REVIEW

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Focus on fatty acids in the neurometabolic pathophysiology of psychiatric disorders

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Abstract

Continuous research into the pathophysiology of psychiatric disorders, such as major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and schizophrenia, suggests an important role for metabolism. This narrative review will provide an up-to-date summary of how metabolism is thought to be involved in the pathophysiology of these psychiatric disorders. We will focus on (I) the important role of fatty acids in these metabolic alterations, (II) whether fatty acid alterations represent epiphenomena or risk factors, and (III) similarities and dissociations in fatty acid alterations between different psychiatric disorders. (Historical) epidemiological evidence links fatty acid intake to psychiatric disorder prevalence, corroborated by altered fatty acid concentrations measured in psychiatric patients. These fatty acid alterations are connected with other concomitant pathophysiological mechanisms, including biological stress (hypothalamic-pituitary-adrenal (HPA)-axis and oxidative stress), inflammation, and brain network structure and function. Metabolomics and lipidomics studies are underway to more deeply investigate this complex network of associated neurometabolic alterations. Supplementation of fatty acids as disease-modifying nutraceuticals has clinical potential, particularly add-on eicosapentaenoic acid (EPA) in depressed patients with markers of increased inflammation. However, by interpreting the observed fatty acid alterations as partly (mal)adaptive phenomena, we attempt to nuance translational expectations and provide new clinical applications for these novel neurometabolic insights, e.g., to predict treatment response or depression recurrence. In conclusion, placing fatty acids in context can contribute to further understanding and optimized treatment of psychiatric disorders, in order to diminish their overwhelming burden of disease.

Introduction

Relevance

Psychiatric disorders including major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and schizophrenia rank as a distant first in the global burden of disease estimates regarding years lived with disability, and share this problematic position with cardiovascular diseases for disability adjusted life years (Vigo et al. 2016). The main reasons for tremendous burden of disease for psychiatric disorders include (I) their early onset and chronic, recurrent nature (Mocking et al. 2016a), (II) limited available treatment options lacking an (etiologically driven) personalized approach (Bockting et al. 2013), and (III) high cardiovascular comorbidity (Assies et al. 2014).

In order to overcome this disease burden, there have been increasing scientific efforts during the past few decades to better understand these disorders from a (neuro)biological perspective. Initial models — based on serendipitous effects on mood of drugs that modulated neurotransmitters — focused on disturbances in the synaptic neurotransmission of monoamines as serotonin, dopamine, and noradrenaline (Hirschfeld 2000; Ruhe et al. 2007). While these monoamine hypotheses certainly have advanced the field of biological psychiatry, it is increasingly being recognized that they only tell a small part of the complex story of psychiatric disorder pathophysiology (Su 2008; Gardner and Boles 2011).

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More recent hypotheses suggest broader metabolic alterations that extend beyond monoamine metabolism (Su 2008; Maes et al. 2009; Assies et al. 2014; Naviaux 2014; Rosenblat et al. 2014; Muller et al. 2015; Mocking et al. 2016a). Complex interacting metabolic pathways are being hypothesized to partly underlie — and be connected with — observed coexistent biological (oxidative) stress, inflammatory, and brain network alterations. Within these pathways, a metabolic factor that particularly attracted increasing scientific attention in the past few decades was fatty acid metabolism (Fig. 1). Several lines of evidence link fatty acid alterations to psychiatric disorders, and suggest interesting cross-links between fatty acids and other pathophysiological mechanisms as outlined below. This proposed role of fatty acids in psychiatric disorder pathophysiology could yield important new insights in (I) psychiatric disorder incidence and their recurrent, chronic nature, (II)

development of new treatment strategies, and (III) reduction of cardiovascular comorbidity.

Methods

In this narrative review, we will provide an up-to-date summary of how fatty acids and their oxygenated products are thought to be involved in psychiatric disorder pathophysiology. We searched for articles on the roles of fatty acids in psychiatric disorders in PubMed and Google Scholar using keywords on fatty acids (e.g., unsaturated fatty acids, arachidonic acid, eicosapentaenoic acid, essential fatty acids, mono-unsaturated fatty acids, omega-3 fatty acids, docosahexaenoic acid, omega-6 fatty acids, lipid peroxidation products, membrane lipids, fish oils, polyunsaturated fatty acids, or saturated fatty acids). In addition, we searched reference lists and cited
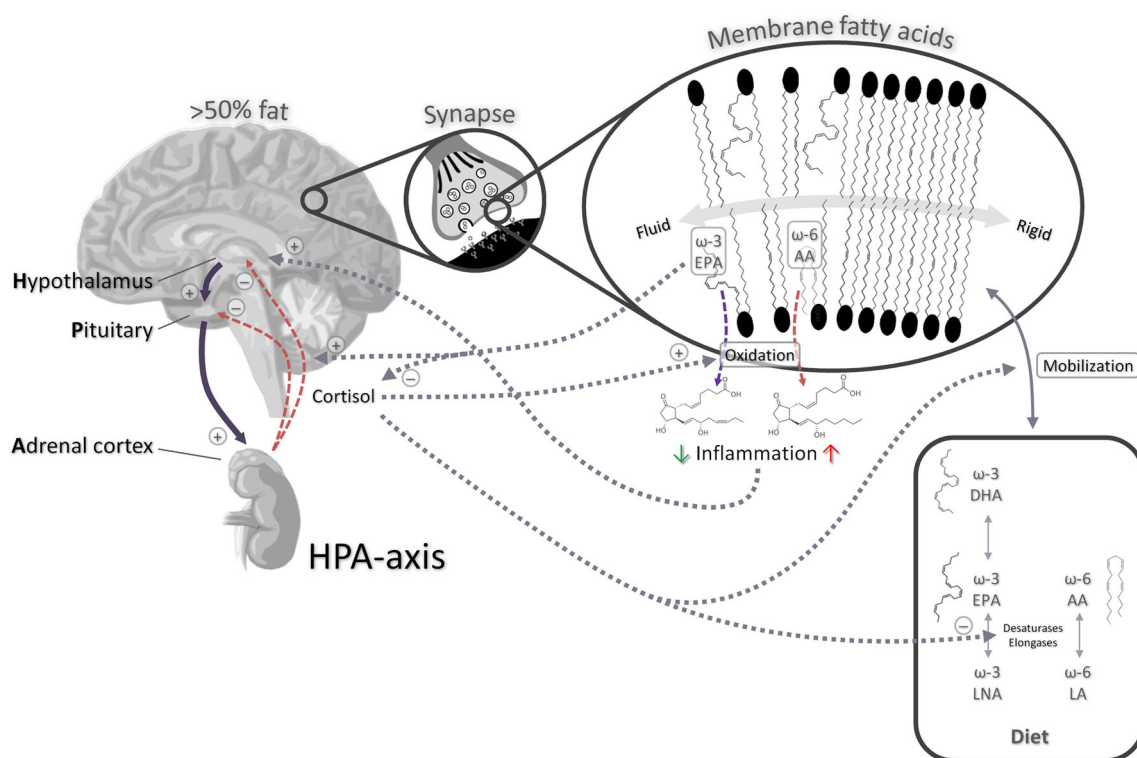

Fig. 1 Simplified scheme depicting the different roles of fatty acids in the phospholipid cell membrane and associations with other pathophysiological mechanisms. Not all fatty acids are created equal, they can be subdivided into three main classes: saturated (no double bonds), mono-unsaturated (one double bond), and polyunsaturated (multiple double bonds). Mono- and poly-unsaturated fatty acids are subdivided based on carbon atom number from which the first double bond is positioned, counted from the methyl end of the fatty acid chain (e.g., in omega-3 fatty acids, the first double bond is located between the third and fourth carbon atom). In addition, fatty acids from all three main classes can be characterized as "long-chain" if they have ≥20 carbon atoms in their chain. The brain consists of >50% of fat. Zooming in, synapses are composed of a phopholipid bilayer neuronal membrane. The more unsaturated fatty acid (more double bonds) it contains, the

more fluid the membrane becomes (left side of the membrane fatty acids panel). However, double bonds are vulnerable for oxidation. Oxidation products from omega-3 fatty acids are generally anti-inflammatory, those of omega-3 fatty acids are pro-inflammatory (lower side). Omega-3 and omega-6 fatty acids cannot be synthesized, and have therefore be derived from the diet, they can be metabolized by desaturase and elongase enzymes (shown right). Activation of the hypothalamic-pituitary-adrenal (HPA) axis (shown left in purple arrows) results in production of cortisol, which activates intrinsic feedback loops (in red). Cortisol has bidirectional relationships with fatty acid metabolism (gray dotted arrows), e.g., it inhibits desaturases and elongases, influences mobilization of fatty acids, and increases oxidation; while omega-3 fatty acids reduce cortisol, increase negative feedback, and inflammation stimulates the hypothalamus

articles for additional articles. Articles were selected based on relevance and quality, as determined by critical assessment and discussion among the review team.

In part 2 we will first describe why fatty acids may be of interest in psychiatric disorder pathophysiology, in part 3 we will describe fatty acid studies in psychiatric disorders, followed by a discussion in part 4. Throughout the manuscript, we will focus on (I) fatty acids' role in the metabolic and associated pathophysiological alterations, (II) whether fatty acid alterations represent epiphenomena, adaptive mechanisms, or risk factors, and (III) similarities and dissociations in fatty acid alterations between different psychiatric disorders. By interpreting fatty acid alterations as partly (mal)adaptive phenomena, we aim at nuancing translational expectations and providing new clinical applications.

Why fatty acids?

Epidemiological evidence

Ecological, cross-sectional, and prospective data

Humans are incapable of de novo omega-3 and -6 polyunsaturated fatty acid synthesis, and therefore depend on dietary intake of these essential nutrients (Assies et al. 2014). This essential nature could underlie several lines of epidemiological evidence suggesting an inverse association between dietary omega-3 fatty acid intake and the prevalence of psychiatric disorders. A first hint of this inverse association was provided in 1998 by ecological evidence showing a lower prevalence of psychiatric disorders in countries where more (fatty) fish is being consumed, the main dietary source of fatty acids (Hibbeln 1998; Hibbeln 2002; Grosso et al. 2014). Later, more detailed cross-sectional studies largely supported this ecological evidence (Grosso et al. 2016; Li et al. 2016). In addition, prospective studies generally also corroborated this relationship (Sanhueza et al. 2013; Vermeulen et al. 2016), providing further support for a possible causal relationship. For example, we recently showed that a higher baseline dietary pattern score, also based on omega-3 fatty acid intake, protected against depression over a 9-year period in the InChianti study (Vermeulen et al. 2016).

Comorbidity patterns

Additional epidemiological evidence for a role for fatty acid abnormalities in psychiatric disorders is found in comorbidity patterns. The high comorbidity rate of psychiatric disorders with cardiovascular disease may hint at a partly shared underlying pathophysiology. Because both are associated with similar alterations in fatty acid intake, this may suggest that these fatty acids are involved in their mutual pathophysiology. In

this regard, psychiatric and cardiovascular disease have been suggested to represent two sides of the same coin (Assies et al. 2014). Furthermore, diseases caused by genetic disturbances in fatty acid metabolism such as peroxisomal disorders including X-linked adrenoleukodystrophy (McNamara 2013), can cause psychiatric symptoms including psychosis, anxiety, and depressive behavior (Kitchin et al. 1987). Of note, one study reported that 39% of X-linked adrenoleukodystrophy patients presented with a psychiatric diagnosis, sign or symptom, including mood symptoms, PTSD, and schizophrenia (Kitchin et al. 1987).

Historical epidemiological perspective

Interestingly, historical epidemiological data also suggest an association between an increase in psychiatric disorder prevalence and a decrease in omega-3 fatty acid intake — together with a relative increase in omega-6 fatty acid intake (Grosso et al. 2014). Over the past 100–150 years, the ratio of omega-6 to omega-3 fatty acids in our modern Western diets has shown a steep increase from ~1–2:1 to ~20–30:1. Although alternative explanations have also been suggested (Dehue 2008; Bracke et al. 2016), this may have contributed to a suggested parallel rise in burden of disease due to psychiatric disorders (Simopoulos 1999; Muskiet 2010; Hidaka 2012; Grosso et al. 2014; van Elst et al. 2014). Similar observations in more recently modernizing countries could suggest that history repeats itself (Sun and Ryder 2016). We recently aimed at testing the hypothesis of a mismatch between our modern diet and our evolution-based biological make-up, and showed a positive association between a dietary mismatch score and depression in a large interethnic population study, that survived correction for confounders (Nederhof 2016).

Biological evidence

Lipids constitute more than half of brain dry weight, of which approximately one third is accounted for by polyunsaturated fatty acids (Guest et al. 2013), by forming the main building blocks of (neuronal) cell membranes (Piomelli et al. 2007; Holthuis and Menon 2014). Through their functional and structural characteristics, fatty acids influence brain physiology in multiple ways, e.g., affecting neuronal membrane structure, inflammatory regulation, hypothalamic-pituitary-adrenal (HPA)-axis activity, and oxidative stress vulnerability (Fig. 1), as described below.

Neuronal membrane structure

Fatty acids form the hydrophobic tails of membrane phospholipids (Piomelli et al. 2007; Assies et al. 2014; Holthuis and Menon 2014). Double bonds cause curvatures in (poly)unsaturated fatty acids. If phospholipids contain fatty

acids with more double bonds, the resulting curvatures decrease adhesive van der Waals forces between them, producing a more fluid membrane. The other way around, the straight saturated fatty acids can be more tightly packed, resulting in a more rigid/stiff membrane. The fluidity of the membrane influences lipid-protein interactions of membrane-bound proteins as neurotransmitter-receptors and –transporters (Fisar 2005; Rituper et al. 2010; Pengcheng Fan 2015). Thereby, (neuronal) membrane fatty acid composition can influence synaptic communication, providing an important potential pathway through which fatty acids may be involved in neuronal connectivity and thereby in psychiatric disorder pathophysiology (Piomelli et al. 2007; Assies et al. 2014; Holthuis and Menon 2014). As an example, the geometrical characteristics of fatty acids in the presynaptic membrane have been suggested to facilitate exocytosis of neurotransmitter-containing synaptic vesicles (Piomelli et al. 2007).

Inflammatory regulation

Through (non)enzymatic oxygenation, fatty acids form the precursors of inflammatory regulating molecules such as eicosanoids, including prostaglandins and leukotrienes (Calder 2006). Importantly, inflammatory mediators derived from omega-3 and omega-6 fatty acids are thought to have opposing effects: those from omega-3 fatty acids are considered anti-inflammatory, while those of omega-6 fatty acids are generally pro-inflammatory. Of note, omega-3 and omega-6 fatty acids compete for the same enzymes for metabolization, not only in fatty acid chain remodeling (e.g., elongation and desaturation), but also mobilization (e.g., phospholipase A2-mediated membrane release) as well as inflammatory mediator production (e.g., cyclooxygenase-mediated prostaglandin production) (Calder 2006; Kiecolt-Glaser et al. 2015). So a greater omega-6 fatty acid supply to these enzymes implies less metabolization capacity for omega-3 fatty acids. This potentially aggravates their mutually antagonizing effects. Given that many psychiatric disorders are thought to be characterized by increased inflammation (Sommer et al. 2012; Kiecolt-Glaser et al. 2015), the increase in dietary omega-6/omega-3-ratio described above may have an important underlying role. This inflammatory modulating effect could also explain the association of fatty acids with cardiovascular disease.

Bidirectional relation with hypothalamic-pituitary-adrenal (HPA)-axis

One of the most-studied pathophysiological mechanisms in biological psychiatry is neuroendocrinological stress, quantifiable in HPA-axis activity leading to production of cortisol (Stetler and Miller 2011). Interestingly, fatty acids influence both HPA-axis stimulation and feedback through their effects on corticotropin-releasing hormone (CRH)-secretion and

glucocorticoid receptor-sensitivity. In brief, lower concentrations of omega-3 fatty acids and relatively higher concentrations of omega-6 fatty acids are thought to lead to HPA-axis hyperactivation, i.e., cortisol increases (Hibbeln and Salem 1995; Murck et al. 2004; Mocking et al. 2012a, 2013b; Bazinet and Laye 2014; Mocking et al. 2015). Vice versa, cortisol influences production, mobilization, and degradation of fatty acids by modulating key enzymes and increasing oxidative stress. In short, the result is that increases in cortisol lead to lower omega-3 fatty acid concentrations (Hibbeln and Salem 1995; Macfarlane et al. 2008; Mocking et al. 2013b). These proposedly bidirectional effects could potentially lead to a "vicious" circle, where a decrease in omega-3 fatty acids would result in increases in cortisol, which on its turn would further decrease omega-3 fatty acid concentrations. In addition, this process could be one of the components of the allostatic load of chronic stress, also leading to cardiovascular disease (Juster et al. 2010).

Oxidative stress vulnerability

Fatty acids strongly differ in their susceptibility to free radical attack, based on the number of double bonds. With every double bond, a fatty acid becomes exponentially more susceptible (Assies et al. 2014). Of note, many psychiatric disorders manifest themselves together with an increase in oxidative stress, defined as an imbalance between increased free radical formation on the one hand, and decreased anti-oxidant defense on the other (Maes et al. 2009; Assies et al. 2014; Black et al. 2015). This may lead to interesting interactions with fatty acid metabolism (Assies et al. 2014) as discussed below.

Other mechanisms

Fascinatingly, fatty acids have also been associated with a wide variety of other (patho)physiological mechanisms. For example, they are precursors of endocannabinoids (Meijerink et al. 2013; Naughton et al. 2013), sphingolipids, and lipid oxidation products (lipoxins) as resolvins, maresins, and protectins (Schneider et al. 2016). Endocannabinoids are neuromodulatory lipids derived from omega-6 arachidonic acid, and thought to be involved in regulation of mood and psychosis vulnerability. (Neuro)protectin D1 is an oxidative derivative from the omega-3 fatty acid docosahexaenoic acid (DHA), and has anti-apoptotic and thereby neuroprotective properties.

In addition, fatty acids have nutrigenomic effects, i.e., they can regulate gene-expression. As an example, several fatty acids and their oxidative derivatives are endogenous ligands to peroxisome proliferator-activated receptors (PPARs), important transcription factors for regulation of metabolism and cellular development (Mutch et al. 2005). In addition, by modulating cyclic AMP-dependent response element binding

protein (CREB) through a p38 mitogen-activated protein kinase (MAPK)-dependent mechanism, omega-3 fatty acids have also been shown to influence brain derived neurotrophic factor (BDNF), an important regulator of brain cytoarchitecture (Rao et al. 2007).

Finally, fatty acids have been reported to influence the gastrointestinal microbiome (Pusceddu et al. 2015); and are associated with one-carbon metabolism and thereby epigenetics (through methyl-group donation for DNA methylation) (Muskiet and Kemperman 2006; Assies et al. 2015). Regarding this latter association, we previously described several ways through which fatty acids can influence one-carbon metabolism, including regulation of oxidative stress, methyl-group donation for fatty acid chain elongation, and epigenetic regulation (Assies et al. 2014).

Fatty acid studies in psychiatric disorders

In this third part we will first describe studies that investigated the association between fatty acid alterations and psychiatric disorder. We will start with cross-sectional studies, and then describe longitudinal studies. Subsequently we will review studies on the association between fatty acid alterations and other pathophysiological mechanisms in psychiatric disorders. Finally, we will provide an overview of clinical applications of fatty acids in psychiatry, including intervention studies.

Associations between fatty acid alterations and psychiatric disorders

Cross-sectional observational studies

The above epidemiological and biological data on fatty acid metabolism in psychiatric disorders increasingly stimulated research in fatty acid alterations in patients. Cross-sectional studies in several psychiatric disorders generally show associations with a pattern of decreased concentrations of omega-3 fatty acids, and an increased omega-6/omega-3-ratio (Freeman 2000; Haag 2003). Evidence seems to be strongest for major depressive disorder (Lin et al. 2010), but a similar pattern seems to exist for schizophrenia (Hoen et al. 2013). Anxiety disorders are less extensively studied (Ross 2009; de Vries et al. 2016); we previously found lower DHA in PTSD patients compared to controls, but only after correction for diet (de Vries et al. 2016).

Importantly, several negative findings have been published as well (Lin et al. 2010; Hoen et al. 2013; Mocking et al. 2015; Medema et al. 2016). A wide range of methodological issues could explain these inconsistencies. First, statistical methodological issues regarding fatty acid expression and testing may influence reported fatty acid alterations, including correct handling of non-detects, expression of fatty acids in relative percentages or absolute concentrations, and multiple testing problems (Mocking et al. 2012c). For example, using zero-substitution for non-detectable values may artificially lower statistical estimates of mean concentrations. In addition, some studies express fatty acids as relative percentages of the total fatty acid pool, while other studies use absolute concentrations, which may influence the extent of the differences. Finally, given the large number of different fatty acids, multiple testing issues may induce type I errors, for which many studies do not systematically correct (Mocking et al. 2012c).

Second, results may be influenced by the focus on omega-3 and omega-6 PUFAs instead of the overall fatty acid alteration pattern (Assies et al. 2010). Given the unique properties of the essential fatty acids of the omega-3 and -6 subclasses, most studies focused on these fatty acids. Nevertheless, increasing data suggest that fatty acid alterations in psychiatric disorders extend beyond the omega-3 and -6 subtypes, and can also be observed in saturated and monounsaturated fatty acids (Assies et al. 2010; Assies et al. 2014). This suggests patterns of alterations in fatty acids and their oxygenated products that can be better studied using lipidomic or metabolomic approaches as are currently increasingly being applied.

In addition, evidence is available suggesting bimodal distributions of fatty acid concentrations, which may influence statistical interpretations. For example, following observations of bimodal distributions of polyunsaturated fatty acids in schizophrenia (Bentsen et al. 2011), we showed that overall fatty acid unsaturation and chain length were also bimodally distributed in recurrent depression (Mocking et al. 2012b). This bimodal distribution has been suggested to represent two endophenotypes (Bentsen et al. 2011).

Alternatively, the inconsistencies in cross-sectional findings could be explained by confounding, e.g., due to lifestyle or medication use (Assies et al. 2014). This may suggest that the observed association between psychiatric disorders and fatty acid alterations merely reflect epiphenomena of the disease, instead of risk factors. One important lifestyle factor is diet. Not all studies apply standard corrections for dietary intake (Lin et al. 2010). In addition, diet is difficult to measure and residual confounding after correction could still influence results. Nevertheless, it could be questioned whether diet should be seen as a confounder. If differences in dietary intake lead to altered fatty acid concentrations that increase disease risk, fatty acids could instead be seen as mediators of the effect of differences in dietary intake (Assies et al. 2014). A more definitive answer on whether fatty acids should be seen as epiphenomena or risk factors can be found by prospective cohort and intervention studies as described below.

Regarding medication use, several (psychotropic) medications may theoretically affect fatty acid concentrations and intake. Some studies investigated fatty acids exclusively in medication free subjects (Lin et al. 2010; Mocking et al. 2015, 2017a), but in general the precise effects of the different

medications on fatty acid concentrations have not been systematically studied in psychiatric patients. Nevertheless, the relation between metabolic alterations and psychiatric diseases was already observed well before the development of psychotropic medication (Assies et al. 2014). Larger samples and individual patient data meta-analyses, providing the opportunity to study the association between medication use and fatty acids in more detail, may yield more insight on the potential confounding effects of medication use.

Furthermore, fatty acid alterations have been mostly studied in peripheral samples, e.g., erythrocyte membranes, given the impossibility of in vivo brain tissue sampling. Nevertheless, (I) blood concentrations generally shown adequate correlations with central measures, as shown in vivo in cerebrospinal fluid, as well as in postmortem and animal studies (Carlson et al. 1986; Connor et al. 1990; Babin et al. 1993; Makrides et al. 1994; Carver et al. 2001; Yao et al. 2002; Cunnane et al. 2012; Jumpertz et al. 2012; Guest et al. 2013), (II) fatty acids both passively and actively cross the blood-brain-barrier (Chen et al. 2008; Mitchell et al. 2011), and (III) findings in post-mortem brains generally corroborate findings from peripheral samples for psychiatric disorders (McNamara and Carlson 2006; Hamazaki et al. 2012; McNamara et al. 2014).

Overall, these cross-sectional findings show a general picture of reduced concentrations of omega-3 fatty acids and an increase in omega-6/omega-3 ratio in at least depression and schizophrenia. Some transdiagnostic studies have aimed to compare fatty acid pattern alterations between psychiatric disorders (Hamazaki et al. 2012; Hamazaki et al. 2015), but evidence is still limited in that regard (Ross et al. 2007).

Longitudinal observational studies

Similar to the above cross-sectional data, prospective studies on the relationship between fatty acids and depression show substantial heterogeneity (Lucas et al. 2011; Grosso et al. 2014; Matsuoka et al. 2017). Although other fatty acid classes have also been prospectively studied, most studies again focused on omega-3 fatty acid concentrations or intake. A meta-analysis of prospective studies showed a protective effect for both fish and EPA + DHA intake on the development of depression over a follow-up of up to 30 years (Grosso et al. 2016). Associations remained after controlling for dietary and socio-economic variables. For omega-3 fatty acid concentrations as biomarkers as opposed to intake, results seem somewhat more inconsistent, with some studies showing a protective association (Beydoun et al. 2015; Berger et al. 2017), and others no relationship (Astorg et al. 2009; Persons et al. 2014). Additional supportive evidence for a prospective relationship comes from studies showing fatty acid alterations that remain during remission (Assies et al. 2010).

Longitudinal data for psychotic disorders show a similar prospective association for both fatty acid intake and concentrations during different stages of the disease (McGorry et al. 2014). Next to protective associations for omega-3 fatty acid intake and concentrations, evidence also exists for a protective effect of omega-9 fatty acid nervonic acid concentrations, a major constituent of myelin membrane sphingolipids (Amminger et al. 2012).

Associations with other pathophysiological mechanisms

As described above in Biological evidence, through their proposed central role in (patho)physiology, fatty acids may have multiple relationships with other pathophysiological mechanisms relevant in psychiatric disorders and cardiovascular disease (Hibbeln and Salem 1995). Here, we describe clinical studies that addressed the relationship between fatty acid metabolism and (I) brain networks, (II) inflammation, (III) the HPA-axis, and (IV) other mechanisms.

Brain networks A vast body of evidence shows alterations in brain networks in patients with psychiatric disorders (Broyd et al. 2009; Rive et al. 2013; Kaiser et al. 2015). The relations of fatty acid metabolism with brain structure and BDNF described above in Neuronal membrane structure and Other mechanisms are reflected in emerging evidence associating fatty acids with brain network structure and function (McNamara 2013; Bos et al. 2016). For example, omega-3 fatty acids were found to be positively associated with (I) white matter integrity (Peters et al. 2013; Peters et al. 2014) and brain glutathione (a major antioxidant) in schizophrenia (Berger et al. 2008); (II) limbic area volumes in healthy controls (Conklin et al. 2010; McNamara 2013; Witte et al. 2014); and (III) activity in depression relevant areas like the prefrontal and anterior cingulate cortex (McNamara 2013). Our own research showed an association between arachidonic acid and amygdala reactivity that differed between unmedicated patients with depression and healthy matched controls (Mocking et al. 2017a). However, most studies have modest sample sizes, and in the absence of prepublished analysis protocols multiple testing problems may exist, given the multitude of possible operationalizations of both fatty acid and imaging parameters (Mocking et al. 2012c).

Inflammation Many psychiatric disorders have been associated with increased inflammation, including depression, schizophrenia, and PTSD (Raison and Miller 2011; Sommer et al. 2014). The relation between fatty acid metabolism and inflammation described above in Inflammatory regulation is reflected in corresponding associations with inflammatory biomarkers as C-reactive protein (CRP) and cytokines (Calder 2006; Mazza et al. 2015). In unmedicated depressed patients, we observed a positive association between

arachidonic acid and CRP, that both were present in higher concentrations than in matched controls (Mocking et al. 2017a). Another interesting clinical example illustrating the inflammatory modulating effects of fatty acids, is that a higher — i.e., more pro-inflammatory — omega-6/omega-3-ratio seems to predict depression onset during treatment with the inflammatory cytokine interferon-alpha in hepatitis C-patients (Lotrich et al. 2013; Su 2015).

HPA-axis Particularly, stress related disorders, such as depression and PTSD, have been shown to be associated with HPA-axis alterations. While PTSD is mainly characterized by blunted cortisol responses (Meewisse et al. 2007; Bicanic et al. 2013); depressed patients (particularly those with severe and/or melancholic depression) show HPA-axis hyperactivity thought to result from impaired HPA-axis feedback through the glucocorticoid receptor (Pariante et al. 2004; Stetler and Miller 2011; Lok et al. 2012). The "vicious" circle, potentially resulting from the bidirectional relationship between fatty acid metabolism and the HPA-axis (described in Bidirectional relation with hypothalamic-pituitary-adrenal (HPA)-axis) fits with our observations of associations between fatty acid metabolism and cortisol in depression. In detail, in two independent cohorts of depressed patients, we observed a similar negative association between fatty acid unsaturation and salivary cortisol. Given that one of these cohorts showed hypercortisolism and the other did not, the relation between fatty acid metabolism and the HPA-axis may be more consistently altered than each system separately (Mocking et al. 2013b, 2015).

Clinical applications

Correcting fatty acid alterations: intervention studies

Lifestyle The above data on a role of fatty acid alterations in psychiatric disorder pathophysiology resulted in several trials aiming at correcting these alterations. Instead of supplementing omega-3 fatty acids as discussed in the next paragraph, the most (physio)logical way to increase omega-3 fatty acid concentrations would be to eat more omega-3 fatty acids (e.g., fatty fish) and less omega-6 fatty acids. Several dietary trials are underway in psychiatric disorders, some already show potential of dietary modification, including increasing omega-3 fatty acid intake, e.g., from nuts and fish (Berk et al. 2013; Sarris et al. 2015; Opie et al. 2016). For example, in depression, a relatively well-conducted 12-week single blind randomized controlled trial of an adjunctive dietary intervention vs. a social support protocol showed a number needed to treat of 4.1 for remission (Jacka et al. 2017). Moreover, combining increased dietary omega-3 fatty acid intake with other dietary and lifestyle factors decreasing oxidative stress, e.g., physical exercise, seems particularly

promising (Gomez-Pinilla 2011; Berk et al. 2013; Daumit et al. 2013; Roca et al. 2016; Naslund et al. 2017). For example, an intervention composed of exercise and dietary management (vs. standard health classes) in obese persons with serious mental illnesses, such as schizophrenia, bipolar disorder or major depression, led to more weight loss than comparable lifestyle-intervention trials in the general population (Daumit et al. 2013).

Fatty acid supplementation Despite the above promising findings for lifestyle modification, it generally seems hard to follow and maintain dietary guidelines. Many people do not yet manage to increase their dietary omega-3 fatty acid intake (Sarris et al. 2015). Therefore, several trials attempted to correct fatty acid alterations using supplements. Most trials supplemented omega-3 fatty acids, mainly in the form of eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA). Some studies also supplemented arachidonic acid or other fatty acids. Most trials have been performed for mood disorders, some studies included patients with psychotic, anxiety or other disorders, including attention deficit hyperactivity disorder, autism, or aggression (Gesch et al. 2002; Zaalberg et al. 2010; Berger 2016; Bozzatello et al. 2016). Below we will briefly discuss recent findings in psychosis prevention, and elaborate on the interesting debate on omega-3 fatty acid supplementation in depression.

In schizophrenia, there has been recent attention for omega-3 fatty acids to prevent psychosis in ultra-high risk individuals. A promising study in young adults aged 13 to 25 years with subthreshold psychosis showed that 12-weeks omega-3 fatty acid supplementation reduced progression to psychotic disorder and general psychiatric morbidity over multiple years (Amminger et al. 2010; Amminger et al. 2015). However, the multicenter NEURAPRO study failed to replicate these initial hopeful findings (McGorry et al. 2017). Besides actual lack of a true effect, some other reasons can be thought of for this non-replication, including a ceiling effect caused by a low transition rate due to concurrent psychosocial and antidepressant treatment (62% vs. 10% in the original study); nonstudy omega-3 fatty acid intake; nonadherence (>50%); or subgroup effects.

For depression, in general, both study quality and effect sizes of omega-3 supplementation studies are modest (Bloch and Hannestad 2012). However, compared to studies of other available treatment options including antidepressants, the effects of omega-3 fatty acid supplementation seem to hold up. Because of the ongoing debate on omega-3 fatty acid supplementation for depression, we will describe the results in more detail in order to nuance findings.

Overall, meta-analytic standardized mean differences for omega-3 fatty acids compared to placebo for depression generally range from 0.11 to 0.56 (Appleton et al. 2015). However, interestingly, meta-analysis outcomes seem to depend on

individual study characteristics: larger effects are seen for studies that supplement EPA to patients with major depressive disorder, as opposed to negligible or absent effect in studies that supplement DHA to subjects with only depressive symptoms or as preventive intervention (Martins 2009; Lin et al. 2012; Martins et al. 2012).

A recent Cochrane meta-analysis of omega-3 fatty acid supplementation for depression observed an overall effect size of 0.30 (95%CI = 0.10–0.50) (Appleton et al. 2015). However, the authors conclude that this significant small-to-modest effect size has small clinical significance because the approximate reduction in Hamilton depression rating scale (HDRS)-score of 2.1 points remains under the National Institute for Health and Care Excellence (NICE)-limit of 3 points for clinically meaningful effects. In addition, the authors are critical in their qualification of study quality. For example, studies that did not add a small amount of fish oil to the placebo to mask a possible fishy aftertaste were judged to be at high risk of bias.

Nevertheless, the Cochrane meta-analysis acknowledges that the overall effect size for omega-3 fatty acids is comparable to that of antidepressants (Appleton et al. 2015). The authors described that the only available study that directly compared omega-3 fatty acids and antidepressant showed comparable benefit, but that the quality of the evidence is low. Nevertheless, they also describe that the reported combined meta-analytic effect size of omega-3 fatty acids of 0.30 (95%CI = 0.10–0.50) is comparable to that of antidepressants: 0.32 (95%CI = 0.25–0.40). The CI is more narrow for antidepressants, suggesting that for omega-3 fatty acid the effect size may be either more clinically important or possibly negligible. Based on this data, the authors suggest that the comparable small-to-modest overall effect for both omega-3 fatty acids and antidepressants merely shows the need for other effective treatments. While there obviously is a need for other more effective treatments, given that omega-3 fatty acids are generally thought to have a more beneficial side effect and tolerability profile than antidepressants, these outcomes could also be interpreted in a way suggesting that omega-3 fatty acids may have a role as (add-on) treatment for depression.

Moreover, the Cochrane meta-analysis shows stronger beneficial effects in the subgroup of studies supplementing solely or predominantly EPA, and in studies that did not use the omega-3 fatty acid alpha-linolenic acid (the precursor of EPA and DHA) as placebo (Appleton et al. 2015). We recently corroborated this finding in an a priori specified meta-regression analysis showing a linear dose-response relationship for EPA (Mocking et al. 2016b). In addition, our meta-regression analysis suggests that omega-3 fatty acids are more effective when given in addition to antidepressants, i.e., augmentation/add-on studies (Mocking et al. 2016b). Furthermore, we recently showed a large meta-analytic effect size for omega-3 fatty acid supplementation specifically for women with post-partum depression (Mocking et al. 2017b).

In conclusion, with (I) an overall effect size comparable to that of antidepressants, (II) a side effect profile that is considered to be relatively safe and tolerable, (III) relative low-costs, and (IV) a larger effect size in studies supplementing EPA next to antidepressants, omega-3 fatty acids may hold clinically meaningful potential, especially when prescribing EPA as an augmentation strategy in major depressive disorder. An extra potential advantage is that omega-3 fatty acid supplementation might have a parallel beneficial effect on comorbid (cardiovascular) conditions as well (Mozaffarian and Wu 2011).

This line of thought has not yet been implemented in clinical practice. Guidelines and handbooks on depression often do not even mention omega-3 fatty acids (Sarris et al. 2015). This may have to do with the relatively small sample sizes of the performed studies (total N of the Cochrane meta-analysis = 1438), resulting in relatively wide confidence intervals (Appleton et al. 2015). However, pooled confidence intervals for most meta-analytic outcomes of omega-3 fatty acids for depression (including the Cochrane's) do not cross zero, and while these pooled meta-analytic confidence intervals include negligible effects, they also include relatively large effects (Appleton et al. 2015). Concerns that have been raised of publication bias and distortion due to sponsoring seem at most comparable to that for antidepressants. Nevertheless, the adage *primum non nocere* may withhold clinicians from clinical implementation. Additional evidence could come from larger but well-executed, long-term, clinical trials that (I) supplement EPA in an add-on design and (II) have attention for biochemical and clinical potential side effects, as discussed below and elsewhere (Assies et al. 2011; Assies et al. 2014). These trials may convince clinicians and guideline-makers to implement omega-3 fatty acid supplementation for depression in clinical practice.

Other clinical applications

Next to supplementation to correct alterations, fatty acids could also be used in other ways to help psychiatric patients. A promising alley could be to determine (the pattern of) fatty acid alterations as part of biomarker panels to personalize medicine, e.g., to improve prediction of prognosis or treatment response.

Although most studies focused on finding fatty acid differences between patients and controls and/or how to correct these differences, some studies aimed at using fatty acids as biomarkers to predict clinical outcome. As an example, in the study mentioned earlier in subjects with ultra-high risk to first-episode psychosis, omega-3 fatty acids and nervonic acid concentrations aided in predicting transition into psychosis within 1 year (Clark et al. 2016). In another study, DHA signaling was one of the top biological pathways overrepresented in validated biomarkers

predicting suicidality in samples of women with bipolar disorder, depression, schizoaffective disorder or schizophrenia and men with bipolar disorder (Le-Niculescu et al. 2013; Levey et al. 2016). Furthermore, as described earlier, omega-3 fatty acids and their omega-6 ratio could predict depression onset during interferon-alpha treatment (Lotrich et al. 2013). Moreover, fatty acids have been associated with antidepressant response (Dinan et al. 2009). In our own study (Mocking et al. 2015, 2017a), we recently showed that low DHA and high AA were prospectively associated with non-response of MDD-patients treated with paroxetine for 12 weeks. Finally, we are currently examining to what extent fatty acid patterns can predict recurrence in remitted recurrent depression (Mocking et al. 2016a).

Fatty acids in inborn errors of metabolism

Fatty acids may play an important role in several inborn errors of metabolism. A full review of the different potential roles of fatty acids in these diseases exceeds the scope of this review, while earlier reviews are available (Fekete and Decsi 2010; Gil-Campos and Sanjurjo Crespo 2012; Lohner et al. 2013). In brief, first, several inborn errors of metabolism require a restricted diet (e.g., phenolketonuria and organic acidaemias), potentially leading to fatty acid deficiencies. Indeed, evidence shows reduced omega-3 fatty acid concentrations in these diseases, and suggests beneficial effects of supplementation (Gil-Campos and Sanjurjo Crespo 2012; Lohner et al. 2013). Second, several inborn errors of metabolism distort fatty acid metabolism. For example, peroxisomal disorders such as X-linked adrenoleukodystrophy distort peroxisomal beta-oxidation of long chain fatty acids. This results in accumulation of saturated very-long-chain fatty acids and DHA deficiency (Gil-Campos and Sanjurjo Crespo 2012). Supplementation of a mixture of oleic and erucic acid (Lorenzo's oil) reduces saturated very-long-chain fatty acid concentrations, but clinical effects remain under investigation (Ahmed et al. 2016), as well as the effects of omega-3 fatty acid supplementation. Mitochondrial fatty acid oxidation deficiencies seem to have less influence on omega-3 fatty acid concentrations (Gil-Campos and Sanjurjo Crespo 2012). A third way in which inborn errors of metabolism affect fatty acid concentrations is through increasing oxidative stress (Assies et al. 2014). For example, several mitochondrial disorders may result in increased oxidative stress and thereby increased peroxidation of omega-3 fatty acids (Gardner and Boles 2011). The precise (long-term) clinical consequences of these findings have yet to be further elucidated (Fekete and Decsi 2010; Gil-Campos and Sanjurjo Crespo 2012; Lohner et al. 2013).

Discussion

Integration of findings

Central role of fatty acids

Taken together, evidence for an important role of fatty acid metabolism in the pathogenesis of psychiatric disorders is increasing. Alterations in fatty acids are of etiological interest, because they are essential components of all outer and subcellular cell membranes (Crawford et al. 2013; Assies et al. 2014). This is represented by their widespread associations with other pathophysiological systems including biological stress (HPA-axis and oxidative stress), inflammation, and brain network structure and function.

Epiphenomena, adaptive roles or risk factors

Whether fatty acid alterations represent epiphenomena, adaptive mechanisms or risk factors is certainly more difficult to disentangle. Based on the data presented in this review, several arguments can be made for a causal role. First, diseases with genetic defects in fatty acid metabolism (e.g., X-ALD) have been associated with psychiatric symptoms. Second, correcting fatty acid alterations seems to improve psychiatric symptoms. Third, associations are not only cross-sectional, but also prospective, and have a historical epidemiological and biological rationale. Nevertheless, given the complexity and multitude of factors influencing fatty acid metabolism, epiphenomenal effects cannot be ruled out yet. Psychiatric disorders are often characterized by suboptimal lifestyles, which may have profound impact on fatty acid metabolism. For example, both diet, smoking, and physical inactivity, but also medication may influence fatty acid concentrations and cause the observed alterations, e.g., by increasing oxidative stress (Assies et al. 2014). Nevertheless, these resulting fatty acid alterations may partially mediate detrimental effects of a suboptimal lifestyle on mental health. In Future research we propose studies that could potentially further tease out these intertwined effects.

Weighing the evidence

Which fatty acid and why?

An interesting observation is that while DHA is the fatty acid that is most consistently found in lower concentrations in patients with psychiatric disorders, it is EPA that seems to have more clinical efficacy, particularly in depression. This questions the rationale that low DHA resembles a shortage/deficit that should be corrected by supplementation (Assies et al. 2014). In addition, while DHA is the most abundant fatty acid in the brain, EPA only represents ≤1% of total brain fatty acids

(Bos et al. 2016). In addition, although EPA can be transformed into DHA, evidence suggests EPA is rapidly and extensively ß-oxidized (generating acetyl-CoA) upon entry into the brain (Bazinet and Laye 2014; Chen and Bazinet 2015). Because this process results in little to no extra EPA available in the brain, and the ß-oxidized products are not specific for EPA, this suggests that EPA's efficacy cannot be explained by an effect in the brain, and that EPA is not only a precursor of DHA but that DHA and EPA have distinct roles.

An explanation could be that the effects of supplemented EPA are mainly mediated by peripheral anti-inflammatory actions. EPA, given its multiple double bonds, is prone for enzymatic and non-enzymatic oxidation (Assies et al. 2014). This may be aggravated by the pro-oxidative environment found in psychiatric disorders (Black et al. 2015). Particularly, EPA's eicosanoid oxidation products generally have anti-inflammatory properties (Calder 2006). Given that inflammation is thought to underlie many psychiatric disorders including depression (Kiecolt-Glaser et al. 2015), this could explain why supplemented EPA is more efficacious than DHA. Interestingly, a recent study corroborated this view, by showing that inflammation serves as a positive predictive biomarker for response to omega-3 fatty acid supplementation in depression (Rapaport et al. 2016). In detail, this proof-of-concept study in 155 depressed patients showed that combined inflammation biomarkers (IL-1ra, IL-6, hs-CRP, leptin, adiponectin) could predict response to EPA vs. DHA or placebo. In detail, only patients with high pre-treatment inflammation biomarker concentrations benefited significantly more from EPA supplementation (40% remission) compared to DHA (14% remission) or placebo (25% remission). This suggests that EPA is a promising candidate to reduce the increased inflammation seen in psychiatric disorders.

Role of oxidative stress

The observation that restoring the low DHA concentrations seems to have less therapeutic effect, requires an alternative interpretation of low DHA as a deficit. Although it seems plausible given the historically epidemiological and biological evidence presented in this review, a causal deficiency should result in (clear) improvement after DHA supplementation. Several explanations might clarify this apparent contradiction. First, due to its six double bonds, DHA is even more susceptible to oxidation than EPA. If not already oxidized ex vivo in the supplementation capsules (i.e., becoming rancid), DHA could easily become oxidized after ingestion in vivo, especially given the pro-oxidant state observed in psychiatric disorders (Assies et al. 2014). Although supplementation capsules most often contain tocopherols as antioxidants, these probably do not provide full protection against oxidation (Halliwell 2000; Naviaux 2012; Assies et al. 2014). Resulting oxidative metabolites of DHA are not yet routinely measured and

therefore not completely understood, but may induce negative effects as well (Higdon et al. 2012). This in and ex vivo oxidation of supplemented DHA would hamper effective restoration of central nervous system DHA concentrations (Assies et al. 2014).

As an alternative interpretation, low DHA and DHA-derived lipoxins together with inflammation could be explained as adaptive processes in reaction to increased oxidative stress. Following this interpretation, cells sense increased oxidative stress, and in response lower the DHA content of their membranes, in order to reduce their oxidative stress vulnerability. This way, low membrane DHA content and its neuropsychiatric consequences, can be interpreted as a logical by-product of underlying increases in oxidative stress (Assies et al. 2014), e.g., from mitochondrial dysfunction (Gardner and Boles 2011; Morava and Kozicz 2013). Following this line of thought, it can be expected that "correcting" this adaptive response has no, or even deleterious effects, since additional DHA will be oxidized and not incorporated in the membranes. If this hypothesis is correct, instead, it should be tried to correct the underlying oxidative stress. Although difficult to implement, oxidative stress could be lowered by, e.g., lifestyle improvement including stopping smoking, increasing physical exercise, and limiting excess caloric intake. Indeed, research shows that if oxidative stress can be diminished, fatty acid alterations seem to (partially) recover (Assies et al. 2014). For example, bariatric surgery-induced weight loss reduced lipid peroxidation (Bell et al. 2010).

Nevertheless, to complicate things, reducing inflammation by EPA supplementation could also reduce oxidative stress, thereby allowing for reactive DHA increases that may hypothetically partly explain observed therapeutic effects. In addition, omega-3 fatty acids may have some anti-oxidant effects on their own and so may directly interfere with increased oxidative stress (Giordano and Visioli 2014). The net effect of omega-3 fatty acid supplementation on oxidative stress in different circumstances has therefore yet to be investigated.

Future research

In order to further disentangle the role of fatty acids and their oxygenated derivatives in psychiatric disorder pathophysiology and to optimally exploit their promise for clinical application, several research areas can be further explored. Studies would benefit from a combined pathophysiological and clinical design, in order to make causal inferences on a biological level from randomized controlled trials. A potential focus would be the interplay between oxidative stress and EPA-supplementation in augmentation studies in depression aiming at inflammatory modulation. Detailed measurement of oxidation products using lipidomics in a network systems biology approach, preferably repeatedly during a well-controlled intervention (e.g., lifestyle and/or supplementation), will hopefully

yield meaningful alterations in metabolic patterns. Studying the dynamics of these network patterns could give insight in the underlying mutual connections (Naviaux et al. 2016).

Furthermore, personalizing interventions should receive special attention. It would be very worthwhile to be able to identify subgroups of patients [e.g., based on (patterns of) inflammatory parameters or nutrigenetics (Mutch et al. 2005; Mocking et al. 2013a)] that will benefit from fatty acid supplementation, or to use fatty acids as markers to identify subgroups of patients that will benefit from other interventions, e.g., antidepressants or neurostimulation (given associations of fatty acids with brain network structure and function). We expect that pathophysiologically tailored treatment strategies will increase effect sizes in individual studies and later meta-analyses.

In addition, although possibly less commercially exploitable due to the difficulty of producing a marketable product, interventions aimed at lowering oxidative stress should be studied. For example, a broad lifestyle intervention focusing on diet (among others less omega-6), physical activity, and smoking, with attention for biological and clinical outcomes may hold great promise to benefit a broad range of disease outcomes, including cardiovascular and mental health. This lifestyle intervention would potentially result in a decrease in oxidative stress and increased co-intake of other essential nutrients as Zn, Cu, I, Se, and amino acids. This may have the additional advantage that increased dietary intake of omega-3 fatty acids can likely be incorporated better (Sarris et al. 2015).

In these studies, it would be commendable to pay attention to differences in results according to sex, ethnic group where relevant, and specific ages. For example, although several studies show gender specific alterations in fatty acids and their oxidation products in psychiatric disorders (McNamara et al. 2007; Ramos-Loyo et al. 2013; Colangelo et al. 2017), this factor is not often systematically studied. In addition, more specific results could be seen if fatty acids would be linked to pathophysiological dimensions instead of only disorders, e.g., using the Research Domain Criteria (RDoC) (Insel 2014). In future research, it could also be determined whether fatty acid alterations and their associated biological processes (e.g., HPA-axis, inflammation) (I) are factors that alone can explain psychopathology, (II) should be seen as additive effects that together cause psychopathology, or (III) instead represent various (biological) domains of psychopathology.

A more experimental line of research concerns the quantum-characteristics of fatty acids, particularly DHA. DHA has been proposed to possess unique properties on a quantum level. In detail, the molecular structure of DHA with its unique six double bonds is thought to facilitate quantum tunneling of electrons across the membrane (Crawford et al. 2013), allowing for precise depolarization of membranes with a high DHA content. This may be essential for cells where rapid and precise depolarization of the membrane is crucial for adequate cell functioning, such as neurons and retinal cells.

Thereby, DHA's properties may explain its extreme conservation — i.e., very high concentrations relative to the rest of the body — in the synapse and retina. Moreover, consequently, the development of oxidative metabolism allowing for synthesis of highly unsaturated fatty acid as DHA, has been hypothesized to be a driving facilitator of brain development through evolution (Crawford et al. 2013). The precise neuroscientific and clinical consequences of these exciting ideas have yet to be investigated further.

Conclusion

Although — contrary to some popular belief — omega-3 polyunsaturated fatty acids are certainly no miracle molecules; increasing data indicate a role for fatty acid alterations in the pathophysiology of psychiatric disorders. Together with associated pathophysiological systems — including biological stress (HPA-axis and oxidative stress), inflammation, and brain network structure and function — fatty acid alterations form a complex neurometabolic network that seems to alter the vulnerability for psychiatric disease. Clinically, this neurometabolic network can be positively influenced by lifestyle modification. If this proves to be unfeasible, EPA supplementation may be an effective surrogate in the form of add-on treatment, particularly in depression, possibly due to its anti-inflammatory effects. Several lines of research are currently being explored further, including the use of fatty acids as biomarkers to predict antidepressant efficacy using lipidomics. Ultimately, improved neurometabolic insights could hopefully contribute to a reduction of the large and still growing burden of disease from psychiatric disorders.

Compliance with ethical standards

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