Shining a light on the effects of omega-3 polyunsaturated fatty acids on the brain: The relationship between cerebral blood flow parameters and cognition

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Introduction

The decline in cognitive function witnessed in older adults is associated with a number of physiological changes which occur in the brain during ageing. For example, both white and grey matter brain volumes gradually decrease in older adults and overall cerebral perfusion is reduced, resulting in poorer delivery of nutrients and energy. The development of neurofibrillary tangles and amyloid plaques also contributes towards neuronal loss. Observational studies at the epidemiological level have suggested that individuals with an increased dietary intake of oily fish and other foods rich in the omega-3 polyunsaturated fatty acids (n-3 PUFAs) docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have better long-term cognitive outcomes and lower incidences of dementia [1]. Further, a positive association between levels of DHA in blood markers (e.g. red blood cells and plasma phospholipids) and better performance on tasks of visual memory, abstract skills, executive function as well as total cerebral brain volume has also been observed [2]. Both DHA and EPA have numerous roles in the body which may impact the overall health and function of the brain, and consequently attenuate cognitive decline. It is known that DHA comprises around 40% of total PUFAs in the brain; incorporation of DHA in cell membrane phospholipids contributes to maintaining the structural integrity of neuronal cell membranes and the formation of lipid rafts which in turn affects numerous signalling pathways and neurotransmitter systems. EPA may influence brain function indirectly via the action of EPA-derived signalling molecules – termed eicosanoids – which are known to regulate inflammatory processes and immune responses. It has also been suggested that the positive effects of dietary n-3 PUFAs in promoting the brain's overall structural integrity and function, namely 'brain health', may be related, at least in part, to enhanced cardiovascular functioning, specifically via increased blood flow to the brain, as a result of the effect of n-3 PUFAs on the cardiovascular system [1, 3].

Cerebral Blood Flow and Cognition

It is known that brain activity depends on a constant supply of oxygen and glucose which are delivered, as required, via the blood. Even though cerebral metabolic demands are comparatively very high, the brain actually has restricted means of energy storage. Therefore, local brain activity must be matched by an associated increase in local cerebral blood flow (CBF), a phenomenon referred to as neurovascular coupling. Early hypotheses

of the relationship between neuronal metabolism and local circulation proposed that increased energy use and/or oxygen consumption of neurons (as a consequence of increased cognitive activity) directly triggered vasodilation. However, although increases in CBF appear quickly in response to increased neural activity, metabolic changes occur more slowly, indicating that the nature of neuron-to-vessel signal- ling is more complex. Overall this suggests that blood flow changes may occur through several intermediate steps, rather than by direct increases in neuronal activity. These steps include the signalling activities of nitric oxide (NO) which regulates neuronal transmission and the release of neurotransmitters which result in smooth muscle relaxation and vasodilation in the brain. Numerous similar signalling processes are also believed to take place, but these are complex and still under investigation.

N-3 PUFAs and Cerebral Blood Flow

The effect of DHA and EPA on the cardiovascular system has been a topic of intense investigation. For example, blood concentrations of epinephrine and norepinephrine have been shown to be lowered by DHA and EPA supplementation, while improvements in haemorheology through fish oils have also been shown [1]. Further evidence obtained from both animal and human studies suggests that n-3 PUFAs beneficially affect several cardiovascular processes, including improved endothelial function, promotion of vasodilatation via relaxation of smooth muscle cells, delayed development of plaques, antioxidant properties, anti-inflammatory proper- ties and decreased stiffening of arterial walls [4]. Current evidence also supports the hypothesis that increased dietary intake of n-3 PUFAs decreases blood pressure in hypertensive patients, however, this effect is reduced in individuals whose n-3 PUFA status is higher prior to supplementation [4]. Given these observed effects of n-3 PUFAs on cardiovascular parameters, it seems rational to assume that n-3 PUFAs may exert secondary effects on brain function and overall brain health via modulation of cerebral haemodynamics. It may also be that the previously observed attenuation in cognitive decline during normal ageing may result from improved cerebrovascular function, an assessment of which can be made via several neuroimaging techniques.

CBF Neuroimaging Techniques

The most widely used non-invasive neuroimaging techniques in the assessment of cerebral haemodynamics are functional magnetic resonance imaging (fMRI) and near-infrared spectroscopy (NIRS).

Functional magnetic resonance imaging (fMRI)

Functional activations in the brain can be detected with MRI via direct measurements of tissue perfusion, blood oxygenation and blood volume. Cerebral haemodynamic activity is usually mapped using an intravascular contrast agent, such as Magnevist (a lanthanide-gadolinium chelate). When the blood-brain barrier (BBB) is intact, the contrast agent is confined to the intravascular space, and this compartmentalisation is the basis of the

observed magnetic susceptibility effects in the surrounding tissues, allowing for the accurate estimation of regional cerebral blood volume (rCBV).

The functional images utilise the blood-oxygen-level dependent (BOLD) contrast, which depicts differences in blood oxygenation. Almost all non-invasive fMRI is possible because blood haemoglobin is diamagnetic (counteracts the magnetic field) when it is oxygenated and paramagnetic (enhances the magnetic field) when it is deoxygenated. This allows for the measurement of the amounts of both oxygenated and deoxygenated haemoglobin within the brain, offering insights into localised increases in neuronal activation through the metabolic consumption of oxygen within the brain.

Near-infrared spectroscopy (NIRS)

Near-Infrared Spectroscopy (NIRS) is a neuroimaging technique that measures the amounts of both oxygenated (oxy-Hb) and de- oxygenated (deoxy-Hb) haemoglobin following the introduction of near-infrared light (photons) through the intact skull via their differing photon absorption properties. The continuous-wave NIRS ma- chine utilises the scattering and absorption information of photons to calculate relative concentration changes (µmol/L) in oxy-Hb, deoxy-Hb and total-Hb (the latter calculated by adding together oxy and deoxy) by means of a modified Beer-Lambert law. When assessed by NIRS, the increase in CBF in the surface layers of the cortex during localised neural activity is typically seen as an in- crease in the total concentration of haemoglobin (total-Hb) and comparative decrease in deoxy-Hb with both parameters corresponding strongly with the fMRI BOLD signal.

Both fMRI and NIRS have strengths and weaknesses when compared. For example, NIRS is a more convenient and less expensive method that offers finer temporal resolution than fMRI. On the other hand, fMRI offers superior spatial resolution and decreased signal-to-noise ratio (SNR). Overall, NIRS can be viewed as an appropriate alternative to fMRI as long as the spatial resolution is sufficient for answering the research question and the weaker SNR is accounted for in the research design.

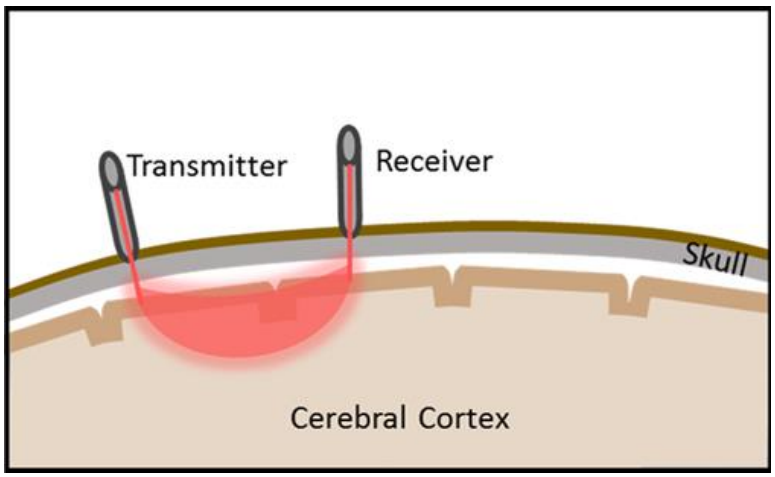

Figure 1. Photon path between NIRS transmitter and receiver pair.

Relationship between N-3 PUFAs, CBF parameters and Cognition

Armed with these neuroimaging tools, the relationship between n-3 PUFAs, CBF and cognition can be investigated and have successfully been applied across all age groups. For instance, McNarama et al. (2010) conducted an 8 week, randomised, double blind, placebo-controlled supplementation study with 3 treatment arms (placebo, 400 mg/d DHA, 1200 mg/d DHA) on a sample of 33 partici- pants (age^m 8.98 years). The study employed fMRI to assess relative changes in cortical activation patterns during sustained attention at baseline and endpoint. Significantly greater changes were observed from baseline in activation of the dorsolateral prefrontal cortex (PFC) in both DHA groups than the placebo group. Additionally, high-dose DHA was associated with decreased activation of the cerebellar cortex compared with both the low dose DHA and placebo conditions, which the authors note is the opposite pattern that had been observed in a paediatric sample with ADHD. Participants' erythrocyte DHA composition was positively correlated with dorsolateral prefrontal cortex activation and was inversely correlated with reaction time, at baseline and endpoint. Taken together, these findings suggest that dietary intake of DHA is associated with alterations in the functional activity of cortical attention networks during sustained attention in children.

Similarly, the findings presented by Jackson et al. [5] demonstrated that dietary intake of DHA is also associated with increased cerebral blood flow during the performance of cognitive tasks in young adults, as measured using NIRS. These authors conducted a 12-week, randomised, double blind, placebo-controlled intervention study with 3 treatment arms (placebo, 1 g DHA and 2 g DHA rich fish oil (n = 65, age^m = 20.6 years). Akin to the findings of the study by McNamara et al. (2010), these authors did not report any interpretable effects of the intervention on cognition, despite the observed changes in cerebral haemodynamics in both active treatment groups.

Another study by Hamazaki-Fujita et al. [1] also provides evidence suggesting that dietary intake of n-3 PUFAs may be associated with cerebral haemodynamic parameters in younger individuals. These authors assessed the relationship between n-3 PUFAs and human cerebral blood oxygenation in a sample of 54, healthy young adults (age^m = 34 years). Using NIRS, the researchers identified that EPA was positively associated with tissue oxygen index (a simplified index for cerebral blood circulation), which in turn was positively associated with arousal level and inversely associated with negative mood (POMS). DHA and EPA were inversely associated with depression–dejection (POMS) and positively associated with arousal level and overall performance in the Uchida-Kraepelin Performance test of mental arithmetic. The researchers concluded that EPA increased the oxygenation level in the PFC, in turn improving various psychological parameters and cognitive performance.

In contrast, a modulating effect of n-3 PUFAs has not been demonstrated in older adults using NIRS. Recently, Jackson et al. [6] conducted a 26-week, randomised, double blind, placebo-con- trolled intervention study with 3 treatment groups (placebo, 2 g DHA rich fish oil, 2 g DHA rich fish oil with added multinutrients) on a sample of 84 healthy adults (age^m = 59.68 years). No effect of either active treatment was found for any of

the NIRS outcome measures or on the cognitive performance tasks. Similarly, van de Rest et al. [7] conducted a 4-week, randomised, double blind, placebo-controlled supplementation study in 20 participants (age^m = 73.1 years) with mild cognitive impairment (MCI). Daily supplementation with 3 g/d EPA+DHA for 4 weeks was found to have no effect on cerebral haemodynamics as measured using NIRS or blood pressure. All subjects improved on most of the neuropsychological tests, but there was no difference between the active and the placebo groups. Taken together, these results are interesting as they suggest that the previously [1] reported cerebral haemodynamic effects of n-3 PUFAs may be specific to younger individuals. A recent study by Witte et al. [8] revealed that one potential reason underpinning these null effects could be that in ageing, the rapid delivery of oxygen and nutrients to the cortex in response to increased cognitive activity becomes less important in comparison to the increased need to maintain the overall structural integrity of the brain. These researchers conducted a randomised, double-blind, interventional study with two treatment groups (placebo, 1320 mg EPA + 880 mg DHA) in 65 healthy adults (age^m = 63.9 years). The authors reported a significant improvement in executive function following the active treatment compared to placebo after the 26- week intervention. In addition, n-3 PUFAs were associated with beneficial effects on white matter microstructural integrity and grey matter volume in frontal, temporal, parietal and limbic areas primarily in the left hemisphere, as measured by MRI.

Conclusions

Taking the literature concerning the relationship between n-3 PU- FAs and cognitive function as a whole, conflicting data regarding the benefit of dietary n-3 PUFAs on cognitive function have been collected from cross-sectional studies and randomised controlled trials (RCTs). Whilst population-based studies have consistently indicated that higher intake of n-3 PUFAs is associated with better cognitive function and lower incidence of cognitive decline and dementia, the results from RCTs have been equivocal. The application of neuroimaging techniques such as fMRI and NIRS in this field have indicated that in the case of younger individuals, supple- mentation with n-3 PUFAs is associated with observable differences in brain function, even when no changes in behaviour are detected. This suggests that functional changes in the brain are subtle to the point where longer intervention periods are necessary to assess the effect of n-3 PUFAs on cognition, or indeed are only observable over the course of a lifetime. It may not be a coincidence then that the only study in healthy younger adults to demonstrate a benefit of n-3 PUFA supplementation over placebo on cognition administered treatment over a period of 6 months [9].

When evaluating the neuroimaging data gleaned from intervention studies in older adults, the picture is less clear. To date, no evidence of an effect of n-3 PUFA supplementation on CBF para- meters as measured using NIRS has been detected in this population, even following a 6-month intervention [6]. Evidence from the study conducted by Witte et al. [8] suggests perhaps that the lack of evidence in favour of modulation of CBF parameters in older adults may be due to the neurological changes

that occur during ageing, although this suggestion requires further exploration. On the other hand, it must also be considered that global changes in CBF – which may be modulated by n-3 PUFA supplementation – cannot be adequately assessed with continuous wave NIRS systems which have hitherto been utilised [6, 7], as only relative changes in the concentration of oxy- and deoxy-Hb rather than absolute changes in these parameters are measured with these devices. The adoption of so-called 'quantitative NIRS' systems which do collect absolute change data in CBF parameters will be able to assess whether gross changes in CBF occur in older adults following n-3 PUFAs in future studies as these systems become more widely available. More- over, as measuring with NIRS offers a number of advantages over fMRI, it is important that investigation with this technique continues, and its ability to be used in the early detection of cognitive decline along with early effects of n-3 PUFAs is explored in more detail. To this end, greater focus on the effects of n-3 PUFAs on brain function and behaviour in middle-aged adults – a population which has up till now been relatively neglected by the literature – may therefore be required. Finally, whilst many studies have focussed on the effects of DHA on brain function, the results presented by Hamazaki-Fujita et al. [1] and Witte et al. [8] suggest that the role of dietary EPA on these outcomes should not be over- looked.

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