Essent. Fatty Acids* 78, 293–304. doi: 10.1016/j.plefa.2008.04.001
- McNamara, R. K., Jandacek, R., Tso, P., Dwivedi, Y., Ren, X., and Pandey, G. N. (2013). Lower docosahexaenoic acid concentrations in the postmortem prefrontal cortex of adult depressed suicide victims compared with controls without cardiovascular disease. *J. Psychiatr. Res.* 47, 1187–1191. doi: 10.1016/j.jpsychires.2013.05.007
- McNamara, R. K., and Liu, Y. (2011). Reduced expression of fatty acid biosynthesis genes in the prefrontal cortex of patients with major depressive disorder. *J. Affect. Disord.* 129, 359–363. doi: 10.1016/j.jad.2010.08.021
- McNamara, R. K., Strimpfel, J., Jandacek, R., Rider, T., Tso, P., Welge, J. A., et al. (2014). Detection and treatment of long-chain omega-3 fatty acid deficiency in adolescents with SSRI-Resistant Major Depressive Disorder. *Pharmanutrition* 2, 38–46. doi: 10.1016/j.phanu.2014.02.002
- Ménard, C., Pfau, M. L., Hodes, G. E., and Russo, S. J. (2017). Immune and neuroendocrine mechanisms of stress vulnerability and resilience. *Neuropsychopharmacology* 42, 62–80. doi: 10.1038/npp.2016.90
- Meneses, J. A., de Trugilho, L. A., Lima, S. A., Freitas, A. C. F., Melo, H. S., Ferreira, M. R., et al. (2017). The influence of a diet based on flaxseed, an omega-3 source, during different developmental periods, on the blood pressure of rats submitted to stress. *J. Matern. Fetal. Neonatal Med.* doi: 10.1080/14767058.2017.1407309 [Epub ahead of print].

- Messamore, E., and McNamara, R. K. (2016). Detection and treatment of omega-3 fatty acid deficiency in psychiatric practice: rationale and implementation. *Lipids Health Dis.* 15:25. doi: 10.1186/s12944-016-0196-5
- Mingam, R., Moranis, A., Bluthé, R.-M., De Smedt-Peyrusse, V., Kelley, K. W., Guesnet, P., et al. (2008). Uncoupling of interleukin-6 from its signalling pathway by dietary n-3-polyunsaturated fatty acid deprivation alters sickness behaviour in mice. *Eur. J. Neurosci.* 28, 1877–1886. doi: 10.1111/j.1460-9568.2008.06470.x
- Mischoulon, D., Nierenberg, A. A., Schettler, P. J., Kinkead, B. L., Fehling, K., Martinson, M. A., et al. (2015). A double-blind, randomized controlled clinical trial comparing eicosapentaenoic acid versus docosahexaenoic acid for depression. *J. Clin. Psychiatry* 76, 54–61. doi: 10.4088/JCP.14m08986
- Mocking, R. J. T., Harmsen, I., Assies, J., Koeter, M. W. J., Ruhé, H. G., and Schene, A. H. (2016). Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Transl. Psychiatry* 6:e756. doi: 10.1038/tp.2016.29
- Mocking, R. J. T., Ruhé, H. G., Assies, J., Lok, A., Koeter, M. W. J., Visser, I., et al. (2013). Relationship between the hypothalamic-pituitary-adrenal-axis and fatty acid metabolism in recurrent depression. *Psychoneuroendocrinology* 38, 1607–1617. doi: 10.1016/j.psyneuen.2013.01.013
- Morena, M., Patel, S., Bains, J. S., and Hill, M. N. (2015). Neurobiological interactions between stress and the endocannabinoid system. *Neuropsychopharmacology* 41, 80–102. doi: 10.1038/npp.2015.166
- Morgese, M. G., Tucci, P., Mhillaj, E., and Bove, M. (2016). Lifelong nutritional Omega-3 deficiency evokes depressive-like state through soluble beta amyloid. *Mol. Neurobiol.* 54, 2079–2089. doi: 10.1007/s12035-016-9809-2
- Müller, C. P., Reichel, M., Mühle, C., Rhein, C., Gulbins, E., and Kornhuber, J. (2015). Brain membrane lipids in major depression and anxiety disorders. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* 1851, 1052–1065. doi: 10.1016/j.bbalip.2014.12.014
- Nakamoto, K., Aizawa, F., Nishinaka, T., and Tokuyama, S. (2015). Regulation of prohormone convertase 2 protein expression via GPR40/FFA1 in the hypothalamus. *Eur. J. Pharmacol.* 762, 459–463. doi: 10.1016/j.ejphar.2015.06.013
- Naliwaiko, K., Araújo, R. L. E., da Fonseca, R. V., Castilho, J. C., Andreatini, R., Bellissimo, I., et al. (2004). Effects of fish oil on the central nervous system: a new potential antidepressant? *Nutr. Neurosci.* 7, 91–99. doi: 10.1080/10284150410001704525
- Nascimento, L. F. R., Souza, G. F. P., Morari, J., Barbosa, G. O., Solon, C., Moura, R. F., et al. (2016). n-3 Fatty Acids induce neurogenesis of predominantly pomc-expressing cells in the hypothalamus. *Diabetes Metab. Res. Rev.* 65, 673–686. doi: 10.2337/db15-0008
- Nemets, B., Stahl, Z., and Belmaker, R. H. (2002). Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* 159, 477–479. doi: 10.1176/appi.ajp.159.3.477
- Nemets, H., Nemets, B., Apter, A., Bracha, Z., and Belmaker, R. H. (2006). Omega-3 treatment of childhood depression: a controlled, double-blind pilot study. *Am. J. Psychiatry* 163, 1098–1100. doi: 10.1176/ajp.2006.163.6.1098
- Newton, T. L., Fernandez-Botran, R., Miller, J. J., and Burns, V. E. (2014). Interleukin-6 and soluble interleukin-6 receptor levels in posttraumatic stress disorder: associations with lifetime diagnostic status and psychological context. *Biol. Psychol.* 99, 150–159. doi: 10.1016/j.biopsycho.2014.03.009
- Nieminen, L. R. G., Makino, K. K., Mehta, N., Virkkunen, M., Kim, H. Y., and Hibbeln, J. R. (2006). Relationship between omega-3 fatty acids and plasma neuroactive steroids in alcoholism, depression and controls. *Prostaglandins Leukot. Essent. Fatty Acids* 75, 309–314. doi: 10.1016/j.plefa.2006.07.012
- Nishinaka, T., Yamashita, T., Nakamoto, K., Kasuya, F., and Tokuyama, S. (2014). Involvement of the long-chain fatty acid receptor GPR40 in depression-related behavior. *J. Pharmacol. Sci.* 125, 112–115. doi: 10.1254/jphs.140015C
- Orr, S. K., Palumbo, S., Bosetti, F., Mount, H. T., Kang, J. X., Greenwood, C. E., et al. (2013). Unesterified docosahexaenoic acid is protective in neuroinflammation. *J. Neurochem.* 127, 378–393. doi: 10.1111/jnc.12392
- Otoki, Y., Hennebelle, M., Levitt, A. J., Nakagawa, K., Swardfager, W., and Taha, A. Y. (2017). Plasma phosphatidylethanolamine and triacylglycerol fatty acid concentrations are altered in major depressive disorder patients with seasonal pattern. *Lipids* 52, 559–571. doi: 10.1007/s11745-017-4254-1
- Pan, J. P., Zhang, H. Q., Wei-Wang, Guo, Y. F., Na-Xiao, Cao, X. H., et al. (2011). Some subtypes of endocannabinoid/endovanilloid receptors mediate docosahexaenoic acid-induced enhanced spatial memory in rats. *Brain Res.* 1412, 18–27. doi: 10.1016/j.brainres.2011.07.015
- Park, H. G., Park, W. J., Kothapalli, K. S. D., and Brenna, J. T. (2015). The fatty acid desaturase 2 (FADS2) gene product catalyzes Δ4 desaturation to yield n-3 docosahexaenoic acid and n-6 docosapentaenoic acid in human cells. *FASEB J.* 29, 3911–3919. doi: 10.1096/fj.15-271783
- Parker, G., Hegarty, B., Granville-Smith, I., Ho, J., Paterson, A., Gokiert, A., et al. (2015). Is essential fatty acid status in late pregnancy predictive of post-natal depression? *Acta Psychiatr. Scand.* 131, 148–156. doi: 10.1111/acps.12321
- Parletta, N., Zarnowiecki, D., Cho, J., Wilson, A., Procter, N., Gordon, A., et al. (2016). People with schizophrenia and depression have a low omega-3 index. *Prostaglandins Leukot. Essent. Fatty Acids* 110, 42–47. doi: 10.1016/j.plefa.2016.05.007
- Passos, I. C., Vasconcelos-Moreno, M. P., Costa, L. G., Kunz, M., Brietzke, E., Quevedo, J., et al. (2015). Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry* 2, 1002–1012. doi: 10.1016/S2215-0366(15)00309-0
- Peet, M., and Horrobin, D. F. (2002). A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch. Gen. Psychiatry* 59, 913–919. doi: 10.1001/archpsyc.59.10.913
- Pettit, L. K., Varsanyi, C., Tados, J., and Vassiliou, E. (2013). Modulating the inflammatory properties of activated microglia with docosahexaenoic acid and aspirin. *Lipids Health Dis.* 12:16. doi: 10.1186/1476-511X-12-16
- Piomelli, D., and Sasso, O. (2014). Peripheral gating of pain signals by endogenous lipid mediators. *Nat. Neurosci.* 17, 164–174. doi: 10.1038/nn.3612
- Raeder, M. B., Steen, V. M., Vollset, S. E., and Bjelland, I. (2007). Associations between cod liver oil use and symptoms of depression: the hordaland health study. *J. Affect. Disord.* 101, 245–249. doi: 10.1016/j.jad.2006.11.006
- Raison, C. L., and Miller, A. H. (2011). Is depression an inflammatory disorder? *Curr. Psychiatry Rep.* 13, 467–475. doi: 10.1007/s11920-011-0232-0
- Rapaport, M. H., Nierenberg, A. A., Schettler, P. J., Kinkead, B., Cardoos, A., Walker, R., et al. (2016). Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol. Psychiatry* 21, 71–79. doi: 10.1038/mp.2015.22
- Rees, A.-M., Austin, M.-P., and Parker, G. B. (2008). Omega-3 fatty acids as a treatment for perinatal depression: randomized double-blind placebo-controlled trial. *Aust. N. Z. J. Psychiatry* 42, 199–205. doi: 10.1080/00048670701827267
- 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 Behav. Immun.* 55, 249–259. doi: 10.1016/j.bbi.2015.12.013
- Rosenberger, T. A., Villacreses, N. E., Hovda, J. T., Bosetti, F., Weerasinghe, G., Wine, R. N., et al. (2004). Rat brain arachidonic acid metabolism is increased by a 6-day intracerebral ventricular infusion of bacterial lipopolysaccharide. *J. Neurochem.* 88, 1168–1178. doi: 10.1046/j.1471-4159.2003.02246.x
- Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., et al. (2006a). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychiatry* 163, 1905–1917. doi: 10.1176/ajp.2006.163.11.1905
- Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Stewart, J. W., Nierenberg, A. A., Thase, M. E., et al. (2006b). Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N. Engl. J. Med.* 354, 1231–1242. doi: 10.1056/NEJMoa052963
- Saito, M., Klibert, J., and Langhinrichsen-Rohling, J. (2013). Suicide proneness in American and Japanese college students: associations with suicide acceptability and emotional expressivity. *Death Stud.* 37, 848–865. doi: 10.1080/07481187.2012.699910
- Sakamoto, T., Cansev, M., and Wurtman, R. J. (2007). Oral supplementation with docosahexaenoic acid and uridine-5'-monophosphate increases dendritic spine density in adult gerbil hippocampus. *Brain Res.* 1182, 50–59. doi: 10.1016/j.brainres.2007.08.089
- Sandi, C., and Richter-Levin, G. (2009). From high anxiety trait to depression: a neurocognitive hypothesis. *Trends Neurosci.* 32, 312–320. doi: 10.1016/j.tins.2009.02.004
- Sastry, P. S. (1985). Lipids of nervous tissue: composition and metabolism. *Prog. Lipid Res.* 24, 69–176. doi: 10.1016/0163-7827(85)90011-6

- Saunders, E. F. H., Ramsden, C. E., Sherazy, M. S., Gelenberg, A. J., Davis, J. M., and Rapoport, S. I. (2016). Reconsidering dietary polyunsaturated fatty acids in bipolar disorder: a translational picture. *J. Clin. Psychiatry* 77, e1342–e1347. doi: 10.4088/JCP.15com10431
- Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium (2011). Genome-wide association study identifies five new schizophrenia loci. *Nat. Genet.* 43, 969–976. doi: 10.1038/ng.940
- Scola, G., Versace, A., Metherel, A. H., Monsalve-Castro, L. A., Phillips, M. L., Bazinet, R. P., et al. (2018). Alterations in peripheral fatty acid composition in bipolar and unipolar depression. *J. Affect. Disord.* 233, 86–91. doi: 10.1016/j.jad.2017.12.025
- Serhan, C. N. (2014). Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 510, 92–101. doi: 10.1038/nature13479
- Serhan, C. N. (2017). Discovery of specialized pro-resolving mediators marks the dawn of resolution physiology and pharmacology. *Mol. Aspects Med.* 58, 1–11. doi: 10.1016/j.mam.2017.03.001
- Serhan, C. N., Fredman, G., Yang, R., Karamnov, S., Belayev, L. S., Bazan, N. G., et al. (2011). Novel proresolving aspirin-triggered DHA pathway. *Chem. Biol.* 18, 976–987. doi: 10.1016/j.chembiol.2011.06.008
- Shelton, R. C., Osuntokun, O., Heinloth, A. N., and Corya, S. A. (2010). Therapeutic options for treatment-resistant depression. *CNS Drugs* 24, 131–161. doi: 10.2165/11530280-000000000-00000
- Shi, Z., Ren, H., Huang, Z., Peng, Y., He, B., Yao, X., et al. (2017). Fish oil prevents lipopolysaccharide-induced depressive-like behavior by inhibiting neuroinflammation. *Mol. Neurobiol.* 54, 7327–7334. doi: 10.1007/s12035-016-0212-9
- Silvers, K. M., and Scott, K. M. (2002). Fish consumption and self-reported physical and mental health status. *Public Health Nutr.* 5, 427–431. doi: 10.1079/PHNPHN2001308
- Simopoulos, A. P. (1991). Omega-3 fatty acids in health and disease and in growth and development. *Am. J. Clin. Nutr.* 54, 438–463. doi: 10.1093/ajcn/54.3.438
- Song, C., Li, X., Leonard, B. E., and Horrobin, D. F. (2003). Effects of dietary n-3 or n-6 fatty acids on interleukin-1beta-induced anxiety, stress, and inflammatory responses in rats. *J. Lipid Res.* 44, 1984–1991. doi: 10.1194/jlr.M300217-JLR200
- Spector, A. A., and Kim, H.-Y. (2015). Discovery of essential fatty acids. *J. Lipid Res.* 56, 11–21. doi: 10.1194/jlr.R055095
- Su, K.-P., Huang, S.-Y., Chiu, C.-C., and Shen, W. W. (2003). Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur. Neuropsychopharmacol.* 13, 267–271. doi: 10.1016/S0924-977X(03)00032-4
- Sublette, M. E., Ellis, S. P., Geant, A. L., and Mann, J. J. (2011). Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J. Clin. Psychiatry* 72, 1577–1584. doi: 10.4088/JCP.10m06634
- Sublette, M. E., Vaquero, C., Baca-Garcia, E., Pachano, G., Huang, Y.-Y., Oquendo, M. A., et al. (2016). Lack of association of SNPs from the FADS1-FADS2 gene cluster with major depression or suicidal behavior. *Psychiatr. Genet.* 26, 81–86. doi: 10.1097/YPG.0000000000000111
- Sugiura, T., Kondo, S., Sukagawa, A., Nakane, S., Shinoda, A., Itoh, K., et al. (1995). 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem. Biophys. Res. Commun.* 215, 89–97. doi: 10.1006/bbrc.1995.2437
- Taha, A. Y., Blanchard, H. C., Cheon, Y., Ramadan, E., Chen, M., Chang, L., et al. (2017). Dietary linoleic acid lowering reduces lipopolysaccharide-induced increase in brain arachidonic acid metabolism. *Mol. Neurobiol.* 54, 4303–4315. doi: 10.1007/s12035-016-9968-1
- Taha, A. Y., Hennebelle, M., Yang, J., Zamora, D., Rapoport, S. I., Hammock, B. D., et al. (2016). Regulation of rat plasma and cerebral cortex oxylipin concentrations with increasing levels of dietary linoleic acid. *Prostaglandins Leukot. Essent. Fatty Acids* doi: 10.1016/j.plefa.2016.05.004 [Epub ahead of print].
- Takeuchi, T., Iwanaga, M., and Harada, E. (2003). Possible regulatory mechanism of DHA-induced anti-stress reaction in rats. *Brain Res.* 964, 136–143. doi: 10.1016/S0006-8993(02)04113-6
- Tanskanen, A., Hibbeln, J. R., Tuomilehto, J., Uutela, A., Haukka, A., Viinamäki, H., et al. (2001). Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr. Serv.* 52, 529–531. doi: 10.1176/appi.ps.52.4.529
- Tejera, N., Vauzour, D., Betancor, M. B., Sayanova, O., Usher, S., Cochard, M., et al. (2016). A transgenic *Camelina sativa* seed oil effectively replaces fish oil as a dietary source of eicosapentaenoic acid in mice. *J. Nutr.* 146, 227–235. doi: 10.3945/jn.115.23941
- Thomazeau, A., Bosch-Bouju, C., Manzoni, O., and Layé, S. (2017). Nutritional n-3 PUFA deficiency abolishes endocannabinoid gating of hippocampal long-term potentiation. *Cereb. Cortex* 27, 2571–2579. doi: 10.1093/cercor/bhw052
- Tiemeier, H., van Tuijl, H. R., Hofman, A., Kiliaan, A. J., and Breteler, M. M. B. (2003). Plasma fatty acid composition and depression are associated in the elderly: the rotterdam study. *Am. J. Clin. Nutr.* 78, 40–46. doi: 10.1093/ajcn/78.1.40
- Timonen, M., Horrobin, D., Jokelainen, J., Laitinen, J., Herva, A., and Räsänen, P. (2004). Fish consumption and depression: the Northern Finland 1966 birth cohort study. *J. Affect. Disord.* 82, 447–452. doi: 10.1016/j.jad.2004.02.002
- Tremoleda, J. L., Thau-Zuchman, O., Davies, M., Foster, J., Khan, I., Vadivelu, K. C., et al. (2016). In vivo PET imaging of the neuroinflammatory response in rat spinal cord injury using the TSPO tracer [¹⁸F]GE-180 and effect of docosahexaenoic acid. *Eur. J. Nucl. Med. Mol. Imaging* 43, 1710–1722. doi: 10.1007/s00259-016-3391-8
- Uyanik, V., Tuglu, C., Gorgulu, Y., Kunduracilar, H., and Uyanik, M. S. (2015). Assessment of cytokine levels and hs-CRP in bipolar I disorder before and after treatment. *Psychiatry Res.* 228, 386–392. doi: 10.1016/j.psychres.2015.05.078
- Vaz, J. D. S., Farias, D. R., Adegboye, A. R. A., Nardi, A. E., and Kac, G. (2017). Omega-3 supplementation from pregnancy to postpartum to prevent depressive symptoms: a randomized placebo-controlled trial. *BMC Pregnancy Childbirth* 17:180. doi: 10.1186/s12884-017-1365-x
- Watanabe, S., Doshi, M., and Hamazaki, T. (2003). n-3 Polyunsaturated fatty acid (PUFA) deficiency elevates and n-3 PUFA enrichment reduces brain 2-arachidonoylglycerol level in mice. *Prostaglandins Leukot. Essent. Fatty Acids* 69, 51–59. doi: 10.1016/S0952-3278(03)00056-5
- WHO (2015) *Suicide*. Available at: <http://www.who.int/mediacentre/factsheets/fs398/en/>
- Wietrzyk-Schindler, M., Szyszka-Niagolov, M., Ohta, K., Endo, Y., Pérez, E., de Lera, A. R., et al. (2011). Retinoid x receptor gamma is implicated in docosahexaenoic acid modulation of despair behaviors and working memory in mice. *Biol. Psychiatry* 69, 788–794. doi: 10.1016/j.biopsych.2010.12.017
- Wilson, R. I., and Nicoll, R. A. (2002). Endocannabinoid signaling in the brain. *Science* 296, 678–682. doi: 10.1126/science.1063545
- Wilson, R. I., and Nicoll, R. A. (2001). Endogenous cannabinoids mediate retrograde signalling at hippocampal synapses. *Nature* 410, 588–592. doi: 10.1038/35069076
- Wood, J. T., Williams, J. S., Pandarinathan, L., Janero, D. R., Lammi-Keefe, C. J., and Makriyannis, A. (2010). Dietary docosahexaenoic acid supplementation alters select physiological endocannabinoid-system metabolites in brain and plasma. *J. Lipid Res.* 51, 1416–1423. doi: 10.1194/jlr.M002436
- Yamashima, T. (2008). A putative link of PUFA, GPR40 and adult-born hippocampal neurons for memory. *Prog. Neurobiol.* 84, 105–115. doi: 10.1016/j.pneurobio.2007.11.002
- Yamauchi, T., Fujita, T., Tachimori, H., Takeshima, T., Inagaki, M., and Sudo, A. (2013). Age-adjusted relative suicide risk by marital and employment status over the past 25 years in Japan. *J. Public Health* 35, 49–56. doi: 10.1093/pubmed/fds054
- Yehuda, S., Rabinovitz, S., and Mostofsky, D. I. (2005). Mixture of essential fatty acids lowers test anxiety. *Nutr. Neurosci.* 8, 265–267. doi: 10.1080/10284150500445795
- Zainuddin, M. S. A., and Thuret, S. (2012). Nutrition, adult hippocampal neurogenesis and mental health. *Br. Med. Bull.* 103, 89–114. doi: 10.1093/bmb/ldso21
- Zimmer, R., Riemer, T., Rauch, B., Schneider, S., Schiele, R., Gohlke, H., et al. (2013). Effects of 1-Year treatment with highly purified omega-3 fatty acids on depression after myocardial infarction. *J. Clin. Psychiatry* 74, e1037–e1045. doi: 10.4088/JCP.13m08453

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2018 Larrieu and Layé. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.