Does omega-3 fatty acid supplementation enhance neural efficiency? A review of the literature

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Abstract

Objective: While the cardiovascular, anti-inflammatory, and mood benefits of omega-3 supplementation containing long chain fatty acids (LCPUFA) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are manifest, there is no scientific consensus regarding their effects on neurocognitive functioning. This review aimed to examine the current literature on LCPUFAs by assessing their effects on cognition, neural functioning and metabolic activity. In order to view these findings together, the principle of neural efficiency as established by Richard Haier (“smart brains work less hard”) was extended to apply to the neurocognitive effects of omega-3 supplementation.

Methods: We reviewed multiple databases from 2000 up till 2013 using a systematic approach, and focused our search to papers employing both neurophysiological techniques and cognitive measures.

Results: Eight studies satisfied the criteria for consideration. We established that studies using brain imaging techniques show consistent changes in neurochemical substances, brain electrical activity, cerebral metabolic activity and brain oxygenation following omega-3 supplementation.

Conclusions: We conclude that, where comparison is available, an increase in EPA intake is more advantageous than DHA in reducing “brain effort” relative to cognitive performance.

Keywords: omega-3, polyunsaturated fatty acids, docosahexaenoic acid, eicosapentaenoic acid, cognition, electrophysiology, neural efficiency
CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.
Introduction

After the adipose tissue, the brain is the organ containing the highest amount of lipids. Indeed, thirty to sixty percent of neural tissue is lipid based, among which are cholesterol, phospholipids, and sphingolipids, all containing long chain polyunsaturated fatty acids (LCPUFA) including docosahexaenoic (DHA), arachidonic (AA), and in minor part (approximately 1%) eicosapentaenoic acid (EPA) (de la Presa Owens and Innis, 1999, Sinclair et al., 2007, Tassoni et al., 2011).

Although both EPA and DHA are cross brain membranes with equal ease, cerebral and retinal DHA levels outweigh EPA several hundred-fold (Arterburn et al., 2006). Chen and colleagues (Chen et al., 2009) showed that EPA is more vulnerable than DHA to β-oxidation and degradation, and hypothesized that this could be one of the reasons that EPA is present in the brain in very low quantities.

DHA is not only abundant in the phospholipid bilayer of all cells including neurons, glial and endothelial cells (Lauritzen et al., 2001) but also regulates the activity of ion pumps and ion channels situated on the membrane (Mondazzi, 2007). As shown in Turner et al.’s cell study (Turner et al., 2003), microsomal phospholipid DHA levels correlate positively with the sodium-potassium pump (NA+/K+-ATPase) activity in the brain of mammals and birds. Since the NA+/K+-ATPase activity helps to maintain a low extracellular sodium concentrations and higher intracellular potassium level, and facilitates signal transduction, generation and transfer of electrical signals in the brain, an increase in cortical DHA levels is likely to assist brain activity. Furthermore, DHA oversees the release and formation of neurotransmitter vesicles in the synaptic
membrane, and the binding between neurotransmitters such as glutamate, dopamine, acetylcholine and serotonin (Kidd, 2007, Chalon, 2006). A change in the production or availability of neurotransmitters in the synaptic cleft is likely to affect neural activity, and eventually cognitive performance.

Although the biological mechanisms associated with omega-3 supplementation are still unclear, previous studies have suggested that the positive action of DHA and EPA on the brain is mediated by their beneficial effects on a range of anti-inflammatory processes facilitating vasodilation (e.g. increased production in nitric oxide, NO) (Calder, 2006; Pifferi et al., 2005) (Robinson, Ijioma, & Harris, 2010) and neuroprotection (increased production of brain-derived neurotrophic factor, BDNF) (Jiang, Shi, Wang, & Yang, 2009b). These processes result from the effects of EPA on the production and release of anti-thrombotic anti-aggregatory eicosanoids such as thromboxanes and prostaglandins (Calder, 2006, Raz and Gabis, 2009).

A result of the anti-thrombotic, anti-aggregatory properties of omega-3 fatty acids, and their regulation of the vascular tone via the increase in nitric oxide production may lead to a rise in cerebral blood perfusion (reviewed in Sinn, 2008). For example, a magnetic resonance spectroscopy study on a mouse model of Alzheimer’s dementia fed with chow containing 0.5% of DHA for 12 months, showed a decrease in cerebral blood volume relative to brain volume (Hooijmans et al., 2007), possibly indicating an increase in vascular tone.

Knowledge of the role of EPA and DHA in neurocognition is limited. Indeed, although the cognitive benefits of LCPUFAs in particular in the visuo-spatial cognitive domain are well-established, the findings from clinical trials conducted in middle aged and
older adults are inconsistent (Stough et al., 2011, Van de Rest et al., 2008, Dangour et al., 2010). However, it is important to emphasize that the comparison of cognitive findings in animal studies and human clinical trials is often compromised by the great variation in study design, type and dosage of fatty acid supplementation (e.g. different EPA:DHA ratio), participant populations, and techniques used to investigate behavioural and neural functioning.

The working hypothesis of this review is that omega-3 supplementation improves both behavioural performance and the corresponding brain measures. In order to test this hypothesis we adopted an integrative approach simultaneously assessing changes in cognition and neural functioning/metabolic activity. The theory of neural efficiency provides a potential means of viewing behavioural and neural changes together. This theory was first suggested by Haier and colleagues (Haier et al., 1988) to explain the inverse relationship between glucose metabolic activity measured with positron emission tomography (PET), a measure of fluid intelligence (Raven’s Advanced Progressive Matrices – APM (Raven et al., 1998)) and behavioural performance during a complex task (Tetris, (Haier et al., 1992)) in a group of young adults aged 18 to 30. Based on these findings, Haier and colleagues hypothesised that brains of individuals with higher intellectual quotient (IQ) may require less energy resources when performing higher order cognitive tasks than those of individuals with average IQ.

In this review Haier et al.’s theory has been extended to the within-subject investigation of the neurocognitive effects of omega-3 supplements. We predicted that an omega-3 supplementation that increases neural efficiency would be one that
shows a relative increase in cognitive performance with a relative reduction in neural activity or metabolic expenditure. By contrast, a reduction in neural efficiency would involve a relative increase in measures of neural activation compared with changes in cognitive performance on the same task.

Thus, the purpose of this review is to summarize the current literature on the effects of omega-3 supplementation on neurocognition. The extension of the theory of neural efficiency is applied to integrate cognitive and brain function measures to help determine whether omega-3 supplementation containing LCPUFAs improves neurocognitive functioning. Although activity of individual neurons cannot be measured \textit{in vivo} in a human sample (with few exceptions), there are a number of electrophysiological techniques that enable researchers to explore brain electrical activity, cerebral glucose metabolism, and functional activation. The techniques included in this review are electroencephalography (EEG), multifocal visual evoked potentials (mfVEP), functional magnetic resonance imaging (fMRI), near infrared spectroscopy (NIRS), and proton magnetic resonance spectroscopy (\textsuperscript{1}H-MRS).

\textbf{Database search}

Scopus (all databases), PubMed, the Cochrane Library, CINAHL, Gale, Google Scholar and Science Direct were used to search for the terms: “\textit{brain imaging}” AND “\textit{omega-3 fatty acids}” AND “\textit{polyunsaturated fatty acids}” AND “\textit{fish oil}” AND “\textit{brain}” occurring anywhere in the article. These search engines were chosen because of their well-established accuracy and exhaustive search across multidisciplinary fields such as psychology, nutrition, biochemistry and medicine (Falagas et al., 2008).
The search was limited to human research papers published in the last 13 years because brain imaging techniques have only recently been developed, and data acquisition and interpretation are constantly evolving. We retrieved 8 studies (see Table 1). Only studies including at least one behavioural measure were reviewed.

Furthermore, studies including populations with neurological, psychiatric, and cardiovascular diseases, as well as pregnant and lactating mothers, were excluded. There are two reasons for this approach. First, omega-3 PUFAs affect a range of neurochemical mechanisms and cardiovascular parameters. As a result, the presence of a neurological or cardiovascular disorder may influence the cognitive and neural effects of an omega-3 rich supplementation. Second, during pregnancy and lactation, a number of physiological changes take place, and the demands for omega-3 fatty acids are greater in pregnant women than in non-pregnant women. This physiological need could distort the interpretation of the effectiveness of omega-3 supplementation against cohorts of the same age (non-pregnant).

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Table 1 here

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Neuroscientific Methods

**EEG/mfVEP**

This section pertains to the use of electroencephalographic (EEG) and visual evoked potential (VEP) techniques in omega-3 fatty acid studies. Specific analysis of the frequency composition of the EEG during the performance of cognitive tasks allows researchers to investigate the relative contribution of brain regions and the extent to which pharmacological interventions may alter the neural activity associated with the performance of these tasks (Klimesch, 1999, Macpherson et al., 2012). Visual acuity can be measured by sweep VEPs, which involves the presentation of a counterphasing visual pattern with gradually varying spatial frequency (Skoczenski and Norcia, 1999). An alternative approach to analyse VEP data is by exploring the nonlinearities of early visual responses by using nonlinear multifocal VEP (mfVEPs). Nonlinearities generated by inefficient recovery from stimulation show characteristics mimicking primate magnocellular (M) and parvocellular (P) physiology (Klistorner et al., 1997, Sutherland and Crewther, 2010, Jackson et al., In press).

In the placebo controlled, double-blind study by Fontani et al. (2005), participants underwent EEG and electromyographic (EMG) investigations after EPA supplementation (Fontani et al., 2005). While EMG data did not differ across supplementations, EEG measurements revealed an increase in theta-2 band frequency (6-7Hz), and a decrease in alpha (8-12Hz) and beta (12-30Hz) band waves during the Go/No-Go and sustained attention tasks. Interestingly, Klimesch’s review (Klimesch, 1999) on EEG and cognitive functions indicates “a large increase
in theta power (synchronisation), but a large decrease in alpha power (desynchronisation) reflect good cognitive and memory performance…” (p. 190). In line with Klimesch’s interpretation, Fontani and colleagues (Fontani et al., 2005) argued that, since EPA-rich supplementation reduced the alpha wave to theta wave ratio and improved cognitive performance, EPA may have induced a state of neural efficiency whereby the brain activates less areas to perform to the same or better standard than before supplementation.

Similar electrophysiological findings were found by Sumich and colleagues (Sumich et al., 2009) in their resting state EEG study in a population of adolescents with attention deficit hyperactivity disorder (ADHD). The authors showed that erythrocyte DHA levels were the best positive predictors of alpha waves, while theta values were positively predicted by EPA levels in erythrocytes (Sumich et al., 2009). Interestingly, both Fontani and colleagues (Fontani et al., 2005a) and Sumich and colleagues (Sumich et al., 2009) reported a positive relationship between EPA and lower waveband frequencies (theta), and between DHA and higher waveband frequencies (alpha and beta). This finding confirms a differential effect of EPA and DHA on neuronal excitability. It also suggests that despite the absence of a manifest role of EPA in the structure and functionality of the brain, an EPA-rich supplementation exerts a beneficial effect on brain performance. However, it is important to remember that since Sumich and colleagues’ sample (Sumich et al., 2009) comprised adolescent with ADHD symptoms, the findings of this study may not reflect the effects of omega-3 PUFAs in healthy adults.
Our recent mfVEP crossover study (Bauer et al., 2011) found that a 30-day EPA-rich supplementation significantly altered magnocellular-generated responses of the first and second order kernel slice (Klistorner et al., 1997). At high stimulus contrast, the N1 and P1 amplitudes of M-related responses were reduced after EPA-rich supplementation compared with measurements at No Diet. The reduction in visual amplitudes suggested a more rapid recovery of neurons in the M-pathway following EPA-rich supplementation. These electrophysiological changes were accompanied by a reduction in mental processing times following EPA-rich supplementation. Two factors were taken into consideration: (1) the EPA-rich supplementation significantly reduced the amplitudes of magnocellular, but not of parvocellular-generated non-linearities of the same group of individuals, (2) the magnocellular pathway anatomically projects to cytochrome oxidase-rich, highly metabolically active areas of the primary and secondary visual cortex (reviewed; Nassi and Callaway, 2007). Thus, it was concluded that the faster visual neural recovery observed in this study under high contrast conditions was the result of alteration in the energy supply for peak metabolic activity.

A limitation of this study is that the 4-week omega-3 supplementation periods used in this crossover study may have detected the immediate visual benefits of the EPA-rich supplementation, but may have not been sufficiently long to measure the visual benefits of the DHA which is incorporated into phospholipid membranes more slowly (Masson, Latini, Tacconi, & Bernasconi, 2007).

Despite these promising results, the positive effects of EPA on brain functioning are still controversial, given that Paajanen et al. (Paajanen, 2007) did not find any
significant effect of a 45-day EPA-rich supplementation on visual evoked potential (VEP) latencies and VEP amplitudes, and cognitive performance on a continuous performance task. However they were not tapping into the nonlinear temporal structure possible with some forms of multifocal VEP (Bauer et al., 2011).

In conclusion, both Fontani et al.’s and our mfVEP studies (Fontani et al., 2005, Fontani et al., 2009, Bauer et al., 2011) demonstrated that a 4-week EPA-rich supplementation modifies cortical activity and improves cognitive performance. Based on Haier et al.’s definition of neural efficiency which states that “smart brains work less”, this finding could be construed as EPA-rich supplementation resulting in an increase in neural efficiency.

**fMRI**

The fMRI signal modelling is based on the assumption that neural activity is coupled with increases and decreases in the concentration of arterial oxygenated haemoglobin, and that these variations alter the blood paramagnetic properties. Since MRI equipment has the capacity to detect changes in magnetic resonance, the fMRI signal constitutes an indirect measure of neural activity (Arthurs and Boniface, 2002).

The only published functional MRI study in the omega-3 research field has shown that an 8-week DHA-supplementation leads to an increase in blood-oxygen-level dependent (BOLD) functional magnetic resonance activation in dorsolateral prefrontal areas, and a decrease in signal in the left middle frontal gyrus, temporal and occipital areas in healthy children during a visual sustained attention task.
(McNamara et al., 2010). Although the authors did not explicitly expect any cognitive improvement it is noteworthy that no behavioural improvement was observed. Taken together, these results may suggest that DHA supplementation alters task-specific networks of activation. Furthermore, they provide preliminary evidence for a role of omega-3 fatty acids in frontal brain region functioning, possibly due to the high DHA storage in frontal cortex (Umhau et al., 2009, McNamara, 2010).

It is important to mention that factors affecting magnetic resonance such as blood flow volume, blood flow velocity, and levels of arterial oxygenation may also alter the fMRI signal. This signal variation could erroneously be interpreted as enhanced neural activity, and lead to erroneous conclusions. For this reason, McNamara and colleagues’ results (McNamara et al., 2010) can be viewed in two ways. The variation in the BOLD response could be due to 1) direct changes in neural function and/or 2) in changes in blood perfusion or levels of oxygenated haemoglobin induced by omega-3 PUFAs during performance of a cognitive task.

From a neural efficiency viewpoint, the increase in functional activation and the unchanged cognitive performance during a continuous attention task following DHA-rich supplementation may indicate that participants needed to work harder to achieve the same level of cognitive performance as prior to supplementation. In conclusion, in McNamara et al.’s fMRI study, a 12-week DHA-rich supplementation did not improve neural efficiency. However, as the sample comprised young children, the findings of this study may not directly reflect the effects of DHA supplementation in healthy adults.
Proton magnetic resonance spectroscopy (\(^1\)H-MRS) utilizing a magnetic resonance imaging (MRI) scanner enables researchers to measure concentrations of brain metabolites such as N-acetyl aspartate (NAA), creatine (Cr), choline (Cho) and myo-inositol (MI) in both white and grey matter (Stanley, 2002). NAA is used as a marker of neuronal and axonal integrity (Stanley, 2002). Equally important is Cr which is related to energy metabolism and whose levels are known to increase during brain development (Soares and Law, 2009; Duarte et al., 2012). While concentrations of NAA and Cr are reduced in neurologic diseases (Soares and Law, 2009), MI and Cho levels correlate positively with age and increase following brain injury (Duarte et al., 2012).

To date only one omega-3 study collected \(^1\)H-MRS data in combination with behavioural measures. McNamara and colleagues (Paajanen, 2007)'s observational study found that erythrocyte DHA levels correlated positively with MI concentrations in the ACC of healthy boys aged 8-10 years. Further, baseline erythrocyte EPA levels positively with NAA, Cr, MI and Cho. Interestingly, children with low erythrocyte DHA levels exhibited lower concentrations of NAA, Cr, MI and Cho than children with high erythrocyte DHA levels. In addition to this, the low DHA group worked more slowly than the high DHA group on a continuous attention task. However, while erythrocyte DHA levels correlated negatively with reaction times, EPA levels did not correlate with cognitive measures.

These findings suggest that DHA levels are the best positive predictors of neurochemical functioning in children. One could also hypothesize that the positive
correlation between MI levels and erythrocyte DHA levels indicates that DHA contributes to the neurodevelopment of school-aged children. Equally remarkable is the positive correlation between peripheral EPA levels and NAA and Cr which suggests that EPA is particularly beneficial to neuronal functioning and cerebral glucose metabolism.

More importantly, the faster cognitive processing speed coupled with higher concentrations in NAA and Cr metabolites in the high erythrocyte DHA group could be associated with of a mechanism of improved neural efficiency. It is however unknown whether the authors attempted to split the population in high and low erythrocyte EPA groups, and if so, if they found any differences in cognitive reaction times and brain metabolites between high DHA and high EPA groups. Also, one may argue that other variables such as gender, health status or parent’s socio-economic status, which are known to impact on brain development, could have impacted on McNamara et al.’s finding. Furthermore, one must highlight that since the nervous system of children is still developing, the neurochemical effects of DHA in this population may not reflect those in a population with a mature central nervous system.

McNamara et al.’s findings regarding the correlation between EPA and NAA levels are in agreement with those of a previous ¹H-MRS study by Frangou and colleagues in adults with bipolar disorder (Frangou et al., 2007). This study reported that levels of NAA in temporal regions increased after a 12-week EPA-rich supplementation, when compared to a placebo group taking paraffin oil. The authors mentioned that there was no improvement in clinical symptoms after the 12-week supplementation period. However, since all participants were on a lithium medication before starting
the supplementation, their symptomatology was already strictly monitored, and therefore no further improvement was expected. From the viewpoint of the theory of neural efficiency, a limitation of Frangou et al.’s study is the absence of a cognitive assessment prior and following the omega-3 supplementation, which would have allowed researchers to determine if the increase in NAA was associated with an improvement in cognitive performance. Since this study was conducted in a population suffering from bipolar disorder, these results may not apply to a non-clinical population. Further, the researchers did not compare the effects of a DHA and EPA supplementation.

In summary, $^1$H-MRS is a potentially valuable research tool to detect changes in the neurochemical profile following omega-3 supplementation. Current $^1$HMRS findings suggest that both EPA and DHA affect the neurochemical functioning. However, there is no evidence of the relationship between cognitive performance and neurochemical functioning following omega-3 supplementation.

**NIRS**

Near-infrared Spectroscopy (NIRS) estimates the fluctuations in oxygen levels during cognitive performance by measuring blood haemoglobin levels in the cortical tissue. Specifically, the amount of light absorbed by the chromophores oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) helps determine the levels of oxy-Hb and deoxy-Hb (Fallgatter and Strik, 1997).

Studies by Hamazaki (Hamazaki-Fujita et al., 2011) and Jackson and colleagues (Jackson et al., 2012a, Jackson et al., 2012b) used NIRS to determine cortical blood
Jackson et al. (Jackson et al., 2012b; Jackson et al., 2012c) investigated the effects of omega-3 PUFAs on levels of oxy-Hb, deoxy-Hb, and the sum of oxy-Hb and deoxy-Hb (Total-Hb). Total-Hb was included in these analyses because a previous study had established that total oxygenation levels correlated positively with cerebral blood volume and cerebral blood flow velocity (Villringer & Chance, 1997). In contrast to Jackson et al.’s studies (2012), Hamazaki and colleagues (Hamazaki-Fujita et al., 2011) explored the relationship between omega-3 serum levels, the tissue haemoglobin index (equal to deoxy-Hb divided by oxy-Hb), and accuracy on an arithmetic task.

Jackson and colleagues (Jackson et al., 2012a) found an increase in total Hb and oxy-Hb in the prefrontal cortex during two attentional and executive tasks (Stroop, peg-and-ball task) and a working memory test (3-back) following a DHA-rich supplementation compared to an EPA-rich supplementation. A reduction in reaction times on the Stroop task was found following the 12-week DHA-rich supplementation period, however given the number of tasks administered and the lack of statistical significance after correcting for multiple comparisons, the authors concluded that there was no substantial evidence of the beneficial effects of the DHA-rich supplementation on cognition (Jackson et al., 2012a).

Similar conclusions were drawn in a later study by the same author (Jackson et al., 2012c) in which, prior to multiple comparison corrections, an improvement in reaction times on a complex processing time task and a rapid visual processing task was found after administration of a high DHA formula and a low DHA formula. Furthermore, in this second study, the authors showed a DHA-induced increase in total Hb and oxyhaemoglobin levels. Since this increase was stronger with a high
DHA dose than with a low DHA dose, it was concluded that the increase in total and oxyhaemoglobin levels may be dose dependent.

Jackson et al. (Jackson et al., 2012b; Jackson et al., 2012c) interpreted their results by highlighting that the increase in oxyhemoglobin could be due to the beneficial effect of DHA on endothelial functioning and the production of nitric oxide, which makes the endothelial walls less rigid, resulting in vasodilation (Cottin et al., 2011; Hooijmans et al., 2007). Similar findings were found in Tsukada and colleagues (Tsukada, Kakiuchi, Fukumoto, Nishiyama, & Koga, 2000) who showed that a 4-week supplementation period with 150 mg/kg/d of DHA improved significantly the cerebral blood flow response to a tactile stimulation in older monkeys, when compared to a group of young monkeys. Since Tsukada and colleagues (Tsukada et al., 2000) did not observe an increase in oxygen consumption, they argued that the increase in cerebral blood flow may be related to an increase in the production or availability of neurotransmitters, in particular acetylcholine, which modulate the neuronal response.

By contrast, Hamazaki-Fujita and colleagues (2011) found a positive correlation between EPA serum levels and the haemoglobin index in the frontal cortex. Furthermore, there was a positive correlation between the number of correct calculations on the Uchida–Kraepelin Performance arithmetic task, and the serum EPA and DHA levels respectively. In agreement with Hamazaki-Fujita and colleagues (Hamazaki-Fujita et al., 2011), previous studies suggested that EPA plays a more manifest role than DHA in promoting the production of anti-thrombotic and anti-aggregatory agents that are likely to increase cerebral blood flow (Sinn & Howe, 2008; Tassoni et al., 2011). Also, studies on the Inuit’s diet showed that the
high levels of EPA in their foods was associated with a higher risk in haemorrhagic, rather than ischemic stroke, which suggests that EPA increases bleeding time and possibly cerebral blood flow (Middaugh, 1990).

An additional way to explain the divergences in findings between these two studies is by highlighting the differences in study design. Jackson and colleagues’ studies (Jackson et al., 2012b; Jackson et al., 2012c) temporarily modified DHA and EPA levels in the human organism, while Hamazaki-Fujita et al. (Hamazaki-Fujita et al., 2011) explored the relationship between cerebral oxygenation and cognitive performance, without inducing any physiological or neurochemical changes. Jackson et al.’s DHA-rich supplementation-related findings (Jackson et al., 2012b; Jackson et al., 2012c) may be due to the initial increase in DHA storage in neural membranes and the facilitation of neurovascular coupling. However, the question as to whether this increase in oxygenation is temporary, and whether cerebral oxygenation stops increasing after a supplementation period longer than 12 weeks is unknown.

In conclusion, it is still unclear whether the cerebral blood flow response is enhanced by an increase in EPA or DHA intake, and whether enhanced cerebral flow response leads to an improvement in cognitive performance. The increase in neural tissue oxygenation observed after a DHA-rich supplementation (Jackson et al., 2012b; Jackson et al., 2012c) during high-order cognitive tasks without a concomitant behavioural improvement does not support the concept of increased neural efficiency for DHA. Although Hamazaki-Fujita and colleagues’ observational study (Hamazaki-Fujita et al., 2011) suggests that an increase in EPA intake may enhance cognitive performance, but this was correlational rather than as a result of a period of supplementation.
Does omega-3 fatty acid supplementation enhance neural efficiency?

This review aimed to explore the multi-dimensional effects of omega-3 supplementations, enriched in either DHA or EPA, on cognitive and brain measures in humans. Thus, we viewed the effects of omega-3 supplementation on cognition and neural activity together by applying Haier and colleagues’ neural efficiency theory (1988). It is important to mention that this is a novel approach as previous omega-3 studies interpreted cognitive and electrophysiological results in isolation, and did not consider the effects of omega-3 fatty acids on the complex interaction between cognitive performance and neural processing.

Overall, the literature suggests that EPA-rich supplementation shows a tendency to increase neural efficiency, while DHA-rich supplementation appears to be less advantageous in terms of time and intensity of functional activation, especially for fMRI related criteria of neural efficiency. It is also clear from our review that, besides our mfVEP paper (Bauer et al., 2011), no published study has directly compared the effects of DHA-rich and EPA-rich supplementations on neural efficiency.

The hypothesis that EPA enhances neural efficiency is important because it indicates that although EPA is stored in the brain in low amounts (Chen, Liu, & Bazinet, 2011; Chen et al., 2005; Chen et al., 2009), it may have rapid and long-standing effects on pathways that regulate cognitive and cortical activity during high order cognitive functions. In particular, EPA has the potential to facilitate enzymatic processes required to produce energy for the survival of cells and organs including the brain (Flachs et al., 2005; Lonergan et al., 2002), and inhibit neuronal damage due to inflammation and oxidative stress (Mills, Bailes, Sedney, Hutchins, & Sears,
2011; Okabe et al., 2011). These processes could be related to the increase in omega-3 levels in mitochondrial membranes and/or to the direct action of omega-3 PUFAs on mitochondrial enzymes that produce adenosine triphosphate (ATP). The increase in energy availability would explain the reasons that EPA-rich supplementation enhanced the neural recovery of magnocellular responses to metabolically more demanding high contrast stimuli (Bauer et al., 2011).

One could also speculate that EPA-rich supplementation leads to an increase in energy availability during higher order cognitive functions, and that its benefits on neural functioning are not limited to the early visual processing. This hypothesis could be investigated in higher order cognitive functions by measuring brain glucose metabolism (e.g. PET investigation) during a task with multiple difficulty levels and varying metabolic demands.

A possible explanation for the difference in results between EPA-rich and DHA-rich supplementations is that while EPA is rapidly esterified into phosphatidylcholine phospholipids that are located in the outer layer of the cellular membrane, DHA is slowly incorporated into the phosphatidylethanolamine phospholipids in the inner cellular membranes (Metherel et al., 2009; Neuringer & Connor, 1986; Stasi et al., 2004). As a result, while plasma EPA levels increase rapidly in the first 4 weeks of omega-3 supplementation, DHA requires substantially longer than 4 weeks and has been reported to take up to 10 to 12 weeks to be maximally incorporated into cellular membranes (Stasi et al., 2004). Given the differences in incorporation of DHA and EPA into cell membranes one could argue that a supplementation period longer than 12 weeks is necessary to demonstrate the beneficial effects of DHA-rich supplementation on neurocognition. This finding is likely to be related to the
increased incorporation of DHA into neural membranes after a supplementation period longer than 4 weeks mainly due to the 10 to 12 weeks to reach peak levels in blood cell membranes (Metherel et al., 2009).

Considerations

Care has to be taken when interpreting neurocognitive results in light of the neural efficiency theory. The theory of neural efficiency lends itself well to a crossover design in which the same group of participants perform a task under different conditions because their neural activity and cognitive performance can be easily equated. Indeed, in this kind of designs a change in functional activation or brain metabolites in a certain brain region is likely to be due to an effect of omega-3 supplementation and indicate a change in the utilisation of neural resources, rather than be due to individual differences in IQ or differences in patterns of functional activation between participants. Conversely, in a parallel-randomised design in which several groups of participants were compared after supplementation, the interpretation of changes in reaction times and electrophysiological measures is less straightforward. Indeed, the groups of participants may differ at baseline in terms of neurochemical functioning, mental abilities and cognitive strategies. Thus, it is harder to determine whether the results indicate a change in neural efficiency or rather, are due to individual differences.

It would also be advantageous to combine data with both high temporal resolution (e.g. EEG) and high spatial resolution brain imaging techniques (e.g. magnetoencephalography (MEG) or fMRI). This would allow the researchers to
investigate both the time course and spatial localization of brain functional activity in combination with cognitive data. With respect to functional data analyses, future fMRI studies in the omega-3 field should consider imaging functional brain connectivity patterns via graph theory. This approach would provide information on changes in connectivity and patterns of brain activation over the course of a behavioural task. It would also be essential to validate the theoretical framework of the neural efficiency as a suitable paradigm to interpret the neurocognitive effects of omega-3 PUFAs.

**Conclusions**

In summary, the theory of neural efficiency appears to be a suitable tool to integrate the neurocognitive properties of omega-3 supplementation. By extending Haier et al.’s neural efficiency theory, we conclude that, where comparison is available, a 4-week EPA-rich supplementation enhances neural efficiency. By contrast, since DHA-rich supplementation increases the amount of brain effort required to perform to the same standard than prior to supplementation, DHA has less effect on neural efficiency, at least over this period of supplementation. The different time-course of incorporation of DHA and EPA into cell membranes and possibly different effect on other biological processes is likely to be one of the reasons for the differences in neurocognitive effects between EPA-rich and DHA-rich supplementations.
References


<table>
<thead>
<tr>
<th>Citation</th>
<th>Treatment</th>
<th>Design</th>
<th>Duration</th>
<th>Number and age (M ± SD) of subjects</th>
<th>Outcome</th>
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| Bauer et al. (2011)     | 2 daily treatments: EPA-rich: 590 mg EPA, 137 mg DHA  
                         DHA-rich: 417 mg DHA, 159 mg EPA | Randomized placebo-controlled trial                                   | 30 days  | n = 26 (9 males, 17 females)  
                         Age: 24.74 ± 4.37 | + EPA-rich supplementation reduced reaction times  
                         on a Complex reaction time task  
                         + EPA-rich supplementation period enhanced the neural recovery of the magnocellular visual system |
| Fontani et al. (2009)   | 2 daily treatments: EPA-rich: 4.6 g of fish oil (2:25 g of N3 containing 1.2 g EPA, 0.6 g DHA) (2:1 ratio)  
                         Placebo: 10 mg policosanol versus 4.6 g oleic sunflower oil (placebo) | Randomized control trial - Testing sessions at day 1, day 21, and day 42 | 21 days  | n = 18 (12 males, 6 females)  
                         Age: 20 to 53 years | + Positive correlations between N1 amplitudes and reaction times on Go/NoGo and sustained attention tasks.  
                         + Significant reduction in reaction times on a sustained attention (complex Go/No-Go paradigm). |
| Paajanen et al. (2007)  | 2 daily treatments: EPA-rich: 1000 mg and 900 mg Bio-carnosine  
                         Placebo: triglyceride-oil, carnosine, silica dioxide, magnesium | Randomized placebo-controlled trial                                   | 45 days  | n = 24 (12 females)  
                         Age: 23.8 ± 2.1 years | 0 No change in reaction times/accuracy of the continuous performance test and visual evoked potentials during a continuous performance task. |
| McNamara et al. (2010)  | 3 daily treatments  
                         Low DHA dosage: 400 mg  
                         High DHA dosage: 1200 mg  
                         Placebo: corn oil | Randomized control trial                                               | 8 weeks  | n = 33 children  
                         Age: 8 to 10 years | + Low DHA versus Placebo: increase in functional activity in frontal and occipital  
                         + High DHA versus Placebo: increase in functional activity in superior frontal gyrus  
                         0 No change in reaction times/accuracy on the continuous performance task. |
| McNamara et al. (2013)  | Not applicable                                                             | Observational study                                                   | Not applicable | n = 38 children  
                         Age: 8 to 10 years | + Low DHA group exhibited lower myo-inositol N-acetyl-aspartate, choline and creatine levels in the ACC than High DHA  
                         + Low DHA group has slower reaction times on the continuous performance task as compared to High DHA |
| Jackson et al. (2012)   | 3 daily treatments: Low DHA dose: 450 mg DHA, 90 mg EPA  
                         High DHA dose: 900 mg DHA, 180 mg EPA  
                         Placebo: olive oil | Randomized double blind control trial                                | 12 weeks | Placebo: n = 20 (6 males)  
                         Low DHA: n = 22 (7 males)  
                         High DHA: n = 22 (3 males)  
                         Age: 18 to 29 years | + Dose-dependent increase in Total Hb and oxy-hb in the prefrontal cortex  
                         0 Reduction in reaction times on the choice reaction time and RMP tasks prior to multiple comparisons correction (High DHA better than placebo) |
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamazaki–Fujita et al. (2011) Brain Research</td>
<td>Observational study</td>
<td>n = 54 healthy participants (14 men) Age: 34 ± 8 years</td>
<td>+ Positive correlation between EPA and tissue oxygenation levels (measurements in the prefrontal cortex) + EPA and DHA positively associated with performance on a mental stress test (Uchida-Kraepelin Performance)</td>
</tr>
<tr>
<td>Jackson et al. (2012) British Journal of Nutrition</td>
<td>Placebo randomized control trial</td>
<td>n = 22 (9 males, 13 females) Age: 21.96 years</td>
<td>+ Significant increase in concentrations of oxy-Hb during the Stroop task and total Hb during the Stroop, peg-and-ball, and 3N-back task following DHA-rich (versus placebo) 0 Reduction in Stroop reaction times prior to multiple comparisons correction (DHA better than placebo)</td>
</tr>
</tbody>
</table>

**Table 1: Omega-3 Fatty Acids and Cognitive Function**

- **Hamazaki–Fujita et al. (2011)**: Not applicable
- **Jackson et al. (2012)**: 3 daily treatments: DHA-rich: 995 mg of deodorised fish oil containing 5 mg plus mixed tocopherols, 450 mg DHA, 90 mg EPA (5:1 ratio) EPA-rich: 995 mg of deodorised fish oil containing 5 mg plus mixed tocopherols, 300 mg EPA + 200 mg DHA (1.5:1) ratio Placebo: 1 g olive oil (placebo)

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**Table 2: Omega-3 Fatty Acids and Brain Function**

- **Hamazaki–Fujita et al. (2011)**: Not applicable
- **Jackson et al. (2012)**: Placebo randomized control trial 12 weeks

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**Table 3: Omega-3 Fatty Acids and Mental Stress Test**

- **Hamazaki–Fujita et al. (2011)**: Not applicable
- **Jackson et al. (2012)**: Placebo randomized control trial 12 weeks