

## Effects of PUFA supplementation evidenced by brain imaging

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**Abstract:** This paper describes how the effects of PUFA supplementation can be indexed by neuroimaging. The role of structural magnetic resonance imaging studies are detailed in respect of testing a brain (lipid) hypothesis and in respect of using a gold-standard image registration technique. The role of magnetic resonance spectroscopy of the brain is considered with respect to a recent advance in the analysis of 31-phosphorus neurospectroscopy data that enables motion-restricted membrane phospholipids to be quantified.

**Key words:** image registration, membrane phospholipids, MRI, neurospectroscopy, PUFA supplementation

In this paper, the effects of polyunsaturated fatty acid (PUFA) supplementation on the brain, as evidenced by brain imaging, will be considered in respect of structural magnetic resonance imaging (MRI) and a recent advance in 31-phosphorus neurospectroscopy.

### Structural MRI

#### *Testing a brain (lipid) hypothesis*

It is instructive to review a brain (lipid) hypothesis put forward by the late Professor David F. Horrobin (6<sup>th</sup> October 1939 – 1<sup>st</sup> April 2003) regarding the aetiology and potential treatment of post-viral fatigue syndrome, which nowadays would be subsumed under the heading of myalgic encephalomyelitis (or chronic fatigue syndrome). Horrobin suggested that abnormalities in fatty acids played a key role in the pathophysiology of this disorder (Horrobin, 1990). Indeed, a randomized, double-blind, placebo-controlled three-month trial of fatty acids (including gamma-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid and linoleic acid) by Behan, Behan and Horrobin, in 63 adults suffering from post-viral fatigue syndrome, gave positive results in favour of the PUFA

supplementation (Behan *et al.*, 1990). Unfortunately structural brain MRI changes were not assessed during this randomized, double-blind, placebo-controlled trial, but subsequently a pilot study has indicated that eicosapentaenoic acid-rich PUFA supplementation in myalgic encephalomyelitis may be associated with beneficial brain changes, with a reduction in the size of the lateral ventricles (Puri *et al.*, 2004). The question of whether, at baseline, myalgic encephalomyelitis is associated with changes in brain structure compared with unaffected age- and gender-matched controls has been addressed by a number of studies; the most recent and largest voxel-based morphometry study of 26 patients and 26 matched controls has shown that this disease appears to be associated with reduced grey matter in the occipital lobes, right angular gyrus and left parahippocampal gyrus, and reduced white matter in the left occipital lobe (Puri *et al.*, 2011).

#### *Gold-standard registration*

In Euclidean three-space ( $E^3$ ), modal rigid body registration is clearly associated with six parameters (three translational and three rotational degrees

of freedom). There are two steps involved in the registration, namely the registration itself and transformation via re-sampling (one image being transformed according to the estimated parameters) (Friston, 1997; Puri, 2004). The re-sampling requires image interpolation, and here there are three main methods available: simple interpolation (nearest neighbour – zero-order hold or trilinear – first-order hold); generalized interpolation (B-spline or o-Mom (maximal-order interpolation of minimal support) basis functions); and windowed sinc interpolation (Friston, 1997, 2007). It is the last of these which is the gold-standard for rigid body transformation, being a method involving convolving the image with a sinc function centred on a point to be re-sampled, and that gives results relatively close to a Fourier interpolation in  $\mathbb{R}^3$  (Puri, 2004; Friston, 2007). Since the sinc function tends to infinity, to reduce the computational expense of the associated calculations it is appropriate to truncate the function by using a Hanning window. Also, only a limited number of nearest neighbours are usually sampled, rather than every image voxel. Using this method, several studies have shown that supplementation with the semi-synthetic omega-3 PUFA deriv-

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ative ethyl-eicosapentaenoic acid is associated with lateral ventricular shrinkage in disorders as diverse as schizophrenia, treatment-resistant depression and Huntington's chorea (or Huntington's disease) (Puri *et al.*, 2000, 2001, 2002).

### 31-phosphorus neurospectroscopy

The way in which brain cell membrane phospholipid metabolism changes in association with PUFA supplementation is of academic and clinical importance. During the last decade of the twentieth century, the main method used non-invasively to study human brain cell membrane phospholipids *in vivo* was via 31-phosphorus magnetic resonance spectroscopy and the quantification of membrane phospholipid metabolism carried out through the measurement of phosphomonoesters, which index membrane phospholipid anabolism, and phosphodiester, which index membrane phospholipid catabolism. Unfortunately, this methodology only provides an indirect measure of membrane phospholipids.

It is now possible non-invasively to study brain cell membrane motion-restricted phospholipids directly, in spite of the large chemical-shift anisotropy of the 31-phosphorus-containing moieties that are confined to a relatively rigid (in nuclear magnetic resonance terms) membranous structure (Puri *et al.*, 2008)). The method involves analysis of the broad spectral component which underlies the narrow peaks which are more usually the focus of attention of 31-phosphorus neurospectroscopy data analysis. Indeed, it is interesting to note that in the past this very same broad component has actually been considered by some to be an unwanted spectral component which should be removed (Estilaei *et al.*, 2001). The broad component integral can be derived using the convolution difference resolution enhancement method from image-selected *in vivo* spectroscopy sequence spectra (Estilaei *et al.*, 2001; Roth and Kimber, 1982). The required broad component is given by the difference between the measured raw signal intensity,  $S$ , and the term  $S(1 - f \cdot \exp(-\pi L t))$ , where  $f$  is the convolution-difference factor (that is, the fraction of the broad component contributing to the acquired signal at a given echo time),  $L$  is an

exponential filter, and  $t$  represents time. The corresponding integral can be obtained by fitting the spectrum to multiple Gaussian lines, minimizing residuals, and summing over all Gaussian-line integrals. Estilaei and colleagues obtained  $T_2$ -magnetization decay curves by plotting the broad component area as a function of the echo time (Estilaei *et al.*, 2001). A suitable fit is given by  $S(t) = S_l e^{-C} + S_s e^{-D}$ , where  $S(t)$  is the total magnetization at  $t$ , and  $S_l$  and  $S_s$  are the respective equilibrium magnetizations for the slow and fast decaying components,  $C = (\text{echo time})/(\text{spin-spin relaxation time for the long } T_2 \text{ component})$ , and  $D = (\text{echo time})/(\text{spin-spin relaxation time for the short } T_2 \text{ component})$ . With spin-spin relaxation time for the long  $T_2$  component ( $T_{2l}$ ) » spin-spin relaxation time for the short  $T_2$  component ( $T_{2s}$ ) (Kilby *et al.*, 1990), and with echo time ( $TE \approx T_{2l}$ ), it can be demonstrated that  $\ln S(TE) = \ln(S_l + S_s) - S_s TE/(T_{2s}(S_l + S_s))$ , while with  $TE \approx T_{2s}$ , the right-hand side of the last equation becomes approximately  $\ln S_l - TE/T_{2l}$  (Estilaei *et al.*, 2001). The required corresponding fitting can then be simply carried out using linear registration.

Our group have analyzed the broad component in two different groups of patients with schizophrenia, one group of whom had committed serious and dangerous acts of violence while psychotic (including homicide) and the other group of whom had no forensic history and were suffering predominantly from negative symptoms, but so far we have been unable to find evidence consistent with the lipid membrane hypothesis of schizophrenia (Puri *et al.*, 2008).

Clearly this new methodology should be used in future studies of PUFA supplementation.

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