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Nutritional modulation of cognitive function and mental health

Abstract

The important role of diet in cardiometabolic health is generally well recognised; for mental health, it is not so well understood. However, lifestyle risk factors for poor physical health are the same risk factors for mental illness, including poor diet. This is reflected by the high level of poor physical health in people with mental illness. Mediterranean, whole food diets have been associated with reduced risk for chronic disease, but very little research has investigated their mental health benefits. We provide a model for the pathways by which food components provided by a Mediterranean-style diet can facilitate healthy brain function. We then review evidence for the role of selected nutrients/food components – antioxidants, omega-3 fatty acids and B vitamins – in the brain and, hence, modulation of cognitive function and mental health. Converging evidence indicates multiple pathways by which these nutrients can assist in brain function, drawing from studies investigating them in isolation. There is very little work done on synergistic actions of nutrients and whole diets, highlighting a need for human intervention studies investigating benefits of Mediterranean-style diets for mental, as well as cardiometabolic health.

Keywords

function, cognitive, modulation, health, nutritional, mental

Disciplines

Medicine and Health Sciences | Social and Behavioral Sciences

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**NUTRITIONAL MODULATION OF COGNITIVE FUNCTION
AND MENTAL HEALTH**

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ABSTRACT

Dietary risk factors for cardiometabolic health are generally well recognised; for mental health they are not so well understood. However lifestyle risk factors for poor physical health are the same risk factors for mental illness, including poor diet. This is reflected by the high level of poor physical health in people with mental illness. Mediterranean, whole food diets have been associated with reduced risk for chronic disease but very little research has investigated their mental health benefits. We provide a model for the pathways by which food components provided by a Mediterranean-style diet can facilitate healthy brain function. We then review evidence for the role of selected nutrients/food components - antioxidants, omega-3 fatty acids and B vitamins - in the brain and hence modulation of cognitive function and mental health. Converging evidence indicates multiple pathways by which these nutrients can assist in brain function, drawing from studies investigating them in isolation. There is very little work done on synergistic actions of nutrients and whole diets, highlighting a need for human intervention studies investigating benefits of Mediterranean-style diets for mental, as well as cardiometabolic health.

Key words: Mediterranean diet, cognition, mental health, antioxidants, polyphenols, omega-3 fatty acids, vitamin B6, vitamin B12, folate, homocysteine

Dietary risk factors for physical illness are also associated with increased risk of mental illness, a growing international priority. A World Health Organisation survey estimated that between one in four to one in six people in most countries, and nearly half of Americans, will meet the criteria for a mental disorder during their lifetime, including anxiety disorders, mood disorders, impulse control disorders and substance abuse disorders [1]. The prevalence of accelerated cognitive decline and dementia is increasing at an alarming rate worldwide, with an estimated 4-6 million new cases of dementia every year [2]. These cognitive and mental health problems therefore carry a significant burden of disease across the lifespan.

There is widespread concern regarding the effects of modern, typically Western dietary patterns, i.e. consumption of high energy food with little nutritional value and inadequate intake of foods containing essential nutrients, on physical health and obesity. Traditional Mediterranean-style diets, characterised by high consumption of vegetables, fruit, legumes, olive oil, fish, cereals, nuts and seeds, moderate consumption of red wine, and low intakes of processed food, red meat, dairy products and vegetable oils, have been associated with improved cardiovascular health and decreased mortality [3], and protective benefits for cancer [4], obesity and diabetes [5]. These findings have largely been supported by a limited number of intervention trials [6-10].

However relatively little attention has been given to the implications of these poor dietary patterns for society's burgeoning mental health problems, which is surprising given the brain's requirements for essential nutrients from food for its structure and function [11-14] – although lifestyle approaches to mental illness are receiving more attention recently [15-21]. Some correlational and longitudinal population studies have suggested that healthy dietary patterns are associated with better mental health [16, 22-27] and reduced risk of cognitive impairment [4, 28-31]. There are very limited dietary interventions investigating

mental health outcomes: only 2 studies were identified in a relatively recent systematic review [6] and some in process [16] with an important call for more research in this area [20, 21, 32].

Nutritional supplement interventions have shown some promise in improving cognitive function and mental health. Randomised controlled trials have shown improved cognition in students with multi-micronutrient supplementation [33], likely to be particularly evident in children who are underperforming/living in low socio-economic areas [34]; substantially reduced violent behaviour in juveniles with mental health issues following micronutrient supplementation [35]; and 26-35% reduction in reprimands for violent behaviour in young adult offenders with micronutrient and omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation [36, 37]. Some nutrients important for brain function, that are also associated with a healthy Mediterranean-style diet, include antioxidants (e.g. vitamins A, C and E; polyphenols), omega-3 polyunsaturated fatty acids (n-3 PUFAs), B vitamins, monounsaturated fatty acids (MUFAs), vitamin D, and minerals including iodine, magnesium, zinc, selenium, potassium and iron. Individually many of these nutrients have, to varying degrees, been investigated for their association with and/or impact on cognition and/or mental health [38]. In particular, while iodine has been identified particularly for its critical role in early brain development [39-41], antioxidants [42-44] B vitamins [45-47] and n-3 PUFA [48] have received notable attention in this area relative to other nutrients.

Although still somewhat on the outskirts of mainstream thinking, increasingly researchers are highlighting links between nutrients and mental health [17, 38, 49-51], and understanding of the underlying complex molecular mechanisms is advancing [52-54]. Importantly, although nutrients are critical for the developing brain, recent research on brain neurogenesis and plasticity confirms that good nutrition is important for optimal brain function throughout the lifecycle [52]. Increasing focus is also now placed by researchers on

brain-nutrition-gene interactions with suggestions that not only does genetic variation determine our individual response to nutrients but that nutrition and other lifestyle factors can influence gene expression and modulate brain function [53]. The purpose of this paper is to give a broad overview of research on food-derived antioxidant compounds – which predominate in a plant-based diet – and then a more detailed review of biochemical pathways of n-3 PUFA and B vitamins in brain function, and how these nutrients might therefore modulate mental health and cognition. Figure 1 gives a diagrammatic overview of the model that informs this.

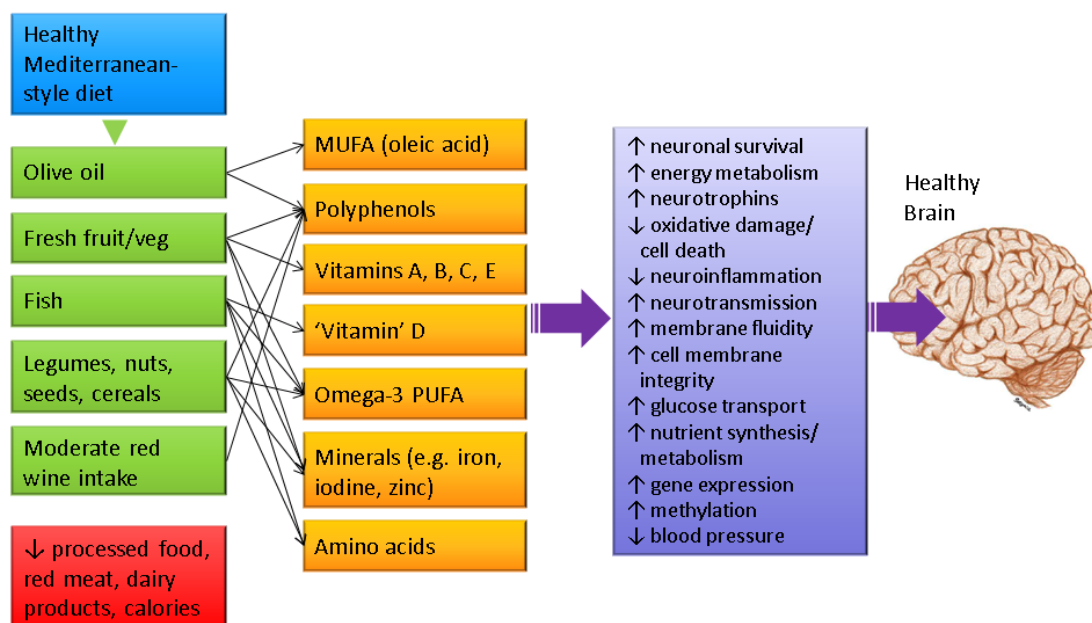


Figure 1: Overview of links between Mediterranean-style diet and healthy brain function via plant compounds and nutrients

ANTIOXIDANTS

Oxidation and the brain

Oxygen is required for the body’s metabolic activities which sustain life; however this process, as well as exogenous damage from environmental sources such as exposure to air pollutants, tobacco smoke, drugs, pesticides and radiation, produces free radicals (e.g., superoxide, nitric oxide and hydroxyl radicals) and other reactive oxygen species (ROS; e.g.,

hydrogen peroxide, peroxynitrite, and hypochlorous acid) [55, 56]. These are unstable molecules with one or more unpaired electrons that, when they exceed the body's oxidant stress defense mechanisms, can start rampant chain reactions: acquiring electrons from other vulnerable molecules leaving those molecules unpaired so they need to find another electron in turn etc. These highly toxic molecules can result in impaired cellular lipid membranes and cell functions, and oxidized proteins, DNA, RNA and cell death – contributing to a range of chronic degenerative diseases, including cardiovascular disease, cancer, and premature aging. The brain is especially vulnerable to oxidative damage for several reasons [57-60]. For example, being lipid-rich and metabolically active with modest antioxidant defense mechanisms, it is particularly vulnerable to lipid peroxidation which decreases cell membrane fluidity and can damage membrane proteins, render receptors, enzymes and ion channels inactive, and ultimately break down membrane integrity. Other factors contributing to oxidation in brain include reaction of neurotransmitters dopamine, serotonin and norepinephrine with oxygen, with a resulting depletion in levels of glutathione, the most abundant endogenous antioxidant in the brain; and release of iron and copper ions following damage to brain in forms that catalyse free radical activity [58]. Drawing from multidimensional evidence in schizophrenia, cognitive decline, bipolar disorder and depression, anxiety disorders, substance abuse, autism and attention-deficit/hyperactivity disorder (ADHD), it has been proposed that pathogenic pathways created by oxidative stress in the brain may comprise a common underlying pathology that contributes to a range of psychiatric disorders [61]. There is an increasing body of evidence to support the role of oxidative stress, together with inflammatory processes, in cognitive impairment, neurodegeneration and psychiatric disorders [60, 62].

Nutrients as antioxidants

Antioxidants can prevent, inhibit or repair damage caused by oxidative stress [63, 64] (Figure 2). Non-enzymatic antioxidants include nutrients, which each have unique structures and related antioxidant functions [56]. Collectively antioxidants act in a variety of ways, including suppressing the formation of ROS, reducing hydroperoxides, sequestering metal ions, scavenging free radicals, stimulating the activity of antioxidant enzymes, or repairing oxidative damage [56]. Enzymes that prevent damage from ROS require dietary minerals selenium, copper, manganese and zinc as cofactors, as well as amino acids for their synthesis [65]. Vitamins A, C and E – of which fruit and vegetables are rich sources – are potent dietary antioxidants that can prevent cytotoxicity resulting from free radicals, act as direct scavengers of ROS and upregulate antioxidant enzyme activity. Vitamin C acts by becoming oxidized itself (providing an electron), thereby stopping the chain reaction, and appears to be particularly important for brain defenses as reflected by its high levels in cerebrospinal fluid and brain relative to plasma [58]. From the vitamin E group of tocopherols and tocotrienols, alpha-tocopherol appears to be the main form present in brain and its deprivation causes neurological damage [58]. Vitamins E and A prevent lipid peroxidation which is critical for the preservation of cellular membranes. Vitamin C works synergistically with vitamin E by restoring its radical scavenging activity [66]. A combination of the antioxidants vitamin C, vitamin E and alpha-lipoic acid was shown to improve flow-mediated dilation in elderly people, presumably by reducing plasma free radicals and restoring endothelial function [67].

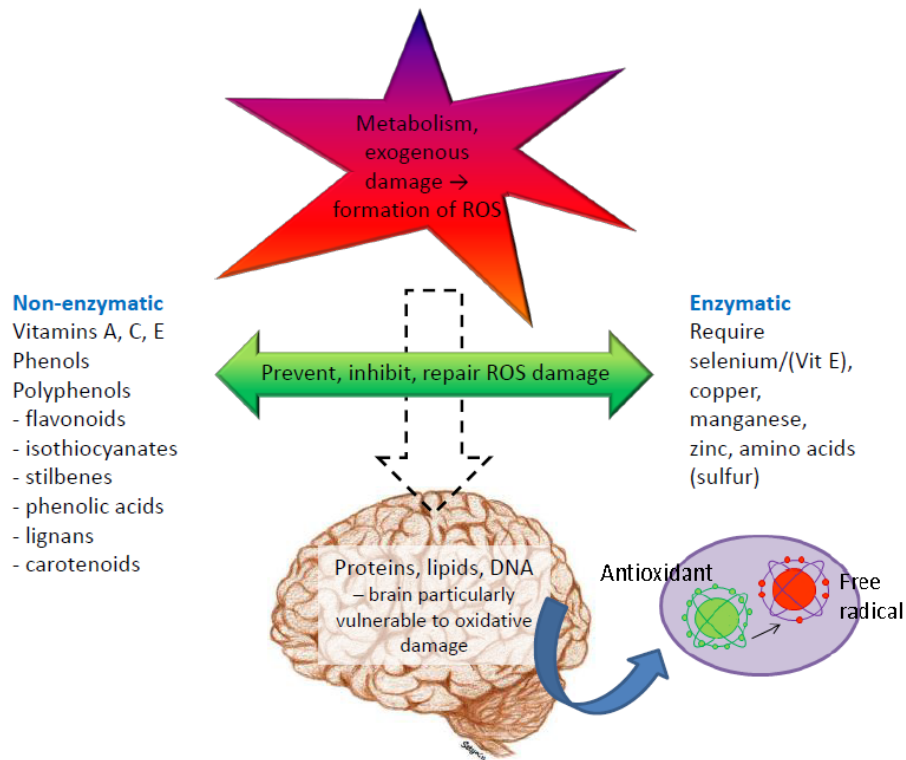


Figure 2: Antioxidant and brain overview. ROS=reactive oxygen species

n-3 PUFAs inhibit production of free radicals and have been shown to reduce oxidative stress created by traumatic brain injury in a rat model [68]; vitamins B₆, B₁₂ and folate prevent oxidation via their role in the metabolism of homocysteine which can cause oxidative stress in endothelial cells [55] (see sections on n-3 PUFAs and B vitamins). Glutathione and peroxiredoxin/thioredoxin are the body's major intracellular antioxidants thereby influencing every system in the body [58, 69]. Although these are not essential nutrients, the enzymes glutathione peroxidase and thioredoxin reductase require selenium as a cofactor, which works synergistically with vitamin E [65], and glutathione has close relationships with intracellular amino acids, especially those that contain sulfur. Accordingly, a range of dietary amino acids has been shown to enhance glutathione production: cysteine, glutamic acid, glycine, serine, arginine and methionine [69].

Polyphenols as antioxidants

Plant-derived food, including fruit, vegetables, legumes, grains [70], nuts [71], red wine [72], tea [73], olive oil [74], herbs and spices [75], also contains thousands of non-nutrient compounds called phytochemicals: phenolic and polyphenolic compounds with antioxidant properties. They all have at least one aromatic ring structure with one or more hydroxyl groups; and can then be classified via their chemical structure into at least ten different classes. The largest is the group of more than 4,000 flavonoids (with the following sub-groups: flavonols, flavones, flavonones, chalcones and anthocyanidins)[73, 76] which act primarily by scavenging ROS as well as metal chelation, breaking chains, preventing ROS formation and protecting ascorbic acid [77]. Importantly, various flavonoids can traverse the blood-brain barrier [58, 77], and there is some evidence for neuroprotective benefits via various mechanisms including direct scavenging of free radicals and assisting antioxidant defense mechanisms within cells via modulation of signaling cascades [77]. Other polyphenols include isothiocyanates [64]; stilbenes (e.g. resveratrol in red grape skin) [78, 79]; phenolic acids [79, 80]; lignans (in linseed) [79]; beta carotene and other carotenoids including lycopene and lutein [55, 81]. Associations between fruit and vegetable consumption and lower risk of chronic disease have been attributed largely to antioxidant properties of phytochemicals [81-83], although they are thought to have other biological functions that are not yet fully understood via modulating the activity of numerous enzymes and cell receptors [75]. Recent studies have focused on Nrf2 [nuclear factor erythroid 2 p45 (NF-E2)-related factor 2], a transcription factor that is activated by phytochemicals and plays a key role in the expression of genes responsible for antioxidants such as glutathione and antioxidant and detoxification enzymes [64, 84]. In support, a most recent paper reported increased neuronal superoxide dismutase and glutathione peroxidase activities via activation of the Nrf2 pathway with curcumin supplementation in a neurodegenerative rat model [85].

It should be noted that, although research has focused predominantly on antioxidant properties of dietary polyphenols, there is evidence that their beneficial effects in brain extend to decreasing inflammation and numerous roles in neurological signaling pathways, e.g. via their role in expression of genes that encode antioxidant enzymes, neurotrophic factors and cytoprotective proteins – all contributing to neuronal stress adaptation and thereby decreasing neurodegeneration [77, 86]. Studies with rodents have reported significant reductions in a range of indices of age-related motor and cognitive decline following blueberry, blackberry, cranberry and strawberry extracts or walnut supplementation [19]. Although oxidative stress markers, measured by DCF fluorescence and glutathione levels in the brain, were reduced, other mechanisms of action were also proposed including improved neural signaling, buffering against excess calcium to prevent lowering of calcium homeostasis and reduction of stress signals (refer to Joseph et al. for a review [19]). Interestingly, hormetic-enhanced stress reduction has been proposed as a common pathway for the attenuation of age-related behavioural deficits observed via caloric restriction as well as polyphenol-rich diets [19]. Finally, Jenner's group proposes that primary systemic health benefits of flavonoids, as well as tocopherols and tocotrienols, may be attributed to a role in maintaining gut health. This is indicated by their discovery that, although bioavailability of flavonoids is low, there is a reliable breakdown into simple phenolic structures in the colon [87, 88]. This may contribute to brain function via the brain-gut axis [89].

Research linking antioxidants and cognition/mental health

Scapagnini et al [60] provide an overview of converging evidence for the role of various antioxidant nutrients or cofactors and compounds, such as selenium, zinc, vitamins C, E and A, carotenoids, and polyphenols - especially curcumin and green tea - in mood, cognition and mental health, prevention of oxidative damage to cellular membranes or DNA in the CNS or improved serotonin, dopamine, and glutathione levels that appear to be

modulated via markers of antioxidant activity. Human studies in mental health include a recently published prospective study in Italy that reported associations between low circulating carotenoids and depressive symptoms both at baseline and prospectively over 6 years, controlling for confounders [90], and reduced risk of Alzheimer disease with high intake of vitamins C and E after multiple adjustments in the Rotterdam study [91]. Bouayed reviewed antioxidant properties of polyphenols and their pharmacological effects on the CNS. Coupled with evidence for ameliorating anxiety and depression in rat models, research investigating their effects on anxiety and depression in humans is warranted [92].

A randomised controlled trial with vitamin C reported improved mood in healthy participants [93] and a recent systematic review of studies of polyphenols and cognitive outcomes reported cognitive benefits with polyphenol consumption [94]. A randomised controlled trial of Pycnogenol (containing phenolic acids, catechin, taxifolin and procyanidins) supplementation reported improved symptoms in children with ADHD [95], accompanied by increased glutathione levels and total antioxidant status [96]. In adults with ADHD a crossover trial comparing Pycnogenol, methylphenidate and placebo over 3 weeks did not show improved symptoms in the treatment groups compared with placebo which may be attributed to methodological limitations with dosage, duration and crossover effects [97]. People with schizophrenia who were given vitamins C and E along with n-3 PUFAs EPA and DHA for four months showed reduced psychopathology on a variety of measures [98]. Although biological plausibility is strong for antioxidant treatment of cognitive and mental health, more human studies are needed.

OMEGA-3 POLYUNSATURATED FATTY ACIDS

Long chain (LC) PUFA arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3) are highly concentrated in the brain and are vital fatty acids for neurological

development [99-102]. Furthermore there is a growing body of evidence for their role in mental health across the lifespan [48, 103]. Their parent fatty acids linoleic acid (LA, 18:2n-6) and alpha-linolenic acid (ALA, 18:3n-3), respectively, are the two essential fatty acids we must obtain from our diets, because humans do not have the enzymes required for their synthesis. A diet rich in vegetables, nuts and seeds will provide abundant ALA. Humans do have the necessary enzymes to elongate and desaturate LA and ALA to AA and DHA respectively, but the amount of DHA that is synthesised from ALA is limiting [104-106]. Although we do not know whether this translates to conversion rates in neural tissue [104], researchers generally suggest that preformed n-3 LC PUFA is the ideal dietary source. Indeed it is argued that DHA should be considered as a semi-essential nutrient [107, 108]; that is, a nutrient that we can synthesise but not in adequate amounts for optimal health and therefore we should consume it directly from our diets – predominantly via fatty fish intake.

Current dietary intake of fatty acids [101, 109-113] suggest that we do not have any deficiency in n-6 PUFA intakes and there is an argument that we are probably consuming too much LA [114, 115], due to high intakes of vegetable oils and processed food. We are certainly not consuming enough LC n-3 PUFA for optimal health, especially DHA [110]. There are major detrimental effects when AA and DHA are deficient in the diet or there is an imbalance between these two fatty acids [116]. This part of the review will focus on known mechanisms for the contribution of LC n-3 PUFA, especially DHA, to optimal brain function, increased neuronal cell growth and survival, and protection from injury. Diagram 1 shows a neuron, associated glial cells, the blood supply and the blood brain barrier. We have identified six key mechanisms by which LC n-3 PUFA affect brain health and each of these are shown by detailed diagrams stemming from Diagram 1. Please note that a great deal of the mechanistic evidence is derived from animal studies and in vitro evidence such as cell

culture work. However due reference to human evidence will also be incorporated where applicable.

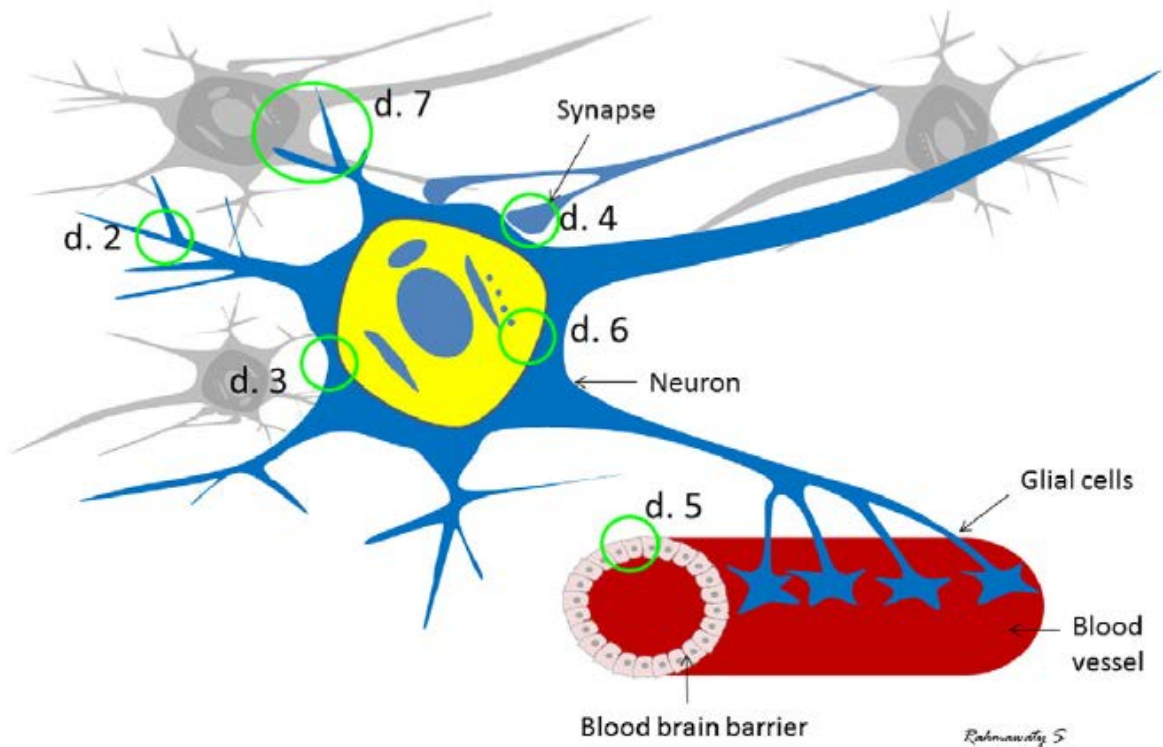


Diagram 1. Neuron associated glial cells

LC PUFA as structural components of the cell membrane of the brain

AA and DHA are major structural components of brain cells [117]. The essential fatty acids, LA and ALA, as well as eicosapentaenoic acid (EPA), are only found in trace amounts in brain phospholipids and EPA (precursor to DHA) is found mainly in phosphatidylinositol (PI) [118]. However, an important role of EPA in the brain may be related to actions of eicosanoids which is explained later. Phospholipid molecules contain hydrophobic tails (repelled by water; therefore aggregate) and a hydrophilic head (attracted to water), enabling them to form lipid bilayers. The different phospholipid structures include phosphatidic acid (PA), phosphatidylethanolamine (PE), phosphatidylcholine (lecithin; PC), phosphatidylserine (PS) and phosphoinositides (PI, PIP, PIP2 and PIP3). These structures enable a multitude of

complex chemical pathways and processes involved in cellular structure and function including signal transduction.

Increasing brain PC, PE, PS and PI levels

In order to synthesise PC, cytidine (the major circulating pyrimide in rats) is required as precursor of cytidine triphosphate (CTP), which together with phosphocholine can be converted to CDP-choline, and then together with diacylglycerol (DAG) can be converted to PC [119]. However, cytidine and CDP-choline are not readily taken up by the brain. In rats, oral intake of CDP-choline does not increase brain levels (0.2% of administered dose ended up in the brain versus 60% in liver) [120]. An alternative way to synthesise PC is by using uridine, which is the major circulating pyrimide in humans and gerbils [121]. The brain is known to be able to take up uridine [122] as there is a high-affinity nucleoside transporter (CNT2) at the blood brain barrier (BBB) that allows the uptake of uridine but not cytidine [123]. Humans use uridine for the synthesis of PC in the brain via the Kennedy cycle [119, 124]. Uridine is converted to uridine triphosphate (UTP) which together with phosphocholine is subsequently converted to CDP-choline, which when combined with DAG forms PC. DHA is used in the formation of DAG, and DHA-rich DAG is preferentially used for the synthesis of phospholipids used for membrane synthesis [125].

CDP-DAG together with serine can form PS and CMP. Subsequently PS can be decarboxylated to form PE and via 3 methylation steps PE can be converted to PC. Furthermore, like PC explained above, PS and PE can be synthesised directly from serine and choline respectively. CDP-DAG together with inositol can be converted to PI [126].

Figure 3 shows the different glycerophosphates (phospholipids) as % of dry weight from human brain gray matter, white matter and myelin (data taken from O'Brien et al. [117]). Generally the choline glycerophosphates (CGP) and ethanolamine glycerophosphates (EGP) are in similar proportions across the age groups with serine glycerophosphates (SGP)

being the lowest. Figures 4a-4c show the major fatty acids associated with the different glycerophosphates (data taken from O'Brien et al. [127]). The greatest proportion of PUFA (40-60%) is found in gray matter in EGP and SGP (Figures 4b and 4c), with very little in CGP (Figure 4a). Palmitic acid differed in the 3 glycerophosphates, being the highest in CGP and extremely low in SGP. Myelin contained the least amount of PUFA (especially in CGP and SGP) and highest amount of oleic acid (and nervonic acid, data not shown). There was no real effect of age, except possibly an increase in oleic acid in gray matter [127] as well as a pronounced decrease in stearic acid and increase in DHA (55 y compared to 9 y) in SGP. The increase in DHA in SGP could be indicative of our neural cell survival (see survival section). Furthermore, even though CGP contains very little DHA, there is a notable increase in CGP DHA levels in gray matter at 55 y compared to earlier years (Figure 4a). This increase could also be due to neuronal cell survival, as plasma CGP-DHA levels are reduced in people with Alzheimer's disease [128] (see section on neurodegeneration).

Note that the data shown in figures 4a-c is taken from n=1 for each age group and there is likely to be some variation, which could come from dietary intake and physiological requirements. Currently we do not have any human data that shows the direct effect of dietary fatty acids with the amount of fatty acids in the brain. We do know however, that dietary EPA and DHA correlate very well with circulating EPA and DHA in plasma and erythrocytes membranes [129]. Most other dietary fatty acids are metabolised prior to uptake into tissues and therefore do not correlate to circulating levels, e.g. dietary LA does not correlate to tissue levels of LA, as LA is metabolised to AA, and AA is then taken up by the tissues. Whilst dietary EPA and DHA do correlate to circulating levels and dietary intakes affect these levels, we do not definitively know what extent these dietary effects are in the brain. The likely greater influences to the variation of brain fatty acids are physiological and pathophysiological. There may be a hierarchy of fatty acid accumulation in the brain (i.e.

DHA is preferentially in EGP and SGP in the gray matter of the brain in Figures 4b and 4c but not in CGP as shown in Figure 4a). Therefore one can see from the graphs that this hierarchy of where DHA is in the brain is most likely not to be highly influenced by dietary intake but is most likely driven by physiology. Furthermore, DHA has been found to be at sub-optimal levels in the brains of people that had Alzheimer's disease (see neurodegeneration), yet dietary intake of DHA does not appear to be deficient [130].

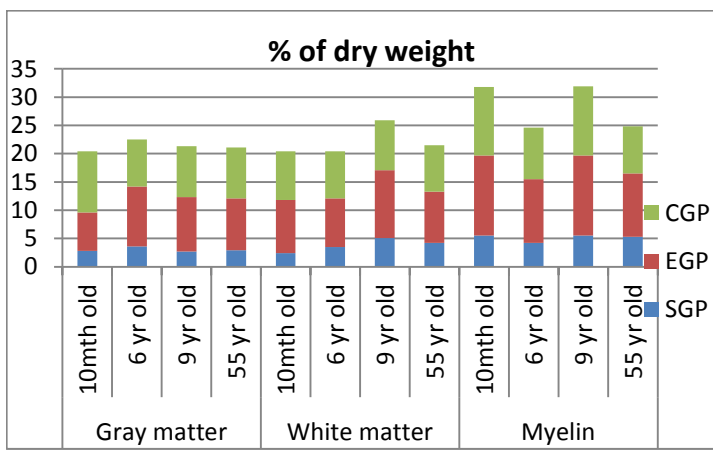


Figure 3: Different glycerophosphates as % dry weight from human (all male Caucasian, n=1 in each age group) gray matter, white matter and myelin (data taken from O'Brien et al⁽¹⁰⁷⁾). CGP = choline glycerophosphates; EGP = ethanolamine glycerophosphates; SGP = serine glycerophosphates.

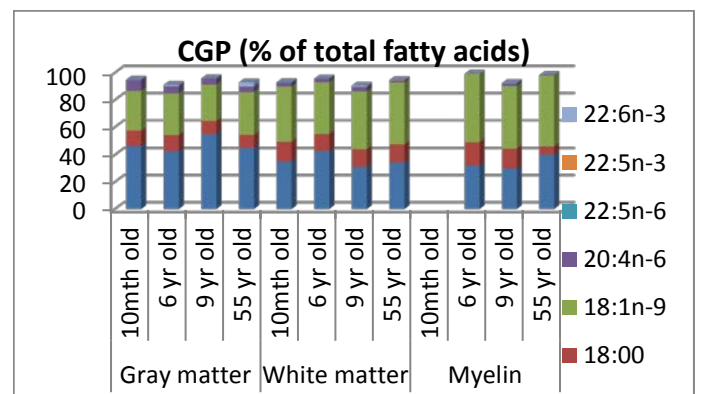


Figure 4a: proportion of fatty acids in CGP (= choline glycerophosphates). 22:6n-3 = DHA; 22:5n-3 = docosapentaenoic acid (n-3); 22:5n-6 = docosapentaenoic acid (n-6); 20:4n-6 = arachidonic acid; 18:1n-9 = oleic acid; 18:00 = stearic acid; 16:00 = palmitic acid. All male Caucasian, n=1 in each age group.

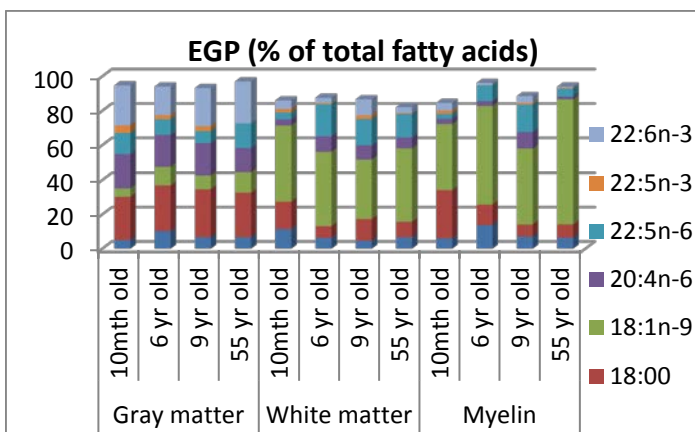


Figure 4b: proportion of fatty acids in EGP = ethanolamine glycerophosphates). 22:6n-3 = DHA; 22:5n-3 = docosapentaenoic acid (n-3); 22:5n-6 = docosapentaenoic acid (n-6); 20:4n-6 = arachidonic acid; 18:1n-9 = oleic acid; 18:00 = stearic acid; 16:00 = palmitic acid. All male Caucasian, n=1 in each age group.

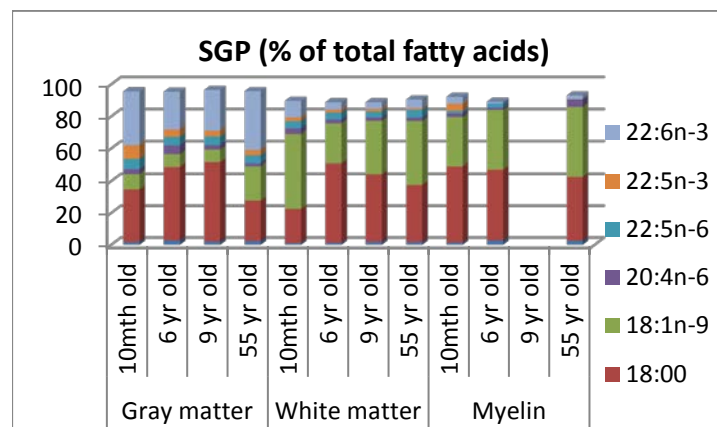


Figure 4c: proportion of fatty acids in SGP (= serine glycerophosphates). 22:6n-3 = DHA; 22:5n-3 = docosapentaenoic acid (n-3); 22:5n-6 = docosapentaenoic acid (n-6); 20:4n-6 = arachidonic acid; 18:1n-9 = oleic acid; 18:00 = stearic acid; 16:00 = palmitic acid. All male Caucasian, n=1 in each age group.

The synthesis of phospholipids requires all the raw ingredients (or substrates) to be present; otherwise the amount and quality of the phospholipid can be compromised. In animal studies, gerbils fed uridine alone did not increase phospholipids (PC, PE, PS and PI). Gerbils fed DHA alone did not increase PC levels but did increase the other phospholipid classes (PE, PS, and PI) to some extent. However gerbils fed both uridine and DHA increased PC levels by 28%. DHA alone increased PE by 26% and in combination with uridine by 59%. DHA alone increased PS by 75% and in combination with uridine by 160%. DHA alone increased PI by 29% and in combination with uridine by 100% [131]. These results suggest that the addition of DHA amplifies the phospholipid synthesis and that there is a hierarchy of preferred synthesis of the different phospholipids species with incorporation of DHA being the highest in PS followed by PI, then PE and PC. The doubling of PS may have implications for increased survival of neurons (see section on survival below).

Animal studies have been supported by cell culture studies using pheochromocytoma neuroendocrine cells (PC12 cells). DHA is taken up by these cells and is activated by acyl CoA synthetases [132, 133], which can now be used for the synthesis of DHA-containing phospholipids. Given that DHA enhances phospholipid synthesis, as explained previously, and the increased phospholipids promotes neurite outgrowth [134], then one can deduce that DHA promotes neurite growth. Furthermore the effect of combined uridine, choline and DHA can result in increased number of synapses and dendritic spines [134] as explained below.

The effect of LC PUFA on neurite growth (Diagram 2)

For successful outgrowth of neurites from developing neurons, the cell first increases its membrane surface area [135]. In order to do this, the cell requires 1) a signal which is provided by the nerve growth factor (NGF) [136]; 2) phospholipase A2 to release the necessary fatty acids (AA and DHA) [137]; 3) a specific target molecule for fatty acids that

can facilitate the necessary fusion of the plasma membrane, which has been identified as syntaxin 3 [138]; and 4) fusion proteins, namely, soluble N-ethylmaleimidsensitive-factor attachment protein receptor (SNARE) to facilitate fusion of membranes [139, 140]. The ability of syntaxin 3 to partner with SNARE requires AA and DHA [138].

Therefore upon the stimulus of the NGF, PLA2 releases AA and DHA from the cell membrane and these fatty acids bind to syntaxin 3, a plasma membrane bound protein, and with the help of SNARE proteins, they promote fusion of the membrane phospholipid bilayer thus enabling neurite outgrowth. In the cell culture studies by Darios et al [138], fatty acids that can facilitate the neurite outgrowth are LA, AA, ALA, DHA, but not saturated fatty acids or monounsaturated fatty acids. LA and ALA are the precursor fatty acids for AA and DHA respectively [101], but are not found in appreciable amounts in the brain. Thus neurite outgrowth is reliant on AA and DHA being present in the brain.



Diagram 2. The effect of DHA on neurite growth

However another study using gerbils showed that EPA and DHA, but not AA, increased brain phospholipids as well as synaptic proteins [121]. This study also showed that the combination of uridine (food sources include tomato and broccoli), choline (food sources include egg, cod fish, wheat germ, cauliflower, spinach, quinoa) and DHA or EPA resulted in a further increase of phospholipids and synaptic protein levels than just the fatty acids (DHA

or EPA) alone. The cell culture studies described by Darios et al [138] above suggest that AA is as effective as DHA to promote neurite outgrowth. In contrast, this *in vivo* study by Cansev and Wurtman [121] showed AA not to be effective. The limitations of cell culture studies is that it is an isolated environment which is usually tightly controlled, whilst *in vivo* studies using animal models (e.g. gerbils) is a closer representation of what will occur in the whole body in a complex system. The reason for the difference between AA not being effective *in vivo*, but is effective in cell culture studies is unknown but as suggested by Cansev and Wurtman [121] could be due to: different affinities in uptake, different affinities for the enzymes involved in DAG and phospholipid formation, differential activation of genes encoding proteins needed for membrane synthesis [141], different rates of deacylation, or different biochemical pathways other than via the Kennedy cycle [142], or the different half-lives where blood DHA and EPA are much higher than AA [143, 144].

DHA has also been shown to stimulate neurogenesis in rat embryo neural stem cells *in vitro* as well as increasing the number of newborn neurons in the granule cell layer of the dentate gyrus in adult rats *in vivo* [145]. Therefore DHA is important not only in the formation of new neuronal cells, but increasing the number of neurones in the adult brain. Furthermore, uridine, choline and DHA have been shown to increase the levels of various proteins required for the synthesis of synapses. Gerbils fed a combination of uridine, choline and DHA resulted in increased levels of the vesicular protein synapsin-1 (41%), post-synaptic protein PSD-95 (38%) and neurite neurofibrillar proteins NF-M (48%) and NF-F (102%) suggesting an increase in the number of synapses [134]. Increased dendritic spines and number of synapses was also achieved following oral supplementation with DHA alone and particularly in combination with uridine [131].

The evidence to date suggests that we need a combination of molecules (uridine, choline, AA, DHA) for neurite outgrowth, synthesis of synaptic membranes and dendritic

spines. It is pleasing to note that mother nature has taken care of this, as breast milk contains uridine, choline, AA and DHA to promote normal growth [146, 147].

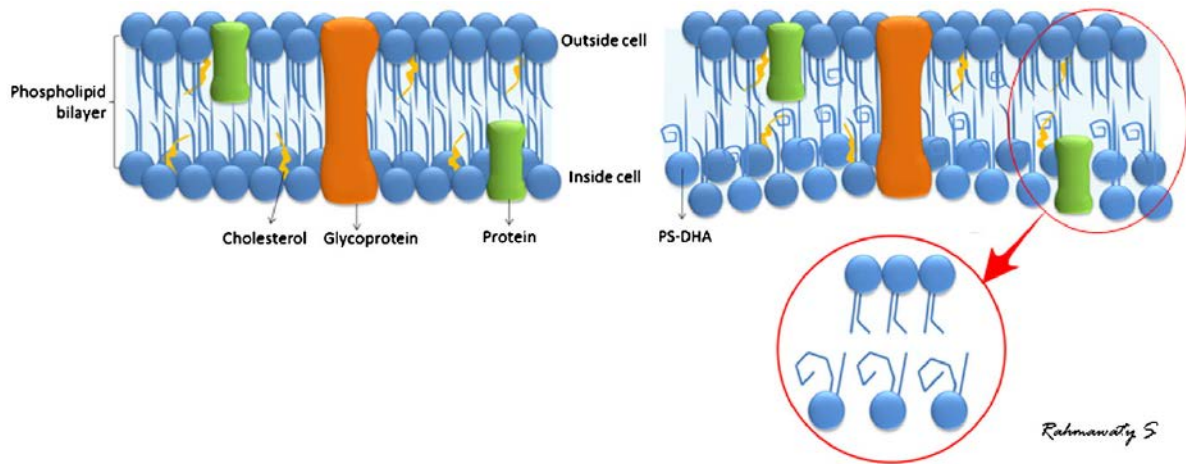


Diagram 3. Phospholipid bilayer DHA

LC PUFA and membrane fluidity (Diagram 3)

Cell membranes are made up of a phospholipid bilayer, with cholesterol and proteins embedded in it (Diagram 3). The spatial arrangements of these phospholipids are dependent on the fatty acyl chains associated with the phospholipids. The usual combination of fatty acids to phospholipids is one saturated fatty acid and one unsaturated fatty acid per phospholipid molecule irrespective of the polar head group [148]. In the brain, the most abundant saturated fatty acids are palmitic (16:0) and stearic (18:0) acids and the most abundant unsaturated fatty acids are DHA, arachidonic acid (AA, 20:4n-6) and oleic acid (18:1n-9) [117, 148] (see Figures 3 and 4 above). The spatial arrangements of these phospholipids are dependent on the fatty acyl chains associated with the phospholipids. For example, the spatial arrangement used by a saturated fatty acid with no double bonds is much less than that of DHA (22:6n-3, with 6 double bonds) [101]. The activity of membrane bound enzymes, like the sodium potassium ATPase are influenced by the fluidity gradient of the membrane [149]. Cell membrane fluidity, or flexibility of movement through a lipid bilayer,

is influenced by highly unsaturated fatty acids like DHA, i.e. the higher the DHA content, the greater the fluidity/flexibility. A good example of scientific evidence that supports this membrane fluidity theory is rhodopsin. Usually when light hits rhodopsin in the eye, elongation of rhodopsin occurs which is necessary for good vision [150] and when DHA is replaced with docosapentanoic acid (22:5n-6) in the eye conformational changes occur that affect the rhodopsin photocycle [151]. Human studies support this in that supplementation with DHA in infants results in increased visual acuity, especially in girl infants [152].

LC PUFA and neurotransmitters (Diagram 4)

The effect of DHA increasing synapses and membrane fluidity such that membrane proteins have improved function also relates to neurotransmitters (diagram 4). It is well known that neurotransmitters are synthesised from specific amino acid precursors; namely, acetylcholine (precursor choline), serotonin (precursor tryptophan), nor-epinephrine and dopamine (precursor tyrosine) [153]. Therefore brain levels of choline, tryptophan and tyrosine will affect the respective neurotransmitter levels. When neurotransmitters are released from the synapse, they bind to specific receptors; namely, serotonin binds to 5-HT1 receptor, nor-epinephrine binds to α -2 beta receptor, dopamine binds to the D1 and D2 receptor (Diagram 4). Taking dopamine as an example, once dopamine binds to its receptor, this increases protein kinase A activity, which in turn phosphorylates ion channels and hence allows them to open up and therefore allowing the signal to be transmitted. Experimental evidence shows that when the LC n-3 PUFA is low, protein kinase A activity is reduced which results in reduced phosphorylation of ion channels resulting in reduction of ion channels opening up [101, 154]. This means that in conditions where LC n-3 PUFA is low, more dopamine is needed to depolarise the cell. Therefore for effective neurotransmission we need LC n-3 PUFA to be present in cell membranes of the brain. In support, a series of rat studies identified that profound n-3 PUFA deficiency impacts on dopaminergic and

serotonergic systems, and that a reversal diet can enable some recovery of dopamine and serotonin levels [155]. A further study identified increased levels of brain derived neurotrophic factor (BDNF) – which is known to facilitate synaptic transmission – after dietary DHA supplementation in rats following a traumatic brain injury which had reduced BDNF levels [68]. In this study, which also showed decreased oxidative stress as mentioned in the earlier section on antioxidants, impaired learning following the brain injury was attenuated with DHA supplementation.

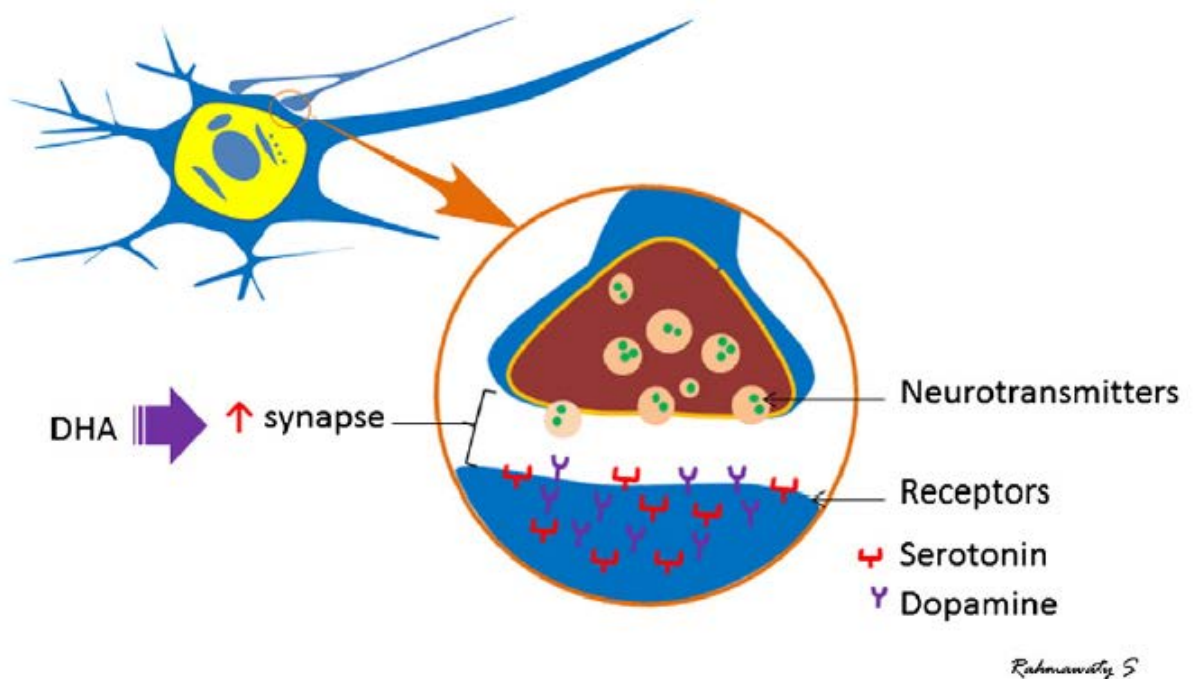


Diagram 4. DHA and neurotransmitters

LC PUFAs and the endothelium: eicosanoids and blood-brain barrier (Diagram 5)

Prior to describing what goes on in the brain, the effect of LC PUFA and eicosanoid production should be explained. A person's cell membrane fatty acid composition reflects their dietary fatty acid intakes. The Inuit's blood fatty acid profile showed very high levels of the LC n-3 PUFA, EPA and DHA and low levels of AA because they consumed a diet high in whales and seals which are rich in LC n-3 PUFA. These LC n-3 PUFA get incorporated

into cells throughout the body and displace LC n-6 PUFA [156]. Documented by early explorers, Inuit had a propensity for spontaneous frequent nose bleeds and when wounded on the battle field, they lay there bleeding for quite a long time before their blood would clot [157]. This was subsequently explained by the eicosanoids formed from the fatty acids released from the endothelial cells lining the blood vessels. The eicosanoids produced from the LC n-3 PUFA are prostaglandins and leukotrienes of the 3- and 5-series, which inhibit the prostaglandins and leukotrienes of the 2- and 4-series produced from AA and result in reduced blood clotting therefore increased blood flow [158]. Eicosanoids from the 3- and 5-series also have anti-inflammatory and vasodilatory properties [159, 160].

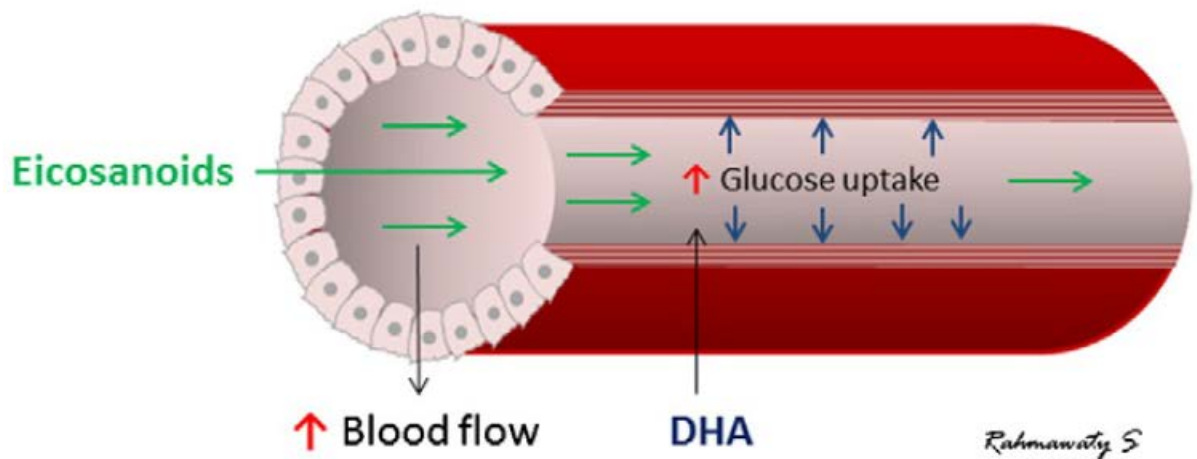


Diagram 5. Eicosanoids and blood-brain barrier

A recent study by Ajmone-Cat et al [161] showed that DHA inhibited the synthesis of inflammatory products, including IL-6, TNF-alpha, in activated microglia in cell culture studies. This effect of DHA could be due to resolvins and neuroprotectins produced from DHA, although more research is warranted, and could have implications for reducing the inflammatory process that is associated with neurodegenerative diseases (discussed later).

In addition to anti-inflammatory and vasodilatory properties, LC n-3 PUFA have an effect on glucose transport and uptake by the brain – via endothelial cells of the blood brain

barrier. It is well known that the brain utilises glucose as its energy source [153] and can use ketone bodies during periods of starvation [162], but not exclusively. Studies based in rats have shown that dietary DHA deficiency resulted in 30-50% reduction in brain membrane DHA levels in phospholipids and this corresponded to a 30% reduction in glucose uptake across the blood brain barrier [163]. It was subsequently shown that glucose transporter in astrocytes (GLUT-1 45kDalton isoform) was reduced by approximately 30% but the neuronal glucose transporter (GLUT3) was unaffected [164]. This reduced GLUT1 in astrocytes is due to reduced post-transcription of the glucose transport protein itself, as mRNA for GLUT1 was not affected [164]. Therefore a deficiency may result in reduced glucose supply to the brain (as shown in rat studies), but it is not known if increased levels of DHA would result in increased glucose supply and uptake by the brain. However, DHA appears to be concentrated in tissues that utilise a lot of energy, such as the brain and retina. Brenna et al [165] took data from a study in monkeys where they measured local cerebral metabolic rate for glucose [166] and plotted that against their own DHA levels with a resulting correlation of $r^2 = 0.68$, $p=0.0003$ [165]. These properties of LC n-3 PUFA are consistent with the hypothesis that they play a role in endothelial function in the brain which may improve blood flow and blood-brain barrier integrity [167], as well as reducing inflammation in the brain. In support, Jackson et al reported a direct effect of a high-DHA supplement on cerebral blood flow in the cerebral cortex of healthy adults compared with placebo [168]. Not only is glucose – and glucose delivery – required for ongoing brain function but reduced cerebral blood flow [167] and inflammation [169] have both been associated with mental illness. Insulin has also been shown to cross the blood-brain barrier. Recent research has demonstrated in a rat model that fructose intake coupled with DHA deficiency led to insulin resistance in the brain, as well as memory impairment; whereas a DHA-enriched diet counteracted these effects via improved synaptic plasticity and reduced glucose-induced peroxidation of the endothelium [170].

Neuronal survival (PS-DHA) (Diagram 6)

Neuronal survival appears to be linked to the amount of PS-DHA in the brain. Human brains will do their utmost to ensure that the levels of PS-DHA are maintained. In situations where DHA deficiency occurs and DHA supply in the brain is limited, DPAn-6 is substituted for DHA (similar to what occurs in the eye, as explained above) in PS in the brain [171] and may play a role in further PS-DHA depletion [172]; this appears to be a survival mechanism. At least in vitro cell culture studies, supplementation with DHA and DPAn-6 (but not oleic acid) increases PS synthesis [173, 174], with DHA being more effective [172].

Alcohol consumption impairs the biosynthesis of PS [175] and therefore contributes to the loss of PS from the brain. PS-DHA is extremely important for neuronal cell survival [172]. Given that neuronal cells do not regenerate very well, it is important that they have a mechanism in place that ensures their survival. One such mechanism is maintaining the high levels of PS via DHA enrichment of PS in their membranes [172]. As explained above, a combination of uridine, choline and DHA more than doubles PS-DHA in gerbils brains [131]. Therefore DHA encourages survival of brain cells and in order to maintain a healthy brain that is able to survive, we need to ensure that there are adequate amounts of DHA and that the brain can synthesise PS-DHA and also prevent its depletion (i.e. no alcohol intake).

Another survival mechanism is via neuroprotectin D1 (NPD1). NDP1 (10, 17S-docosatriene) is synthesised from DHA [176] due to an insult like ischemia. Ischemia induces a cascade of events where there is a rapid release of fatty acids (AA and DHA) by phospholipase A2, which can be converted to a variety of oxygenated metabolites (see section on neurodegenerative diseases). DHA is converted by the enzyme 15-LOX to 10, 17S-docotriene, known as NPD1 [176]. NPD1 is a neuroprotectin molecule because it is known to reduce leukocyte infiltration and reduce pro-inflammatory gene expression [177].

Other DHA metabolites are the prostaglandins F4 neuroprostanes [178]. These neuroprostanes are increased in neurodegenerated diseases like Alzheimer's disease [179, 180] which may be a signal for oxidative stress [172]. However, in cell culture studies, neuroprostanes formed from DHA are potent inhibitors of NF-kb signalling and may contribute to the anti-inflammatory actions of DHA [181]. These results are yet to be confirmed in animal models of Alzheimer's disease as well as human studies.

Certainly, it has been shown in animal models of Alzheimer's disease that DHA supplementation protects against neuronal damage [128]. This protection against neuronal loss could be due to the maintenance of PC-DHA levels in the brain, which prevents neuronal death, and/or via anti-inflammatory mechanisms, and/or via the promotion of neural growth. More research is warranted to elucidate the exact mechanisms by which DHA exerts its effects.

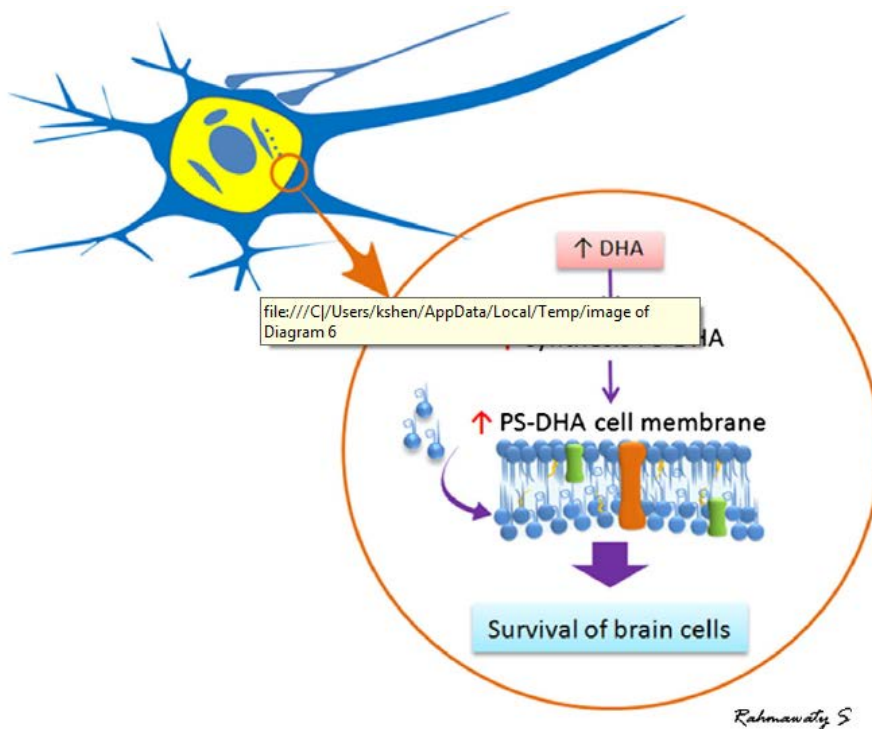


Diagram 6. Neural survival (PS-DHA)

Neurodegeneration (Diagram 7)

Ageing has been described in a recent review by Ledesma as an internal clock plus oxidative stress [182]. The total lipids in the brain increases for the first 20 years of life, followed by a gradual decline until 80 years of life and major changes occur after 80 years of age resulting in a rapid decline of total lipids in the brain as a result of neurodegeneration [182]. Figure 5 shows the levels of the different phospholipid classes (PC, PS, PE, PI) in the whole brain (gray and white matter) for the first 40 years of life (data taken from Rouser Yamamoto [183]).

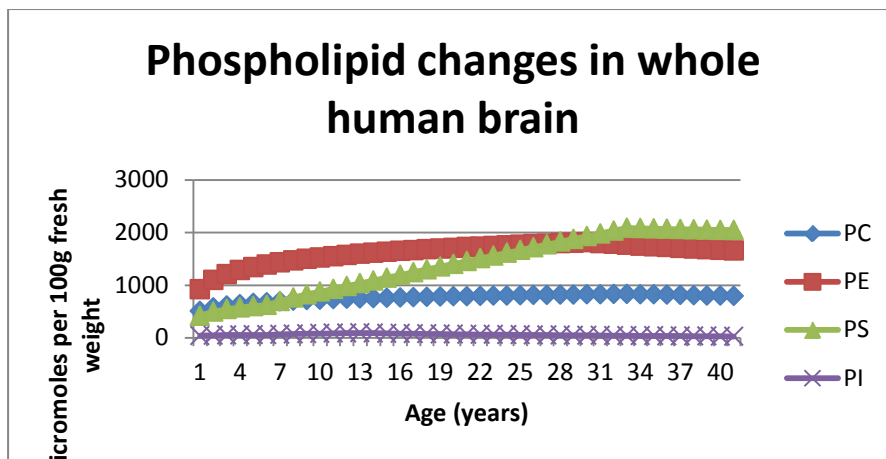


Figure 5: levels of the different phospholipid classes (PC, PS, PE, PI) in the whole brain (gray and white matter) for the first 40 years of life (data taken from Rouser Yamamoto⁽¹⁶⁶⁾; extrapolated from 13 healthy male whole brains aged 6 months to 98 years).

Ageing is associated with decreased neurotransmitter release [184] and alters neurotransmitter signalling [185]. The aged brain has little dead neuronal cells [186] but performance decreases with age. Oxidative stress (ROS) increases, the cell's ability to detoxify decreases and the cells go through adaptive processes to survive [187]. Different degrees of severity of ROS lead to decreases in dendritic remodelling and increases in excitotoxins, which hamper neuronal function [182].

As explained under the neurite outgrowth section, for synaptic vesicle fusion to occur, two bilayers must merge, resulting in extreme structural changes. The ability of cell

membrane to show curvature (i.e. DHA rich cell membrane) is a key requirement for fusion [188]; therefore the more highly curved the more fusogenic. Synaptic membranes are rich in AA and DHA at molar levels [189]. The ability to change the strength of a synaptic connection (referred to as synaptic plasticity) is believed to underlie memory and learning processes [182]. Barnes in 1979 showed a correlation between the age-associated decline in synaptic plasticity and neuro-cognitive impairment in rats [190]. Since then it has been shown that learning and memory deficits are related to strengthening of the synapse (memory formation) and synapse weakening (memory loss). The thresholds for the induction of memory formation and memory loss increase and decrease with age, respectively [191]. The older one gets, the more forgetful one gets [192, 193], the lower the ability to remember things and the greater the memory loss [194]. However, restoration of AA and DHA levels in the brain could rescue the age related impairment in memory formation [195].

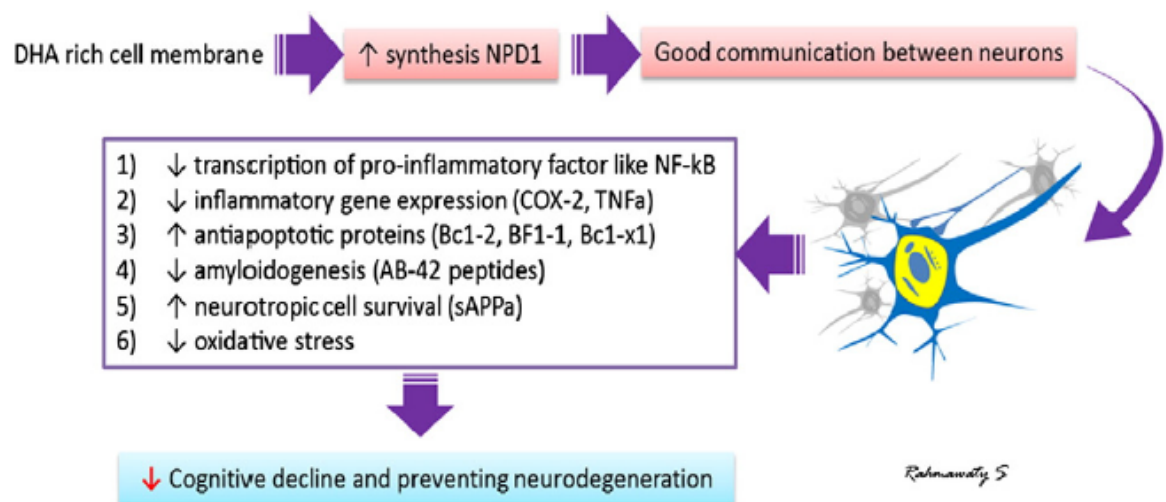


Diagram 7. DHA preventing cognitive decline

Ageing is associated with a decrease in NR2B (a subunit of the NMDA receptor) which is related to a decline in learning [196]. Ageing is also related to decreases in the AMPA receptor subunits (GluR2) in rats, which potentially could alter the calcium flux that may be related to neurodegeneration associated with ageing [197]. GluR2 is also necessary for the growth and maintenance of dendritic spines [198]. An ageing brain has been shown to

have lower PUFA content. Dyall et al have shown that supplementation with EPA and DHA in rats fully reversed the age related decrease in NR2B and GluR2 subunits and also restored some of the phospholipid loss [199].

Phospholipase A2 can release DHA from the membrane and be converted to NDP1 by 15-LOX. NDP1 protects neuronal cells in various ways (see Diagram 7): It 1) reduces the transcription of pro-inflammatory factors like NF-kB; 2) reduces inflammatory gene expression (COX-2, TNF-alpha); 3) reduces pro-apoptotic proteins (Bax, Bik); 4) enhances anti-apoptotic proteins (Bcl-2, Bfl-1, Bcl-xl); 5) reduces amyloidogenesis (AB-42 peptides); 6) enhances neurotrophic cell survival (sAPPa); and 7) reduces oxidative stress, thereby reducing apoptosis and brain cell degeneration [200]. This suggests that DHA, via NDP1 is protective and promotes brain survival. However, during oxidative stress, DHA can be converted to neuroprostanes (F4, D4, E4, A4, J4) which promote apoptosis and exacerbate the oxidative damage to neuronal cells, promoting cell death [200]. Therefore in this situation, we require antioxidants to prevent oxidative stress (refer to section on antioxidants).

It has been shown that supplementation with DHA in animals [201] and in humans [202] can improve cognitive function, and may prevent cognitive decline in people with mild cognitive impairment [48, 203]. Increased anxiogenic like behaviour is found in rats that have reduced DHA [154, 204] and susceptibility to psychological stress in humans can be improved with fish oil supplementation [205]. Certainly brain levels of choline, ethanolamine [206] and DHA [207] have been shown to be sub-optimal in people with Alzheimer's disease. Furthermore, breakdown products of phospholipids (indicative of phospholipid loss from the brain) are elevated in people with Alzheimer's disease [206]. In an experimental mouse model of Alzheimer's disease, it was shown that neuronal dysfunction occurred months before the appearance of abnormal plaques [208] and similarly in humans cognitive decline precedes neurodegenerative diseases like Alzheimer's disease. Hence there is

potential for therapeutic intervention in people with mild cognitive decline to prevent the progression to neurodegenerative diseases. Given the potential additional benefit of supplementation with DHA, uridine and choline in combination, these clinical trials on the potential behavioural benefits are warranted.

VITAMINS B₆, B₁₂, FOLATE AND HOMOCYSTEINE

There has been considerable interest in the role of B vitamins in cognition and brain function, particularly vitamin B₆, folate and vitamin B₁₂, which influence homocysteine levels throughout the body. The B vitamins represent a group of 8 water-soluble essential nutrients: vitamins B₁ (thiamine), B₂ (riboflavin), B₃ (niacin), B₅ (pantothenic acid), B₆ (pyridoxine), B₇ (biotin), B₉ (folate/folic acid) and B₁₂ (cobalamin) [209]. Historically, a severe deficiency in these vitamins was associated with profound clinical manifestations, such as beriberi and anaemia; and neurological changes or impairment in brain function were also commonly observed. However, what were once major public health problems in some parts of the world have declined, replaced by evidence of a sub-clinical deficiency in B vitamins [210]. Sources of B vitamins include a wide range of unprocessed foods such as whole grains, lentils, beans, potatoes, bananas, chili peppers, nuts and animal products. Folate is depleted during harvesting, storage, distribution and cooking, and in the refinement of grains such as white rice and corn. The low bioavailability of folate in our food supply combined with its role in fetal growth, development and prevention of neural tube defects led to calls for folate fortification of foods [210]. In the latter half of last century, subclinical deficiency of vitamin B₆, folate and vitamin B₁₂ as a cause for physical and mental health problems has been investigated.

Vitamins B₆, B₁₂ and Folate

Vitamin B₆, vitamin B₁₂ and folate all play an important role in human metabolic processes. There are three naturally occurring forms of vitamin B₆: pyridoxine, pyridoxal and pyridoxamine, and all three can also occur as phosphorylated compounds. The principal form present in food and in the body is pyridoxal 5'-phosphate (PLP), which functions as a carbonyl-reactive coenzyme for many reactions involved in amino acid metabolism, including metabolism of sulphur-containing amino acids such as homocysteine, formation of neurotransmitters epinephrine, norepinephrine, serotonin, and γ -amino butyric acid (GABA), taurine synthesis (a conjugator of bile acids and important in eye and brain function), and conversion of tryptophan to niacin by kynureninase [209].

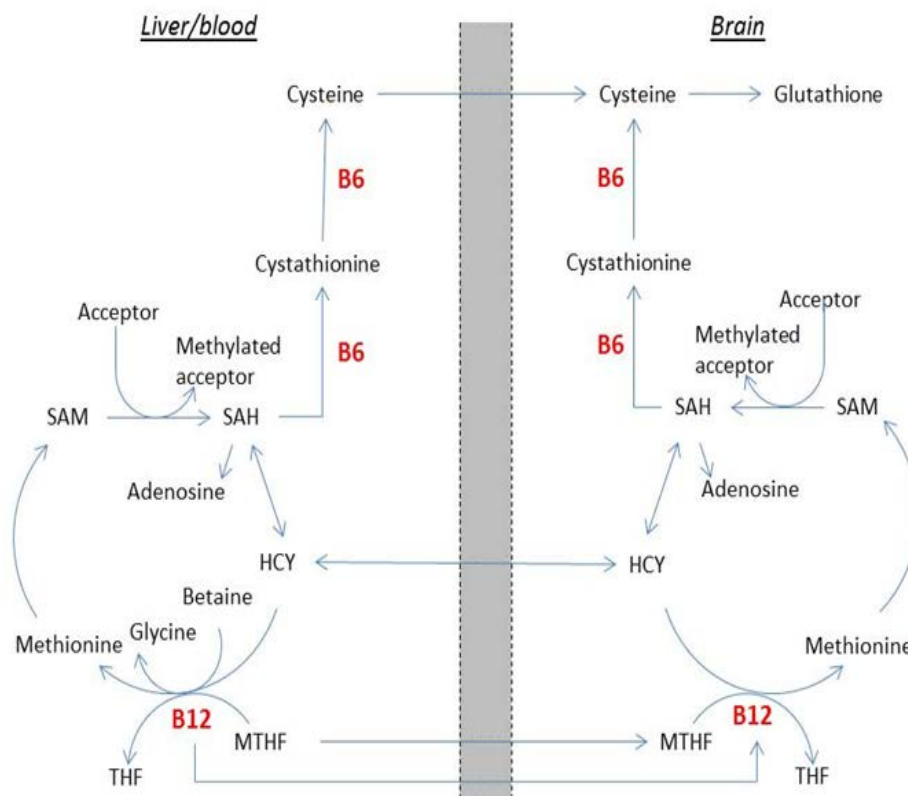


Figure 6. B vitamins and homocysteine metabolism. B6, vitamin B6; B12, vitamin B12; HCY, homocysteine; MTHF, 5-methyltetrahydrofolate; SAH, S-adenosylhomocysteine; SAM, S-adenosyl methionine; THF, tetrahydrofolate. Adapted from Obed and Herrmann (2006).

Folate refers to several compounds related to folic acid, including tetrahydrofolate (THF). The most stable form of folic acid (pteroyl glutamic acid) is the primary form found in pharmaceuticals and used in food fortification, although it is not the natural form occurring in foods and the body. THF plays an important role in 1-carbon transfers in the body, receiving 1-carbon radicals (also known as methyl groups) and donating them during various biochemical reactions, and is essential for the DNA biosynthesis cycle [209, 210]. Specifically, the 5-methyl THF form together with vitamin B₁₂ are also required for methionine synthase to add a methyl group to homocysteine to form S-adenosylmethionine (SAM) (an active form of methionine and important methyl donor in all cells) and THF as part of the methylation cycle (see Figure 6). Under normal physiological conditions this allows rapid removal of homocysteine and the levels of homocysteine to remain relatively low in the cell [211].

Due to the role of vitamin B₁₂ in methylation cycle, a deficiency in vitamin B₁₂ also results in a functional folate deficiency, with folate being trapped in the methyl-5 THF form. Although the DNA and methylation cycles both regenerate THF, folate catabolism and excretion via the skin, urine and bile also occurs and levels must be replenished through the diet [209]. Folate deficiency will reduce the methylation and DNA cycles. During development, an inadequate intake of folic acid can increase the risk of improper closure of the neural plate which goes on to form the spinal cord and cranium between 21 to 27 days post conception. Folic acid requirements are increased during pregnancy especially during periods of rapid fetal growth to decrease the risk of fetal neural tube defects including spina bifida and anencephaly [210].

Vitamin B₁₂, or cobalamin, is a compound only synthesised by bacteria. Its two coenzyme forms, methylcobalamin and deoxyadenosylcobalamin, are used by the enzymes methionine synthase and methylmalonyl-CoA mutase respectively. Methylmalonyl-CoA

mutase plays a role in the conversion of methylmalonyl-CoA to succinyl-CoA in the catabolism of propionate in the mitochondria. In the cytosol, methionine synthase transfers a methyl group from 5-methyl THF form of folate to homocysteine to produce methionine (Figure 6). Vitamin B₁₂ therefore also plays an important role in the use of folate and the lowering of homocysteine levels in humans. Clinical vitamin B₁₂ deficiency is not usually due to inadequate dietary intake, but rather malabsorption due to autoimmune atrophy of the gastric mucosa, referred to as pernicious anaemia in severe cases [209]. Pernicious anemia is known to increase with age. The deficiency causes megaloblastic anaemia similar to that seen in folate deficiency and/or neurological dysfunction. The effects of the deficiency can be traced back to the requirement of vitamin B₁₂ for conversion of folate by methionine synthase – the methyl-folate trap – and the reduction in DNA synthesis. [210].

Homocysteine

Although elevated plasma or serum homocysteine (hyperhomocysteinemia) was once considered no more than a marker for an impaired methylation cycle, it is now implicated in human disease in its own right, and widely recognised as a marker for cardiovascular risk [212, 213]. Homocysteine is a sulphur-containing amino acid produced exclusively from the methylation cycle (Figure 6); it is not available from dietary sources [211]. The methylation cycle also determines removal of homocysteine. Donation of a methyl group by SAM generates S-adenosylhomocysteine (SAH). Under normal physiological conditions, when intracellular homocysteine levels are low, SAH then is rapidly converted to homocysteine by SAH-hydrolase within the cell. However, as intracellular homocysteine rises, the SAH-hydrolase reaction shifts to favour production of SAH instead, with a resultant rise in intracellular SAH [211]. SAH is known to be a potent inhibitor of SAM-dependent methylation reactions. Alterations in SAM/SAH ratio will result in a decrease in activity of

methyltransferases, with implications for methylation reactions involving DNA, proteins, phospholipids and neurotransmitters [214].

The B vitamins play an important role in removal of homocysteine and therefore maintenance of normal low levels. Folate and vitamin B₁₂ are required for the methylation of homocysteine to methionine and remethylation and synthesis of SAM. Pyridoxal phosphate (vitamin B₆ in its active form) is a coenzyme of cystathionine synthase and cystathionine lyase, which are required for metabolism of homocysteine to cysteine [215]. The metabolism of homocysteine is mostly similar throughout the body, including the brain, although some differences occur. Although homocysteine can also be remethylated by an alternative pathway via betaine-homocysteine methyl transferase (BHMT), it appears that this pathway does not occur in the brain [216]. However, the action of this pathway may still affect brain function through reduction of systemic homocysteine levels. Homocysteine can also be transported into neurons via a specific membrane transporter [217].

Homocysteine can be easily transported in and out of cells, and measures in urine or blood reflect intracellular homocysteine production and use. Free homocysteine represents less than 5% of total homocysteine in plasma, as most homocysteine is present in a protein-bound form [211]. Plasma total homocysteine is a reliable marker of homocysteine levels, with normal values in the range of 7-14 $\mu\text{mol/l}$ [218]. An elevation in plasma or serum homocysteine for an extended period of time is known as hyperhomocysteinemia [211]. Severe hyperhomocysteinemia ($>100 \mu\text{mol/l}$) has a number of genetic causes which affect homocysteine metabolism and is associated with vascular disease, mental retardation and seizures. Moderate (15-30 $\mu\text{mol/l}$) or intermediate (30-100 $\mu\text{mol/l}$) hyperhomocysteinemia is more commonly present in the general population. Apart from folate, vitamin B₁₂ or vitamin B₆ deficiency, other determinants of moderate hyperhomocysteinemia include lifestyle factors such as smoking, coffee and alcohol consumption, exercise and diseases such as renal

failure, diabetes, hypothyroidism and malignancies [218]. In addition, homocysteine levels are higher in men, increase with age and also whilst taking some medications including methotrexate, anticonvulsants, lipid-lowering drugs and oral contraceptives [211, 218]. For further review on total plasma homocysteine levels and determinants of hyperhomocysteinemia, see Refsum et al, 2004 [218].

B vitamins, homocysteine and brain function

The possible ways in which subclinical deficiency of B₆, folate and/or B₁₂ could impair brain function and increase mental health risk are multiple (Figure 7). Although there are some proposed mechanisms which implicate B vitamins independently, most are related to the associated increase in homocysteine.

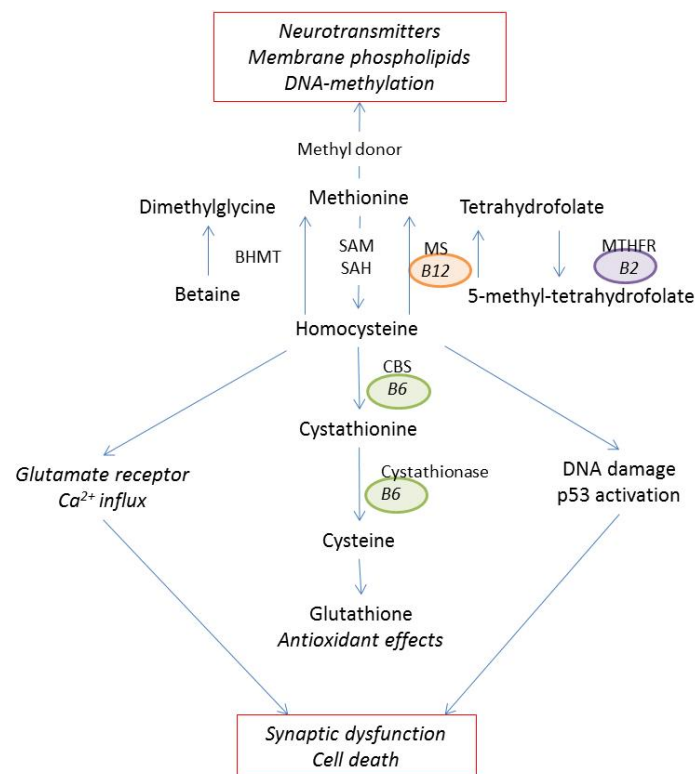


Figure 7: Roles of B vitamins and homocysteine in one-carbon metabolism, transsulfuration pathway and brain function. Homocysteine can be transported into neurons via a specific membrane transporter. Remethylation of homocysteine to methionine occurs in the presence of folate and B12. Methionine is an important source of methyl groups in the brain. Homocysteine can also be converted to cysteine (a precursor of glutathione) in the presence of B6. Homocysteine can cause DNA damage directly or through reduction in DNA methylation, leading to synaptic dysfunction and apoptosis. Homocysteine can lead to excitotoxicity through direct actions on glutamate receptors. Although the pathway for remethylation of homocysteine via BHMT does not occur in the brain, it may still influence brain function through actions on systemic homocysteine levels. Adapted from Mattson and Shea (2003).

BHMT, betaine-homocysteine methyltransferase; *MS*, methionine synthase; *MTHFR*, 5, 10-methylenetetrahydrofolate reductase; *SAH*, S-adenosylhomocysteine; *SAM*, S-adenosylmethionine.

B vitamins and homocysteine actions on cerebral vasculature

Elevated homocysteine is a known risk factor for cardiovascular disease [212, 213]. Considering the shared incidence of vascular disease and poor mental health, including depression [219, 220], schizophrenia [221] and cognitive impairment [222], homocysteine may influence brain function via vascular mechanisms. Elevated plasma total homocysteine has been associated with white matter lesions and silent brain infarctions in older people with and without Alzheimer's disease, both markers of damage to cerebrovascular circulation and risk factors for future clinically apparent stroke and cognitive decline [223, 224]. A study in patients with subcortical vascular encephalopathy (a distinct type of vascular dementia), cerebral large vessel disease and healthy controls found elevated plasma homocysteine in patients with subcortical vascular encephalopathy compared with the other two groups [225]. This indicates that increased homocysteine may exert its effects by injuring small penetrating cerebral arteries and arterioles rather than larger brain-supplying arteries.

Animal studies also point towards a possible effect of homocysteine on the microvasculature of the brain. Feeding mice a B-vitamin-deficient diet for 10 weeks induced hyperhomocysteinemia and damage to hippocampal microvasculature without evidence of neurodegeneration [226]. This was accompanied by impaired spatial learning and memory in the mice. The authors concluded that this damage could occur in the absence of or preceding neurodegeneration. There is also evidence that homocysteine can increase microvascular leakage in the brain [227], leading to vascular remodelling which could disrupt the blood-brain barrier [228].

B vitamins and homocysteine actions on the brain

Neurotransmitters

B vitamins are required for the effective production of the monoamine neurotransmitters serotonin, epinephrine, and dopamine. Specifically, vitamin B₁₂ and folate

are required for the generation of SAM, a methyl donor in the serotonin and catecholamine pathways. Furthermore, when intracellular homocysteine levels are elevated due to deficiency in B vitamins, the SAH-hydrolase reaction pathways will shift to generate SAH leading to inhibition of methylation [211]. In the brain, this can lead to decreased methylation, and therefore decreased production of neurotransmitters. Supporting this are reports of 26% higher SAH levels in the prefrontal cortex of Alzheimer's disease patients compared with normal controls and increased inhibition of catechol-*O*-methyltransferase and phenylethanolamine N-methyltransferase (two methyltransferases related to catecholamine methylation) with increasing brain SAH levels [229]. Lowered activity of these methyltransferases was also associated with poorer cognitive function, a lower age of onset and increased severity in markers of neurodegeneration. Furthermore, low concentrations of a marker of serotonin in the central nervous system (5-hydroxyindole acetic acid in cerebrospinal fluid, CSF) have been observed in folate-deficient patients with neuropsychiatric illnesses [230], epilepsy [231] and depression [232], and there is evidence that administration of intravenous pyridoxine hydrochloride increases synthesis rate of the neurotransmitter serotonin in the brain of the Rhesus monkey [233]. Further, 5-hydroxyindole acetic acid and other CSF markers of dopamine turnover (homovanillic acid) and noradrenaline (3-methoxy-4-hydroxyphenylglycol) were reduced in a sub-group of depressed patients with high plasma total homocysteine [234]. The patients with elevated homocysteine also presented lowered CSF SAM and lowered serum, red cell and CSF folate but not serum vitamin B₁₂ compared with other depressed patients, healthy and neurological control groups.

Folate may also be directly involved in the regulation of neurotransmitter metabolism. The direct mechanism by which this would occur is still not fully known; however it has been postulated that tetrahydrobiopterin (BH₄) metabolism, a cofactor for the synthesis of monoamine neurotransmitters which has some structural similarities to folate, could be

involved [211]. Folate may play a role in the regeneration of BH4 after oxidation, and the enzymes of folate metabolism, MTHFR and dihydrofolate reductase (DHFR), have been suggested to be involved in BH4 metabolism. This is supported by reports of correlations between lower red cell folate, CSF monoamine metabolites and CSF BH4 in depressed patients [232].

Neurotoxic effects

Homocysteine has been shown to be neurotoxic, leading to DNA damage and apoptosis [235]. In the nervous system, elevated homocysteine promotes excitotoxicity through stimulation of NMDA receptors, and induce neuronal DNA damage, triggering apoptosis and effects on synaptic and glial function [236, 237]. The associated methyl donor deficiency impacts on DNA repair, causing uracil misincorporation and leading to DNA strand breakage [238]. DNA damage then activates poly-(ADP-ribose) polymerase (PARP) leading to cell-cycle arrest or apoptosis through ATP depletion and activation of tumour suppressor protein (p. 53 [237]). These effects of B vitamin deficiency and/or elevated homocysteine on DNA repair through DNA nucleotide misincorporation appear to be not only important in development but also in post-mitotic neurons in the adult [237]. Homocysteine induces apoptosis in rat hippocampal neurons in cell culture, with DNA-strand breakage, activation of PARP and NAD depletion observed [235]. This precedes mitochondrial dysfunction, oxidative stress and caspase activation. The authors therefore proposed a possible endangering effect [235], where elevated homocysteine may sensitize neurons to the oxidative stress and excitotoxicity already observed in neurodegenerative disorders [239, 240]. There is also evidence that homocysteine and/or folate deficiency induced DNA damage can sensitize rat hippocampal neurons to oxidative damage induced by amyloid B-peptide, specifically through reduced repair of amyloid B-induced oxidative modification of DNA bases [238].

These effects of elevated homocysteine on neuronal apoptosis could be enhanced during aging or in neurodegenerative disorders by the presence of oxidative stress and altered intracellular calcium homeostasis which accompany them [237]. Homocysteine has also been shown to be neurotoxic to neurons and neuron cells in culture, particularly in the presence of elevated glycine which would occur in the case of stroke or head trauma [236]. These findings could partially explain the observed increased mental health risk in certain clinical populations, including following stroke or traumatic brain injury, and in frail older people [241-243].

Oxidative stress

B vitamins may exert neuroprotective effects through modulating homocysteine-induced oxidative stress in the brain. Homocysteine is known to induce oxidative stress through activation of glutamate receptors and consequent reactive species generation, or by autoxidation to homocysteine and other disulphides releasing O_2 and H_2O_2 [244-247].

Studies in animals and humans suggest a role of hyperhomocysteinemia in oxidative stress associated with poor mental health and also a role for B vitamins in protecting against these effects. Chronic hyperhomocysteinemia is associated with markers of oxidative damage and increased DNA damage in the parietal cortex and blood of rats. Concurrent administration of folic acid prevented these reported effects [246]. Furthermore, folate deprivation in neuronal cultures produces neurodegenerative changes characteristic to Alzheimer's disease, increased cytosolic calcium, increased ROS and decreased oxidative buffering capacity, accompanied by an increase in homocysteine [245]. Children with autism have been shown to have a metabolic profile consistent with impaired methylation status and increased oxidative stress, including lower plasma methionine, SAM, homocysteine, cystathionine, cysteine and total glutathione and higher plasma SAH, adenosine and oxidised glutathione compared with healthy controls [248]. After supplementation with

folic acid, betaine and methylcobalamin (vitamin B₁₂), aspects of this abnormal metabolic profile (methionine, SAM, SAH, adenosine, homocysteine, oxidised glutathione, cysteine, total glutathione) were improved and some reflected the normal levels displayed in the healthy control children. However, changes in speech and cognition were not assessed, although some clinical improvements in these were observed by the attending physician.

Although homocysteine can be remethylated into methionine in the presence of folate and vitamin B₁₂, homocysteine can also be converted into cystathionine by the enzyme cystathionine- β -synthase (CBS) and then to cysteine by γ -cystathionase (Figure 6). This pathway results in increased levels of the antioxidant glutathione, a possible compensatory mechanism which counteracts the potential oxidative effects by homocysteine in normal function [237]. Elevated homocysteine and decreased glutathione have been implicated in Alzheimer's disease and Parkinson's disease [239, 249], which could point towards a disruption of the transsulfuration pathway as a possible underlying factor in neuropsychiatric diseases. This effect could be further enhanced by elevated homocysteine induced by vitamin B₆, folate and/or vitamin B₁₂ deficiency. A previous set-back to this theory was that although production of glutathione from homocysteine-derived cysteine occurs most frequently in the liver, this pathway was thought to be incomplete in the brain for some time [237]. However, this previously-held belief that conversion of cystathionine to cysteine did not occur in the brain has been challenged by work in human brain cells and slices which showed an intact and functional transsulfuration pathway [250]. From this point, given the dependence of sulfur metabolism on the interaction between gene regulation and B vitamins [251], further investigations into the neuroprotective effects of vitamin B₆, folate and vitamin B₁₂ through redox homeostasis are important.

B vitamins, epigenetics and inheritance of psychiatric disorders

In addition to the effects of B vitamin deficiency due to decreased intake during adulthood and/or decreased absorption in later life on mental health risk discussed above, there is also some evidence that deficiency before or during development could be implicated in mental health in later years and subsequent generations. Poor mental health is generally thought to have at least some heritable factor. However, there has been a move towards a focus on low birth weight and “programming” factors through epigenetics, or a change in gene expression not through alteration in actual DNA sequence but rather DNA methylation or chromatin structure [252, 253]. Nutrient deficiency at a specific time in fetal development could have long-lasting effects through tissues, organs and systems including the central nervous system, in later life. There also is growing evidence that epigenetic alterations can be transferred to subsequent generations, which may explain the apparent heritability of complex psychiatric disorders despite the failure to identify candidate genes [254].

Interestingly, there was a 2-fold increased incidence of schizophrenia [255], and increased incidence of major affective disorders (unipolar and bipolar) [256] and addictive disorder especially in men [257] in the Dutch offspring cohort with gestation during the 1944-45 Dutch hunger winter. Although diets during the famine were deficient in many macro- and micronutrients, a 2.5 fold increased incidence of neural tube defects has been observed in the cohort, indicating possible folate deficiency in mothers at the time and a possible epigenetic effect of nutritional deficiency in this cohort [253]. The timing of the nutritional insult appears to influence risk, with increased schizophrenia and addiction reported in offspring exposed to the Dutch hunger winter in the first trimester [255, 257], whilst increased affective disorders were reported in offspring exposed during the second and third trimesters [256]. The authors proposed that neurodevelopmental events that occur at late

gestation, including migration of neurons from ventricular zone to the neocortex and neuronal differentiation [258], could be affected by an insult at this time resulting in disrupted migration or impaired synaptic connections. There is also evidence to suggest people with affective disorder and schizophrenia have problems with neuronal structure and synaptic connections which could be neurodevelopmental in origin [259-261].

These proposed effects on development and function through gene expression could be implemented through gene-silencing via DNA methylation or gene activation through methylation of suppressor genes [253]. Folate, vitamin B₆ and vitamin B₁₂ are all directly or indirectly involved in one-carbon metabolism and DNA methylation through production of SAM, a donor in over 80 methylation reactions. Animal models of schizophrenia [262, 263] have pointed towards hypermethylation of the reelin gene promoter and down-regulation of reelin and GAD₆₇ expression, which produces two proteins involved in neuronal migration, axonal branching, synaptogenesis and cell signalling (reelin) and synthesis of the neurotransmitter gamma-aminobutyric acid (GAD₆₇) [253]. Human post-mortem studies in schizophrenia and bipolar disorder have pointed towards the reelin and GAD67 as areas of interest [264, 265], and reduced reelin mRNA has been observed in autism [266]. Other candidates for alterations in gene expression leading to schizophrenia include the SOX-10 gene, which codes for an oligodendrocyte-specific transcription factor [267].

Homocysteine, B vitamins and mental health problems

Whilst early clinical observations indicated that frank deficiencies in B vitamins were associated with cognitive deficit or dementia, it is only since the 1990s that deficiencies in the “low-normal” range have been considered for a role in dementia [268]. Since then, cross-sectional and prospective studies have reported associations between lowered B vitamins and/or elevated homocysteine in plasma or CSF and increased cognitive decline or dementia risk (see Smith [268] for review). Evidence from randomised controlled trials for a positive

effect of homocysteine-lowering B vitamin supplementation on cognitive decline is limited to date [269]. However, there is evidence of a possible treatment effect at earlier stages of cognitive decline. A recent trial of older people with mild cognitive impairment, an early risk factor for dementia, found supplementation with high-dose folic acid, vitamin B₁₂ and vitamin B₆ for 24 months was associated with a slowing cognitive decline compared with placebo, particularly in those with elevated homocysteine [270]. These clinical benefits were accompanied by a slower rate of brain atrophy in the treatment group as assessed by MRI [271].

A study conducted in acutely ill hospitalised older patients using a mixed nutrient supplement containing B vitamins (B₂, B₆, B₁₂ and folate) for 6 weeks found improved vitamin status and decreased self-rated depressive symptoms in the treatment group compared with placebo after 6 months but no effect on cognitive function [272]. Plasma total homocysteine was assessed in a sub sample at baseline and 6 weeks, and mean plasma total homocysteine was lowered by 22% in the treatment group compared with placebo. Those with plasma total homocysteine levels in the lowest quartile ($\leq 10\mu\text{mol/l}$) after the treatment period had lower depression scores compared with the highest quartile ($\geq 16.1\mu\text{mol/l}$) [273]. It should be noted that older patients which this study excluded due to severe illness, dementia or living in institutional care are perhaps even more likely to be undernourished and therefore deficient in B vitamins, and therefore more likely to benefit from supplementation. Furthermore, as depression is a risk factor for cognitive decline in this group [274, 275], the effect of B vitamin supplementation on mental well-being in older people should be explored further.

Cross-sectional research to date has shown some associations between lowered B₆, folate and B₁₂ and/or elevated homocysteine and increased depression [269]. Recently published research has shown an association between increased dietary folate intake and

reduced incidence of depression in young women [276]. Associations between increased depressive symptoms and lower serum folate levels, but not vitamin B₁₂ were recently observed in 2524 adults aged 20-85 years [277]. Vitamin B₁₂ intakes were not significantly associated with behaviour scores in a sample of 709 Australian adolescents aged 17 years, which the authors suggested could be because the mean intake of the sample was above the recommended dietary intake and/or due to the generally superior absorption of vitamin B₁₂ in this younger population compared with older adults. However, lower intakes of vitamins B₁, B₂, B₃, B₅, B₆ and folate were associated with higher externalising (aggressive/delinquent) behaviour and reduced intake of vitamin B₆ and folate were associated with higher internalising (withdrawn/depressed) behaviour in this group [278]. There is also a small but growing body of evidence showing of a beneficial treatment effect of B vitamin supplementation on depression [269]. In addition, results of randomised controlled trials investigating folate supplementation as an adjuvant to standard psychotropic medication have been promising, perhaps due to folate-induced restoration of neurotransmitter function (see Bottiglieri et al [211]). Considering the links between folate, vitamin B₁₂ and vitamin B₆ in metabolism and their role in lowering homocysteine levels, further clinical trials across mental health should combine the three B vitamins as a more effective method of correcting deficiency, lowering of homocysteine levels and impacting on clinical outcomes.

DISCUSSION

We have presented multidimensional support for a pivotal role of some key nutrients and plant-derived phytochemicals from a healthy whole food diet in optimal brain function, with important implications for cognitive function and mental health. There is a relatively small body of interventions investigating nutritional supplements, with more research required. Trials investigating effects of nutritional supplements on mental health assist in

strengthening the evidence base, but do have their limitations. There is evidence that combinations of nutrients work together and yet a dearth of research investigating synergistic properties of nutrients at biochemical, physiological or psychological levels. It is noteworthy, for instance, that improvements in neuropsychological performance and growth were greater in Chinese children following supplementation with zinc plus micronutrients than with zinc or micronutrients alone [279]. It has been argued that psychiatric illness requires broad spectrum micronutrients due, for instance, to their multiple roles in neurotransmitter synthesis – although research in this area is lacking [280].

Furthermore, there is a paucity of dietary interventions that focus on mental health and wellbeing. As highlighted by Jacques and Tucker [281], ‘we don’t eat nutrients, we eat foods’ (p. 1). Not only do we eat foods in certain patterns, but it is likely that nutrients are more effective in the complex matrix of a healthy diet, attenuating oxidative and inflammatory pathways while amplifying a wide range of protective pathways. To assist in addressing the global crisis around chronic illness, poor mental health, and degenerative diseases with our aging population, considerable focus is required on research to unravel synergistic properties of nutrients and investigate benefits of Mediterranean-style whole food diets for mental as well as cardiometabolic health.

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