

## Essential fatty acids and mental health

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The biological basis for the major psychiatric disorders is presumed to be a deficit or excess of neurotransmitters or abnormalities in their interactions with their respective receptors or transporters. Accordingly, the vast bulk of biological research, from genetics to psychopharmacology and from the study of signal transduction systems to *in vivo* molecular imaging, has placed the neurotransmitter and its target proteins centre-stage. This belies the fact that the dry weight of the mammalian brain is approximately 80% lipid (the highest of any organ) and also the steady accumulation of data demonstrating the crucial role of lipids, particularly long-chain polyunsaturated fatty acids (LC-PUFAs), in modulating neural function. The essential fatty acids (EFAs) are LC-PUFAs obtained exclusively through diet and they comprise 15–30% of the brain's dry weight. Their effect on neuronal membrane dynamics and therefore on receptor, transporter and neurotransmitter function is profound (see below). Moreover, the well-documented shift in the Western diet away from EFAs (and the omega-3 family in particular) parallels the large rise in all psychiatric disorders seen over the past century. Finally, along with the resurgence of interest in lipid-neuronal membrane interactions, there are now a considerable number of quality randomised controlled trials demonstrating the efficacy of EFAs in a diverse number of psychiatric conditions. (Additional references to those in the reference list are available from the corresponding author on request.)

### FUNCTIONAL BIOCHEMISTRY OF THE ESSENTIAL FATTY ACIDS

The EFAs are divided into two groups, omega-3 ( $\omega$ -3) and omega-6 ( $\omega$ -6) fatty acids, depending on where the first double

bond in the carbon chain occurs. The principal sources of EFAs are oily fish and certain vegetable oils. These are then processed into other long-chain polyunsaturated fatty acids (LC-PUFAs) by elongation and desaturation. The principal central nervous system-related EFAs are eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids (both  $\omega$ -3) and arachidonic acid ( $\omega$ -6). They are important components of phospholipids and cholesterol esters, which are themselves integral to the neuronal cell membrane, especially synaptic and dendritic membranes, but also intracellular membranes such as mitochondria and vesicles. If unavailable, they will be replaced by non-EFAs, changing the behaviour of the phospholipid molecules and affecting the tertiary and quaternary structures of membrane-bound receptors and associated neurotransmitters. The membrane phospholipid bilayer forms the matrix within which membrane proteins, such as receptors and ion channels, are embedded and to which membrane-associated proteins involved in second messenger systems are attached.

Additionally, cell signalling systems are regulated by lipid products, such as diacylglycerols, prostaglandins, leukotrienes, free fatty acids and hydroxy-fatty acids derived from phospholipid membranes. Moreover, EFAs are the precursors of the eicosanoids, a complex group of highly biologically active compounds encompassing the prostanoids (including prostaglandins, thromboxanes and prostacyclins) and leukotrienes. Eicosanoids derived from  $\omega$ -3 EFAs have fewer inflammatory effects than those derived from  $\omega$ -6 EFAs, underpinning the opposing effects that the  $\omega$ -6 EFA families sometimes have (see below). Eicosanoids perform numerous regulatory functions in the brain and throughout the rest of the body, in particular for the regulation of immune and inflammatory responses.

There are now numerous animal studies relating to a wide variety of adverse effects associated with diets low in EFAs. As a converse example, De la Pressa Owens & Innis (1999) demonstrated that in pigs supplemented with EFAs from birth there was a doubling of the major monoamines in the frontal cortex.

### MODERN DIET IS ASSOCIATED WITH DRAMATIC REDUCTIONS IN EFA INTAKE

The modern Western diet has evolved into a meat and saturated fat-rich diet, with falling consumption of fresh vegetables and fish. This has been coupled with a staggering rise in the consumption of seed oils (such as sunflower and soybean), whose polyunsaturated fatty acid content is predominantly  $\omega$ -6, at the expense of  $\omega$ -3, EFAs. The  $\omega$ -6: $\omega$ -3 ratio is estimated to have been 0.4–2.8:1 in Palaeolithic and evolutionary diets (Eaton *et al*, 1998). These models did not even consider seafood consumption, which would bring the ratios even lower. The  $\omega$ -6: $\omega$ -3 ratio is now estimated to have risen to 17:1 in our typical Western diet (Eaton *et al*, 1998). Moreover, wild and free-ranging animals have significantly more  $\omega$ -3 fatty acids in their tissues than do currently produced commercial livestock. An overproduction of pro-thrombotic eicosanoids such as thromboxane, as well as pro-inflammatory leukotrienes and cytokines from a diet over-rich in  $\omega$ -6 EFAs, has resulted and may be contributing to the rise in the incidence of such diseases as atheroma, thrombosis and a variety of inflammatory conditions (Pischon *et al*, 2003). Such a sustained change in diet, as will now be discussed, may also be affecting mental health.

### DIETARY REDUCTIONS IN EFA PARALLEL THE RISE IN PSYCHIATRIC DISORDER

Bearing in mind that fish are the principal source of  $\omega$ -3 EFAs, Hibbeln (1998) reports that the documented 60-fold variation across countries in the annual prevalence of major depression is strongly inversely correlated with national fish consumption. A similar inverse relationship

exists for the prevalence of post-partum depression and fish consumption. In a survey of 3204 adults in Finland, infrequent fish consumption was associated with depressive symptoms in women ( $P < 0.01$ ) and a similar trend, although not statistically significant, was noted in men (Tanskanen *et al*, 2001).

For bipolar affective disorder, Hibbeln's group have demonstrated that prevalence rates rise precipitously below an apparent annual fish intake threshold of approximately 75 lb per person, with prevalence rates of, for example, 0.04% in Taiwan (81.6 lb per person) and 6.5% in Germany (27.6 lb per person), which is a nearly 60-fold difference. The same group did not find a relationship between fish consumption and prevalence rates for schizophrenia.

For suicide, daily fish eating had a positive effect (odds ratio=0.81) in reducing the risk of death from suicide compared with subjects having a non-daily consumption in 17-year follow-up of 256 118 Japanese subjects (Hirayama, 1990). With regard to dementia, in a study of elderly men, estimates of high  $\omega$ -6 fatty acid intake were associated with cognitive impairment and, conversely, fish consumption was inversely associated with cognitive impairment, the significance in both cases persisting after controlling for confounders (Kalmijn *et al*, 1997).

## LOWER EFA LEVELS IN PSYCHIATRIC ILLNESS

In one of several consistent studies on depression, Peet *et al* (1998) demonstrated that total  $\omega$ -3 fatty acid levels were decreased (5.39 mg/100 mg phospholipid compared with 9.04 mg/100 mg phospholipid for controls;  $P=0.02$ ), DHA especially (1.61 mg/100 mg phospholipid compared with 2.50 mg/100 mg phospholipid;  $P=0.04$ ), on red blood cell membranes in patients with major depressive disorder ( $n=15$ ) compared with normal controls. The same group reported similar data in schizophrenia (Peet *et al*, 1995). We have demonstrated lowered plasma levels of cholesterol (Garland *et al*, 2000) and EFA (details available from the author upon request) in populations of patients with self-harm. There are now also considerable data supporting plasma EFA deficiency in attention-deficit hyperactivity disorder (e.g. Richardson & Puri, 2000) and dementia (Tully *et al*, 2003).

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## SUPPLEMENTATION IN CLINICAL POPULATIONS: THE EVIDENCE

All but one of the four EFA supplementation randomised controlled trials (RCTs) in depression report significant improvement with supplementation. The largest of these studies (Peet & Horrobin, 2001) involved 70 patients, who remained on adequate standard therapy throughout the trial; at optimum dosage, there was a three-fold treatment-to-placebo effect, using a 50% reduction in Hamilton Rating Scale for Depression (HRSD) scores as evidence of clinical response. For bipolar affective disorder, in a 4-month RCT (Stoll *et al*, 1999) of high-dose  $\omega$ -3 fatty acids, patients ( $n=30$ ) had longer periods of remission in the  $\omega$ -3-treated group ( $P < 0.02$ ) and significant improvements in depressive, but not manic, symptomatology were observed, suggesting that depressive symptoms may be more responsive than manic symptoms to supplementation. For schizophrenia, the evidence is less equivocal. As reviewed recently (Joy *et al*, 2003), only one of five small studies demonstrated substantial clinical improvement, and larger studies are clearly needed. There are only limited and inconsistent data on supplementation in attention-deficit hyperactivity disorder and dementia, although there are striking data on Huntington's chorea ( $n=17$  patients) where treatment was associated not just with stabilisation but with reversal of clinical signs (Vaddadi *et al*, 2002).

There are various, generally positive data in psychopathic/aggressive/impulsive populations. In a carefully conducted RCT in young adult prisoners, a combination of  $\omega$ -6 and  $\omega$ -3 EFAs reduced offences by 26.3%, increasing to 35.1% if on supplementation for a minimum of 2 weeks ( $P < 0.01$ ; Gesch *et al*, 2002). The greatest reduction occurred for the most serious incidents including violence. As reviewed elsewhere (Hallahan & Garland, 2004), EFAs have proved beneficial also in stabilising aggression in a normal population of young university students at exam time

( $n=41$ ) compared with randomised controls and in a population ( $n=30$ ) of patients with borderline personality disorder treated for 8 weeks. Finally, we are shortly to conclude recruitment into an RCT of EFAs in a population of patients with self-harm.

## CONCLUSIONS

There is no doubt that cerebral lipids, and EFA-derived LC-PUFAs in particular, have significant direct and indirect actions on cerebral function. Not only does the lipid composition of neural membranes affect the function of their embedded proteins, but also many LC-PUFAs are converted to neurally active substances. There is good evidence that psychiatric illness is associated with depletion of EFAs and, crucially, that supplementation can result in clinical amelioration. As well as challenging traditional views of aetiology and therapeutics in psychiatry, the clinical trial data may herald a simple, safe and effective adjunct to our standard treatments for many disabling conditions.

## DECLARATION OF INTEREST

None.

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