

Consumption of seaweeds and the human brain

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Received: 12 August 2016 / Revised and accepted: 25 December 2016
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Abstract Much of the content of the human head is brain matter. This functions as the epicenter of human physical existence, including a sense of well-being and the manifestation of human consciousness. The human brain is a precious and complex organ which increases from 350 to 400 g in infants to 1.3–1.4 kg in adults; it comprises ca. 78 % water, 12 % lipid, 8 % protein, and 1 % carbohydrate. Significant progress in behavioral and analytical science has accelerated understanding of the multifaceted responses of the brain to stimuli, whether it be the microbial breakdown products of ingested foods, the influences of environment, or in relation to genetic predisposition. The science of seaweeds, and particularly their broad range of applications, is gathering momentum as studies repeatedly underscore the natural health and nutritional benefits of dietary macroalgae. This article reviews research highlighting the potential impacts of the consumption of a variety of seaweeds on human brain health and includes theories in relation to the benefits to early *Homo sapiens*. The emphasis is on a varied diet including macroalgae and the gut/

microbe/brain axis, the importance of polyunsaturated fatty acids, and the impacts of anti-oxidant activities in neuroprotection. These elements have the capacity to help in the defense of human cognitive disorders, such as dementia, Alzheimer's disease, depression, bipolar diseases, and adverse conditions characterized by progressive neurodegeneration. Psychological benefits associated with the moderate consumption of a diet fortified with macroalgae are also discussed in terms of reduction of depressive symptoms and furthermore highlighting possible improvements in sexual function.

Keywords Seaweeds · Food · Essential nutrients · Micronutrients · Brain development · Neural system · Neural diseases · Polyunsaturated fatty acids · Taurine · Magnesium · Zinc · Vitamin B₁₂ · Iodine · Antioxidants

Introduction

Investigating the sophisticated complexities of the human brain is uniquely introspective, and modern studies in neurology highlight a fascinating frontier worthy of considerable further investigation. Hominization (the history of the human lineage) is reported to have its primitive beginnings at least 4–6 million years ago (mya), with the most significant changes in brain development occurring over the past 2.5–2 million years (Aiello and Wheeler 1995; Hawks et al. 2000; Glazko and Nei 2003). As a result, modern-day humans are left with an organ that is the source of all the qualities that define humanity. It is the epicenter of function and intelligence, the interpreter of the senses, the initiator of body movement, and the controller of behavior (National Institute of Neurological Disorders and Stroke (NINDS) 2015).

As a developing life form, modern-day *Homo sapiens* realized a competitive advantage through the serendipitous

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development of a more complex and sophisticated brain (Hawks et al. 2000; Sakai et al. 2012; Stewart 2014; Erlandson and Moss 2015). The precise geological timeline for human brain development is very difficult to pinpoint. However, evidence from archeological discoveries suggested that significant growth of the frontal region of the neocortex was likely to have occurred sometime during the Pleistocene Period, i.e., 2.5–2 mya (Hawks et al. 2000; Schoenemann 2006; Preuss 2011). The neocortex is the most recent brain matter acquired by humans and other mammals, and expansion and structural organization of the prefrontal region (i.e., the frontal cortex) are a key difference between humans and our closest primate relatives (Teffer and Semendeferi 2012; Hofman 2014; Rilling 2014). The frontal cortex is the region of the brain that is associated with cognitive capacities, and it is theorized to house the “seeds of human intelligence” (Allman 2000; Smaers et al. 2011; Teffer and Semendeferi 2012).

Beyond physical survival from predators, steps in the development of modern-day humans were, in large part, mandated by diet and the acquisition of food, the nutritional quality of which dictated overall biological fitness. Food, by definition, is “a material consisting essentially of protein, carbohydrate, and fat used in the body of an organism to sustain growth, repair, and vital processes, and to furnish energy” (www.merriam-webster.com/dictionary/food). For *H. sapiens* to meet these metabolic demands, food had to be searched, selected, consumed, and broken down in the gastrointestinal tract (GIT). The GIT is the primary residence of the human microbiome, which is estimated to consist of several trillion microbes and thousands of different species, fulfilling a role as the mediators to absorption of the nutrients required for growth, repair, energy, and vital processes (Whitman et al. 1998; Camp et al. 2009; Thomas et al. 2011; Rath et al. 2012). The link between the acquisition and maintenance of human gut microbiota and their influence on overall health and development extends directly to brain health and development (Forsythe and Kunze 2013; Xu et al. 2015), and it is currently believed to begin immediately at birth (Vaishampayan et al. 2010; Fouhy et al. 2012). As highly integrated organs, the brain and the gut communicate in an innate, bidirectional manner and, as neural development is initiated in utero, it influences immunological development (Berthoud 2008; Maha Al-Asmakh et al. 2012; Marques et al. 2013) as well as the regulation of food intake (Kadohisa 2015). Most recently, research began to focus on the microbial production and modulation of selected metabolites by various gut bacteria and their effect on the brain and other organs. Examples of these include serotonin, an important neurotransmitter, and adrenocorticotrophic hormone (ACTH), involved in the hypothalamic–pituitary–adrenal (HPA) stress response (Sudo et al. 2004; Maha Al-Asmakh et al. 2012; Yano et al. 2015).

Nutritional elements such as taurine, zinc, magnesium, iodine, and the essential polyunsaturated fatty acids (PUFAs), specifically alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA), all significantly influenced, and continue to do so, brain health and development. The impacts of inflammation, reactive oxygen species (ROS), and NO imbalance on physical and psychological well-being are all highlighted in terms of oxidative stress and neural response. Knowledge of these factors paves the way for theorizing that there are critical roles that selective consumptions of seaweeds are likely to have played in human development. Evidence for this possibility is offered in the present review, for the first time, in the context of the nutritional value of dietary macroalgae by highlighting the essential elements that this food source can provide for balancing cellular functionality and supporting well-being. A detailed summary of brain structure and function is first provided, followed by the physiological and cognitive impacts of various essential nutrients: from the discovery by Balard in 1826 of bromine extracted from kelp, and its subsequent experimental treatment for epilepsy (Hempel 1880; Dujardin-Beaumetz 1885), to the present-day realization of the potential value of seaweeds for neural nutrition.

The impetus for divergence—essential brain nutrients

Structure of the brain

While conclusive historical evidence is not likely to be found, scientists could justifiably speculate that dietary seaweeds played a critical role in the growth and developmental sophistication of the early human brain. To build a case for this statement, one must start with the current status of what is known about the human brain and its differences from the brains of the closest living relatives, i.e., the chimpanzees. The fossil record indicates that humans diverged from a common ancestor approximately 5–7 mya. It was only over the last 2.5–2.0 my that the brain size of *H. sapiens* approximately tripled (Schoenemann 2006; Holloway et al. 2009; Cunnane and Crawford 2014). However, neuroimaging has revealed that the human prefrontal cortex differs from that of closely related primates less in relative size than it does in organizational complexity and the capacity for information processing (Roth and Dicke 2005; Preuss 2011; Hofman 2014; Rilling 2014). Much of that complexity is facilitated by the presence of a large ratio of white/gray matter, that is, like a white core surrounded by, and integrating into, an outer covering of gray matter. The white matter is comprised mostly of myelinated axons and glial cells. These components actively affect how the brain learns and functions. Glial cells in the white matter of the brain facilitate learning by modulating the distribution of

nervous action potentials through millions of neural communication links, each one containing an axon coated with a fatty, insulating myelin sheath (Fields 2008).

Using three-dimensional magnetic resonance imaging (3D MRI), Sakai et al. (2012) compared the cerebral tissue developmental trajectories among chimpanzees, rhesus macaques, and humans. Their results clearly demonstrated a significantly greater increase in brain white matter in humans, especially during early infancy. These results also complement work by Schenker et al. (2005) who, by using MRI techniques on the live brains of 10 human and 17 ape subjects, concluded that the white/gray matter in the human brains well exceeded the relative proportions of the apes. In that study, the researchers subdivided the frontal cortex into three sectors for comparative measurements, and in all cases, the volume of the human measurements was significantly greater than those of the great apes or gibbons. The species-specific increase in white matter in the human brain over time suggested that enhanced myelination processes contributed to the larger brain volume and improved the synaptic conductivity of fibers between and among different brain regions (Preuss 2011; Hofman 2014). Fields (2008, 2011) reported that investigations into the speed of conductivity revealed that nerve impulses race down axons in the order of 50–100× faster when coated with myelin. By increasing the speed of information transfer between parts of the brain involved in mastering complex cognitive tasks, myelin-producing glial cells are considered essential for learning and effective information processing.

In a study by McKenzie et al. (2014) on mice, in which their myelin regulatory factor was inactivated (i.e., blocking myelin production), it was demonstrated that myelin-forming cells, the oligodendrocytes, altered the structure of white matter in untreated control mice. The treated mice were unable to master the complex design of the running wheel, whereas the control wild-type mice adapted to it after 1 week. Those mice mastering the complex wheel also showed myelin-forming oligodendrocyte (glial cells) genesis and increased myelin formation, suggesting a correlation to learning a new (complex) task. Using a neuroimaging method called “diffusion MRI,” Scholz et al. (2009) measured white matter changes in volunteers who learned juggling as a new skill; after 6 weeks, brain scans showed that myelin had increased over that of the control group. Interestingly, this was regardless of how proficiently they learned the new skill, which suggested that the act of learning itself was responsible for the changes. This information corresponds implicitly to the accelerated increase in myelination in human infant brains following birth (Fuster 2002; Deoni et al. 2011; Deoni et al. 2012) when learning new things specifically related to survival is paramount. Myelin is composed of 70–85 % lipid and 15–30 % protein on a dry weight basis, and constituents of the lipid component include a significant amount of cholesterol, as well as certain galactolipids and sphingolipids such as cerebroside, lecithin,

and phospholipids (Morell and Quarles 1999; Saher et al. 2005; Hartline 2008).

It is now widely accepted that other glial cell components of white matter called astrocytes control synaptic firing and data processing at the synapses. Glia chemically conveys information in a wave-like fashion throughout the brain, rather than utilizing localized electrical connections, as neurons do. Some glial cells, called microglia, defend the brain against disease and neurological disorders, while others interact with neurons, controlling and working alongside them. Glia induce the production of myelin, breach the blood–brain barrier, and participate in aspects of vision, memory, muscle contraction, and unconscious brain function, such as sleep and thirst (Fields 2011; McKenzie et al. 2014; Jo et al. 2015). Thus, glial cells within the white matter play a central role in brain protection and cognition and, in particular, learning, memory, and information processing, which are fundamental aspects of human intelligence (Scholz et al. 2009; Liu and Chopp 2016). Glial cells constitute 85 % of hominin brain cells, as compared to neurons that make up the remaining 15 % (Fields 2011).

PUFAs

The structural features of the human brain are highly enriched in lipids, constituting approximately 50–60 % on a dry weight basis. The major class of lipids present in the brain are phospholipids, and the most abundant long-chain polyunsaturated fatty acid components are docosahexaenoic acid (DHA:C22:6, n-3) and arachidonic acid (AA:20:4, n-6). The fatty acid profile of a typical healthy human brain is characterized by approximately equal proportions of DHA and AA, which is true not only for the human brain but for all brains and neural membranes (Crawford 1992; Martínez and Mougán 1998; Youdim et al. 2000; Mouritsen 2005; Mouritsen and Crawford 2007). After an extensive search of Medline databases using a broad range of key PUFA and neural disorder terminologies, Haag (2003) concluded the following: the ratio of membrane n-3 to n-6 PUFAs can be modulated by dietary intake and that this ratio influences processes vital to normal brain function and optical acuity. These important biological processes include neurotransmission, photoreception, and prostaglandin production (Yehuda and Carasso 1993; Simopoulos 2008; Bazan et al. 2011). Eicosapentaenoic acid (EPA: C20:5, n-3) is another important membrane n-3 PUFA (Mouritsen 2005; Chen et al. 2014), and results of a study by Chen et al. (2009) on wild-type C57BL/6 mice perfused with ¹⁴C-EPA or ¹⁴C-DHA suggested that EPA was rapidly β-oxidized upon uptake by the brain. This could possibly account for its apparent deficiency in the brain phospholipid profile. DHA is approximately 300× more abundant than EPA in brain tissues (Chen et al. 2011). Of significance is that the acquisition of n-3 and n-6 PUFAs is dependent upon diet.

DHA is critical for visual acuity, and it is implicated in the activities that underlie cognitive development, such as modulating synaptic efficiency, transmission speed, and myelination processes. Furthermore, DHA is suggested to play a putative role in the connectivity of higher order cortical pathways (Kupfermann 1975; Wiggins 1982; Lauritzen et al. 2001; Cao et al. 2009; Grayson et al. 2014; Chhetry et al. 2016). The functional neurological significance of the essential PUFAs, in particular DHA, is best described by studies demonstrating compromised cognitive abilities accompanied by deficiencies of these vital fatty acids and improvements realized by their dietary supplementation. In a study undertaken by Cutuli et al. (2014), mice fed diets containing a mixture high in DHA and EPA showed improved hippocampal cognitive function, increased neurogenesis and microglial number as well as enhanced neuronal density in the brain after just 4 weeks. In an interesting, long-term dietary study on rhesus monkeys, Grayson et al. (2014) demonstrated a detrimental effect of life-long n-3 fatty acid deficiency upon multiple aspects of brain functional connectivity. Those monkeys fed a diet high in DHA throughout their lifetimes had an abundance of this fatty acid in their neural membranes, and their cortical, modular organizational network resembled that of the healthy human brain.

Human studies are frequently carried out on neonatal subjects because the most rapid brain growth commences in the mid-trimester of fetal development, continuing throughout the second year of life. There is a tenfold increase in brain size during this period, accompanied by an approximate 30-fold increase in DHA content and a 15-fold increase in AA (Clandinin et al. 1980; Al et al. 1990, 1995; Martínez and Mougan 1998; Ghys et al. 2002; Birch et al. 2007). Dijck-Brouwer et al. (2005) investigated umbilical artery and vein fatty acid compositions and early neonatal neurological condition in 317 term infants and concluded that lower fetal AA, DHA, and EPA status influences neonatal neurological condition in a negative manner. These results correspond positively with an earlier randomized, double-blind study by Helland et al. (2003) who analyzed the mental processing composite scores of 76 four-year-old children. The children were born to mothers who either consumed cod liver oil (direct DHA and EPA source) or corn oil (linoleic and linolenic acids, AA, and EPA/DHA precursors). The results led them to conclude that direct maternal supplementation of very long-chain n-3 PUFAs during pregnancy and lactation improved the intelligence of children at 4 years of age. Numerous other clinical studies highlighting the significant neurological and cognitive value of pre- and postnatal dietary long-chain PUFAs have been reported (Hibbeln et al. 2007), leading to the supplementation of infant formula with these important essential fatty acids (Bouwstra et al. 2006; Birch et al. 2007; Luchtman and Song 2013; Cunnane and Crawford 2014).

In terms of the impact of n-3 PUFAs on white matter pathologies, numerous studies have shown beneficial effects derived from direct dietary supplementation of these long-chain fatty acids. For example, white matter damage is responsible for secondary neurological outcomes in spinal cord injuries, adversely affecting neurons, glia, and axons (Smith and Jeffery 2006; Kozłowski et al. 2008). Following up on previous studies, Ward et al. (2010) demonstrated the therapeutic potential of DHA in attenuating the neurological deficits in rat brains after spinal cord injury. These researchers investigated the effects of acute intravenous administration of DHA alone or in combination with a DHA-enriched diet on rats subjected to thoracic injury. By 1 week post-injury, DHA injection led to significantly reduced axonal dysfunction, and by 6 weeks, damage to myelin and serotonergic fibers was also reduced. Interestingly, for some of the neurological parameters measured, the combination of DHA injection and DHA-enriched diet led to greater neuroprotection than DHA injection alone. In addition to reducing neurological shortcomings following injury, dietary supplementation with n-3 fatty acids has been shown to play a protective role as well. An example of this was demonstrated by Pu et al. (2013) who fed mice a diet enriched in DHA and EPA for 2 months before subjecting them to traumatic brain injury. The results revealed that n-3 supplementation elicited multifaceted protection against behavioral dysfunction, hippocampal neuronal loss, inflammation, and loss of myelination and impulse conductivity. Taken together, these findings suggested there were prophylactic benefits to be realized associated with long-term ingestion of dietary n-3 PUFAs against neural health challenges. These data are particularly pertinent with respect to maternal DHA and EPA supplementation in the protection and development of the neonatal brain (Dijck-Brouwer et al. 2005; Tuzun et al. 2012; Liu et al. 2013).

The dietary sources for the polyunsaturated fatty acids are both indirect and direct. The precursor to AA synthesis, linoleic acid, is found in oils of various seeds, such as sunflower, corn, and soybean, and the main sources of α -linolenic acid, the precursor to DHA and EPA, are some higher green plants (macro and micro) algae, fatty fish, and plankton. Direct or preformed sources of AA and DHA are egg yolk, animal meat and organs, marine (micro and macro) algae, cold water fish, and shellfish that directly or indirectly feed on algae (Mouritsen 2005; Bazan et al. 2011). Some modern foods are also artificially enriched in, e.g., DHA, such as DHA-enriched eggs or formula. The metabolic conversion of linoleic acid to AA is relatively efficient, but the conversion of α -linolenic acid to EPA and DHA is much less so, approximately 5–10 % to EPA and 2–5 % to DHA, and females are more effective to support this conversion than men. Direct consumption of preformed EPA and DHA, therefore, offers more efficient availability and subsequent utilization of these crucial n-3

fatty acids (Emken et al. 1994; Gerster 1998; Uauy et al. 2000; Brenna and Carlson 2014).

It is interesting to note that whereas we tend to think of fish and shellfish as the original sources of polyunsaturated n-3 fatty acids like EPA and DHA, fish and shellfish, in the same way as with humans, lack sufficient enzyme activity (fatty acid desaturation and elongation enzymes) to produce large amounts of these precious fatty acids. The original and main source of n-3 PUFAs is to be found lower in the food web, specifically with algae (micro and macro) that synthesize them in large amounts de novo (Kumar et al. 2011; Schmid et al. 2014). This constitutes the basis for the enrichment of n-3 PUFAs in the lipids of other marine organisms throughout the aquatic food chain (Burri et al. 2012; Paiva et al. 2014).

Taurine

In a review article regarding the evolution of the human brain, it is prudent to highlight dietary sources of brain-essential nutrients, and while the long-chain polyunsaturated fatty acids are fundamentally significant, other important nutrients play a key role in brain health and development. These additional essential nutritional elements include, among others, taurine, zinc, magnesium, iodine, and vitamin B₁₂, and each will be discussed briefly in terms of their purported impact on brain health and development, beginning with taurine. Taurine is a phylogenetically ancient compound, present in high concentrations in red algae, marine fish, and shellfish, as well as the meat of mammals. It is absent or present in only trace amounts in the plant kingdom (Huxtable 1992). Taurine is a free amino-sulfonic acid, mainly acquired through diet, and it is present in large amounts in the central nervous system and in the retina (Froger et al. 2012). Taurine's neuroactive properties include osmoregulation, membrane stabilization, calcium homeostasis, as well as neuromodulation, and the highest concentrations occur in the developing brain. Levels in adults are approximately 1/3 those of neonates (Huxtable 1992; Chen et al. 2001; Dominy et al. 2004). In a study using human fetal brain cells, Hernández-Benítez et al. (2013) showed that taurine significantly enhanced the percentage of neurons formed. In that investigation, taurine also increased cell number and neuronal generation, with maximum effect occurring at 4 days of culture.

Magnesium

Among other physiological functions (see Nils-Erik et al. 2000 for an extensive review), magnesium (Mg) has been shown to play an important role in neuroprotection and cognition. Mg is an essential mineral that can be sourced from legumes such as peas and beans, pumpkin and squash seeds, nuts, and macroalgae. Meat, poultry, and most fish contain very little of this micronutrient (NRC Food and Nutrition

Board 1989; MacArtain et al. 2007; Paiva et al. 2014). The primary mechanism for Mg-induced neural protection is generally thought to be related to a noncompetitive channel blockade of the *N*-methyl *D*-aspartate (NMDA) receptor, thereby reducing excitotoxic neuronal damage. The Mg ion is known to modulate the voltage-dependent blocking of the NMDA receptors, controlling their opening during coincidence detection, a process critical for synaptic plasticity and important for the ability to store new information in neural networks (Nowak et al. 1984; Harrison and Simmonds 1985; Collingridge et al. 2013). Moncayo and Ortner (2015) conducted recently a review of the current literature to identify the multifactorial determinants of cognition and to support or refute what may amount to the presently accepted dogma. These authors presented the conclusions of studies that demonstrated a functional relationship between magnesium levels and thyroid function, deficiencies of which led to clinical cognitive difficulties such as a lack of concentration in adult patients and difficulty in learning. In terms of effect on memory and learning abilities, Sprague-Dawley rats fed a supplemental magnesium compound for up to 24 days demonstrated an increased brain magnesium content and the rats exhibited enhanced learning abilities and memory functions (Slutsky et al. 2010).

Zinc

Zinc (Zn) is an important trace element for human health, normally present in a minor plasma pool with rapid turnover, such that a daily intake of Zn is required to achieve the steady-state and to maintain and support all its functions (Frederickson et al. 2000; Rink and Gabriel 2000; Bonnaventura et al. 2015). After iron, zinc is the most abundant transition metal in humans, and it is found in all tissues throughout the body, with 85 % in muscle and bones, 11 % in the skin and liver, and 1.5 % in the brain. With respect to brain weight, this translates to 11 µg Zn/g organ dry weight, with concentrations highest in the hippocampus and in the gray matter (Rink and Gabriel 2000; Sandstead et al. 2000; Chasapis et al. 2012). The presence of Zn within the neuronal circuitry of the brain, essentially linking cognitive pathways, plays an important role in learning, development, and memory. Zn has been shown to modulate intracellular and intercellular neuronal signaling and to regulate cell division and proliferation. Zn deficiencies in the brain can lead to numerous adverse effects, including lack of concentration, difficulties with learning and memory, loss of neurons, decreased brain volume, low infant birth weights, and cognitive abnormalities in developing neonates (MacDonald 2000; Bourre 2006; Sensi et al. 2011; Prasad 2013; Moncayo and Ortner 2015). In the central nervous system (CNS), Zn plays a specialized role as a neurosecretory product or cofactor. As such, it is highly concentrated in the synaptic vesicles of a specific contingent of neurons (Frederickson et al. 2000). Zn modulates

the strength of synaptic ionotropic glutamate AMPA receptors (AMPA). AMPA is a trans-membrane receptor for glutamate that mediates fast synaptic transmission in the CNS, and its activity is implicated in nearly all aspects of brain development, function, and plasticity (Kalappa et al. 2015). AMPARs and NMDAs are members of the ionotropic glutamate receptor family, and because they are localized in the postsynaptic density of most of the glutamatergic synapses in the brain, they mediate excitatory transmission and play an essential role in learning and memory (Traynelis et al. 2010; Morris 2013). Kalappa et al. (2015) used specialized chemical tools enabling them to efficiently intercept and visualize mobile Zn, and they verified that synaptically released Zn is an endogenous modulator of AMPARs. Using wild-type mice and mice genetically modified to lack synaptic Zn, they determined that endogenous Zn inhibited synaptic AMPA currents in the dorsal cochlear nucleus (DCN) and hippocampus. Exposure to loud sound reduces presynaptic Zn levels in the DCN and abolishes Zn inhibition, implicating Zn in experience-dependent AMPAR synaptic plasticity. The researchers concluded that Zn is a key player in the complexity of AMPAR synaptic plasticity in the mammalian brain, crucial for memory, learning, and proper functioning and adaptability.

Zn is present in relatively small amounts in many foods but is particularly plentiful in various cuts of meat, especially liver, and it is extremely abundant in oysters. Crustaceans and most seaweeds are also robust sources of this important micronutrient (Stengel et al. 2004; Dietitians of Canada 2014; NIH Zinc Factsheet 2016; Cabrita et al. 2016). Despite the apparent availability of dietary Zn in the modern world, issues of deficiencies do exist and are primarily a result of malnutrition, with an estimated 17.3 % of the world's population at risk of inadequate Zn intake (Wessells and Brown 2012). Earlier, in 2002, the World Health Organization (WHO) (2002) issued a report estimating that Zn deficiency affects about one-third of the world's population, particularly in sub-Saharan Africa, Southeast Asia, and the Eastern Mediterranean where cereals constitute a significant part of the diet (Prasad 2013). The presence of an abundance of phytates in plant-based diets is also a factor in Zn deficiency. Phytates are found in grains, legumes, nuts, and seeds, and they have a strong affinity for divalent cations such as zinc, binding tightly to them and reducing their bioavailability (Sandstead 1991).

Vitamin B₁₂

A deficiency in vitamin B₁₂ is intrinsically associated with factors impacting brain development, including altered cerebral blood flow, compromised cognition control, and language function in humans. B₁₂ is necessary to ensure adequate methylation by *S*-adenosylmethionine in the synthesis of neurotransmitters, myelin, and phosphatidylcholine (von Schenck et al. 1997; Bourre 2006; Stabler 2013; Roy et al. 2015; Gupta

et al. 2016). Newborn infants experiencing a diet devoid of B₁₂ are the most susceptible to deficiencies since their body stores, estimated to be about 25 µg, are utilized at approximately 0.1 µg day⁻¹ for tissue synthesis during the first month of life. By extrapolation, without replenishment, this endogenous B₁₂ should last about 8 months. This is even more precarious if the mother is also deficient in B₁₂, and typical symptoms of infantile vitamin B₁₂ deficiency are cerebral and optic nerve atrophy, apathy and coma, hypotonia, as well as developmental delay (von Schenck et al. 1997; Roumeliotis et al. 2012). Vitamin B₁₂ is found exclusively in animal products such as meat, eggs, fish, and milk (Otten et al. 2006; Dror and Allen 2008), with one exception. It is also confirmed in *Pyropia* spp. of seaweeds and is quite likely in others that have yet to be adequately analyzed (Croft et al. 2005; Watanabe 2007).

The adequacy of maternal intake and adsorption of B₁₂ during pregnancy and lactation has a stronger influence on infant status than do maternal stores, and even relatively short-term maternal dietary restriction can result in poor infant vitamin B₁₂ status (Rosenblatt and Whitehead 1999). In a detailed chart review of 27 infants in India diagnosed with vitamin B₁₂ deficiency, Goraya et al. (2015) noted that the infants showed normal development during the first 4–6 months of their life. Initial deficiency symptoms included irritability, lethargy, feeding difficulties, refusal of solid foods, pallor, and failure to thrive, followed by neurodevelopmental regression. Affected infants responded well to B₁₂ supplementation, but long-term neurodeficits in motor, cognitive, and language domains occurred in those with delayed diagnosis. Vitamin B₁₂ deficiency is known to be associated with demyelination and can result in severe brain atrophy, with the frontal and temporal lobes most severely affected (Lövlblad et al. 1997; Roy et al. 2015). Delayed myelination or demyelination of nerves leads to central and peripheral nervous system dysfunction because B₁₂ is a coenzyme in the methyl malonyl-CoA mutase reaction necessary for myelin synthesis. In addition, astrocytes and microglia appear to play a role in the demyelinating neuropathy of vitamin B₁₂ deficiency, although these mechanisms are very complex and require further study to improve our understanding of them (Dror and Allen 2008; Briani et al. 2013). In an investigation of the functional alterations in the different regions of the brain due to vitamin B₁₂ deficiency, Gupta et al. (2016) used resting-state, functional magnetic resonance imaging (rsfMRI) to compare brain function between B₁₂-deficient adult patients and age-matched controls. All patients in the study had gait abnormalities, sensory disturbance, mental impairment, and suggestions of neuropathy that responded significantly to vitamin B₁₂ supplementation as assessed by improvement at 6 weeks. Results of this investigation led the researchers to conclude that it is, indeed, the brain networks associated with cognition control that are altered in patients with vitamin B₁₂ deficiency.

Iodine

Iodine deficiency during pregnancy and infancy may impair growth and neurodevelopment of offspring and increase infant mortality (Zimmermann 2009). This important element is necessary for the synthesis of thyroid hormones, which are essential for central nervous system development, including neurogenesis, neuronal migration, axon and dendrite growth, synaptogenesis, as well as myelination (Prado and Dewey 2014). Humans are unable to make iodine, so it must be obtained from food, and the most robust natural sources are derived from the marine environment. Present-day secondary sources include bread, milk, beans, and eggs (NRC Food and Nutrition Board 1989; Zimmermann 2009; Dietitians of Canada 2014). Despite the apparent availability of iodine-fortified foods and the governmental-controlled addition of iodine to kitchen salt in some countries, WHO (2007) estimated that, in 2004, two billion people around the world were at risk for iodine deficiency. The report stated that iodine deficiency was the world's greatest, single cause of preventable mental impairment and it negatively impacts the intellectual ability of an individual by between 10 and 15 intelligence quotient (IQ) points. Iodine content in seaweeds is widely recognized, and it is especially prevalent in brown seaweeds, and this will be discussed in the following section.

Vanderpump et al. (2011) conducted a cross-sectional survey to assess iodine status in 737 girls aged 14–15 years attending school in the UK. Urinary iodine measurements indicated mild iodine deficiency ($50\text{--}99\ \mu\text{g L}^{-1}$) in 51 % ($n = 379$) of the participants, moderate deficiency ($20\text{--}49\ \mu\text{g/L}$) in 16 %, and severe deficiency ($<20\ \mu\text{g L}^{-1}$) in 1 % of participants. Results of a cross-sectional survey of 1709 schoolchildren aged 8–10 years in Australia also indicated inadequate dietary iodine intake in that country (Li et al. 2006). Of utmost importance in terms of brain development and cognition is the availability of dietary iodine, both to the developing fetus and in the first few years after birth (Prado and Dewey 2014). In Austria, the urine samples of 246 pregnant women were analyzed for iodine deficiency and results indicated only 13.8 % of the cohort were in the recommended range of $150\text{--}249\ \mu\text{g L}^{-1}$ (Lindorfer et al. 2015), suggesting potential for a significant number of Austrian offspring to be born with a cognitive disadvantage. These data speak to the necessity of a consistent and stable food supply of iodine required for the cognitive development of the human brain.

To investigate the impact of iodine deficiency on cognitive function, Zimmermann et al. (2006) performed a randomized, double-blind intervention trial on school children in Albania ($n = 310$). After 24 weeks of iodine supplementation, a series of cognitive and motor tests were administered to the participants, and compared to the placebo group, the iodine-treated group demonstrated significant cognitive improvement. In this study, information processing, fine motor skills, and

visual problem solving were found to be improved by iodine repletion in moderately iodine-deficient children. Maternal iodine deficiency is particularly detrimental to cognitive function, and it is well known to have adverse effects on the neurodevelopment of offspring (Zimmermann 2009; Prado and Dewey 2014). Bath et al. (2013) analyzed the iodine content in urine samples from the first trimester of pregnancy of 958 women and matched the results to the IQ in the offspring at age 8 years and to reading ability of children at age 9 years. Results of the study verified that low maternal iodine status ($<91.1\ \mu\text{g L}^{-1}$) was clearly associated with an increased risk of suboptimum scores for verbal IQ at age 8 years and reading accuracy, comprehension, and reading score at age 9 years.

Brain-essential elements and impact on evolution

In addition to PUFAs, taurine, magnesium, zinc, vitamin B₁₂, and iodine there are other brain-essential nutrients such as iron, copper, selenium, choline, and various B vitamins (Bourre 2006; Marques et al. 2013). However, the intention of this review is to highlight some of those with significant impact on cognitive health and development that may have influenced human evolution based upon their availability, or not, 2.5–2.0 mya. The very high energy and nutritional requirements of the developing human brain point to the importance of maternal stores and the continued replenishment of brain-selective nutrients for the neonate on through infancy and early childhood (Uauy et al. 2000; Navarrete et al. 2011; Cunnane and Crawford 2014; Prado and Dewey 2014).

In humans, it is thought that the brain maintains biological priority during fetal development under normal and moderate degrees of nutritional deficiencies (Crawford 1992), but recently, this concept has been challenged, and even short-term maternal nutrient deficiencies have been found to have adverse effects on brain development (Gluckman and Hanson 2004; Modgil et al. 2014). Following up on rodent studies that demonstrated significant changes in fetal body and brain composition, associated with poor maternal nutrition during pregnancy, Antonow-Schlorke et al. (2011) tested this effect in primates. Based upon evidence previously established regarding the beneficial effects of a moderate 30 % dietary restriction on health and longevity in several species, including nonhuman primates, the researchers assessed the effect of a 30 % maternal dietary reduction on early fetal cerebral development in the baboon. Results showed major cerebral developmental disturbances without fetal growth restriction or marked maternal weight reduction. Mechanisms evaluated included neurotrophic factor suppression, cell proliferation and cell death imbalance, impaired glial maturation and neuronal process formation, downregulation of gene ontological pathways and related gene products, as well as upregulated transcription of cerebral catabolism. Clearly, a nutritionally balanced maternal diet is critical for the development of a healthy infant, and the

continued availability of brain-essential nutritive components would help ensure cognitive vigor into adulthood.

Accompanying the developmental changes in brain size and function in early *H. sapiens* were increased body size, changes in nutrient metabolism, the deposition of neonatal subcutaneous body fat, a reduced gut size, an extended gestation period, bipedalism, and significant changes in head shape and jaw function (Milton 1987; Aiello and Wheeler 1995; Leonard and Robertson 1997; Leonard 2002; Leonard et al. 2010; Watkins et al. 2010; Navarrete et al. 2011; Lieberman 2011; Cunnane and Crawford 2014; Mouritsen 2016). Reflecting on the function of food to sustain growth, repair and vital processes, and to furnish energy, it is reasonable to expect a close relationship between the diet and the structural and functional changes documented in early hominins, leading to modern-day humans. The triggers for these adaptations would have been the evolutionary norm, but it is possible that the evolution of the sophisticated *H. sapiens*' brain had serendipitous beginnings, indirectly influenced by diet, climate, and local environment.

An examination of the most widely accepted timeline of human evolution based upon fossil evidence shows there were numerous variations of the distant ancestors and relatives in the family tree of modern *H. sapiens*. Although the dearth of physical records makes for a rather murky evolutionary pathway, general consensus has pinpointed the first major burst in hominin brain size at about 2.0–1.7 mya (Leonard et al. 2010). The human lineage is estimated to have diverged from our closest living relatives, the chimpanzees, around 5–7 mya (Glazko and Nei 2003). However, the changing patterns of resource distribution associated with the extensive drying and expansion of the African savannahs between 2.5 and 1.5 mya may have been the impetus for a shift in foraging behavior among early members of the genus *Homo* (Leonard and Robertson 1997). Foraging over longer distances for food would have contributed to bipedalism and a different body stature (Lieberman 2013) as increasingly larger ranges had to be traversed, and in the case of our primitive ancestors, this would undoubtedly lead to significant changes in diet (Hawks et al. 2000; Navarrete et al. 2011). Evidence that positive selection in humans has targeted the regulation of many genes known to be involved in neural development, function, and also in nutrition has been detected (Haygood et al. 2007). Positive selection refers to the selective pressure that leads to the fixation of specific variants that increase in frequency until they become part of the genetic make-up in the relevant population. Similarly, Blekhman et al. (2008) used a multi-species microarray to measure and compare gene expression levels in kidney, liver, and heart tissues from humans, chimpanzees, and rhesus macaques. These authors identified distinct functional differences between humans and other primates. Results of their analyses were consistent with the long-standing hypothesis that shifts in diet underlie many

regulatory adaptations in humans, playing an important evolutionary role in lineage-specific directional selection.

As body size increased, so did energy requirements, and the balance of supply and demand would drive development and advanced sophistication. More active species tend to consume more energy-rich diets (Leonard and Robertson 1997) and the physical and metabolic systems of early hominins further adapted by reducing gut size, which was also an indication of higher quality foods, of which cooking would have eventually contributed to (Wrangham and Conklin-Brittain 2003; Wrangham 2009). Increased fat deposition at the neonatal stage, extended gestation times, and larger brains are energetically costly traits. However, natural selection apparently prevailed and circumstances must have accommodated (Luca et al. 2010; Navarrete et al. 2011). The substrates for brain development, i.e., PUFA n-3 and n-6 would need to be present in the original baseline diet prior to encephalization of the neonate and after brain expansion in the child, as would other brain-essential nutrients (Brenna and Carlson 2014; Cunnane and Crawford 2014; Sistiaga et al. 2015). The consumption of a high-quality diet is recognized as both a prerequisite for and a consequence of encephalization (Kyriacou et al. 2014).

Diets of early hominins

There are obvious limitations in determining the precise components of early hominid diets, and the lack of lignified tissues in, e.g., macroalgae further reduces the probability of finding fossilized remains of this food source. The tools most commonly used include reconstructions of the biomechanics of fossilized jaws, bone and teeth isotopic data, tooth wear patterns, and lithic, taphonomic, and zoo-archeological data (Sistiaga et al. 2015). Correlations of plant populations to results of stable isotopic analyses of fossilized teeth or bones have identified specific types of metabolic pathways that are reflected in the diets of the consumer. During photosynthesis, vegetation preferentially takes up ^{12}C over ^{13}C , but plants utilizing the Hatch-Slack pathway for energy metabolism, so-called C_4 plants, are less discriminating than C_3 plants that utilize the Calvin cycle. Therefore, C_4 plants are typically characterized by a high ^{13}C -to- ^{12}C ratio, averaging around 12 ‰ and C_3 plants have a ratio around 28 ‰ (Bumsted 1981). This ratio is incorporated into the tissue carbon of the consumer and provides a dietary signature of the types of plant foods consumed. C_4 plants are primarily grasses and sedges, with some rare dicots, whereas in the tropics, C_3 plants are primarily trees, fruits, shrubs, and nongrassy herbs and forbs (Cerling et al. 2013).

Isotopic analysis has been carried out on numerous fossilized remains of early hominins; the results of which indicated that before 4 mya, hominin diets consisted primarily of C_3

plants, akin to the diets of nonhuman primates. By about 3.5 mya, multiple hominin taxa began to increasingly incorporate C_4 foods into their diets, although the trend and ratio varied by region (Sponheimer et al. 2013). For example, a study by Sponheimer and Lee-Thorp (1999) on tooth enamel from four 3 million year old *Australopithecus africanus* fossils from the Makapansgat site (South Africa) demonstrated wide dietary variability. Isotopic analysis of one specimen placed it well within the range of C_3 consumers, whereas the majority of the Makapansgat hominins obtained dietary carbon from C_4 vegetation or from animals that consumed such vegetation. These authors questioned why these particular hominins exploited C_4 resources to such an extent, despite living with such an abundance of C_3 resources, and exhibiting an adaptation for foraging in trees. Dental micro-wear, consisting of pits and scratches, also suggested a diet other than 100 % grasses and sedges, compared to present-day grass eaters. Furthermore, lacking the cranio-dental specialization for chewing tough, fibrous foods, and the absence of evidence that *A. africanus* used tools, they postulated that this lineage eventually became extinct around the same time *Paranthropus robustus* appeared, approximately 2.5 mya. While useful in terms of determining types of vegetation ultimately consumed, isotopic analyses cannot identify specific plants, but it does demonstrate significant variation in the hominin diet, resulting no doubt from an opportunistic foraging strategy. An interesting caveat in the theory that dietary seaweeds positively influenced *H. sapiens* brain development related to C_3 or C_4 evidence is that the ^{13}C -to- ^{12}C ratio varies widely among seaweeds. Maberly et al. (1992) analyzed no less than 9 species of green macroalgae, 15 species of brown macroalgae, and 22 species of reds collected from various places around the east coast of Scotland. Their results ranged from 8.81 to 34.74 ‰, effectively discounting isotopic analysis as a tool to define seaweed consumption. However, evidence of dental micro-wear would suggest the possibility of bits of sand that could accompany the consumption of shellfish and seaweeds.

While the study of hominin evolution and the factors that influenced the size and complexity of the human brain is ongoing, there is hard evidence to indicate that dietary changes occurred in parallel with the development of this sophisticated organ (Luca et al. 2010; Cerling et al. 2013; Sponheimer et al. 2013; Wynn et al. 2013; Erlandson and Moss 2015). To accommodate the nutritional necessities for enhancing brain size and the associated cognitive abilities, a consistent and specialized diet containing all the brain-essential nutrients would be required over the evolutionary long term. In a comprehensive literature review, Stewart (2014) proposed that early hominins, in response to extensive environmental fluctuations, exploited C_4 -based wetland dietary resources. These resources would include tough sedges and grasses, and perhaps freshwater vertebrates and invertebrates, which could

contribute some brain-selective nutritional elements. While the meat of other C_4 consumers is another potential source of these critical nutrients, its availability on a long term and consistent basis is questionable, especially when foraging was the primary means of food acquisition. For nonresidual nutrients such as zinc, iodine, or B_{12} , regular intake is essential if brain development was to be enhanced and sustained in terms of size and cognitive capacity. Of utmost importance in neonatal brain growth and development is the quality of the maternal diet prior to, during, and after a lengthy gestation period.

Coastal diets

The food resources associated with coastal diets would provide that essential level of nutritional quality. With sustainable, plentiful supplies over multiple generations, it is feasible that members of early *Homo* ancestors could have experienced reduced selection pressures, in the face of luxury nutrient supply. Important components of that nutritional abundance found in coastal environments are DHA and AA that facilitate production of structural lipids and which are known to be essential for increased brain growth. These would have played corresponding, integral roles in functional complexity that benefitted coastal communities specifically (Brenna and Carlson 2014; Kyriacou et al. 2014; Marean 2014). To accommodate the extraordinary energy demands of the developing infant brain, human neonatal infants accumulate the highest levels of body fat of any mammalian species and they continue to gain fat during early postnatal life (Leonard et al. 2010). This reserve of baby fat contains three to four times more AA and DHA as compared to human adult body fat (Farquharson et al. 1992), and for a foraging lifestyle, a rich coastal environment would be a significant source of a consistent supply of these nutrients.

Foods found on ancient marine shores would include fish, crustaceans, snails, seaweeds, bird eggs, and perhaps occasional dead marine vertebrates. Undertaking nutritional analyses of a selection of terrestrial and marine fauna, Kyriacou et al. (2014) assessed the number of a specific limpet or mussel species required to meet the daily iron and protein needs of early hunter-gatherers. The authors concluded that while the absolute numbers of units required were high, marine crustaceans could supply a systematic and reliable source of these fundamental nutrients, which are comparable to meat from terrestrial environments. However, Marean (2014) hypothesized that a true coastal adaptation, which implied a systematic use of varied coastal resources, would require at least a rudimentary understanding of seasonal tidal cycles and their influence on shellfish availability. Seaweeds of different types, on the other hand, can be found all across the intertidal zone, from the high water mark to the subtidal regions and they could be readily and repeatedly harvested for food by all

family members, including women and children. This stable supply of nutritional vegetation would be less impacted by spring and autumnal equinoxes and would provide fundamental and consistent supplementation of a diet of marine animals. As modern-day *H. sapiens* requires a well-balanced, dietary regime for the continued manifestation of health and wellness, a sustained abundance of foods rich in brain-essential nutrients would have been an impetus for the development of a larger, more sophisticated brain. To trigger the development of such a richly complex organ prior to the development of tools and weapons made from stones, our earliest ancestors, in all likelihood, exploited shore-based habitats (Cunnane and Crawford 2014).

Seaweeds

The case for seaweed in human brain evolution

From a dietary standpoint, seaweeds collectively contain all the elements required for human growth and nutrition, including DHA, AA, and EPA, albeit the lipid components are in relatively low concentrations, as compared to some fish sources (MacArtain et al. 2007; Pereira 2011; Mouritsen 2013; Paiva et al. 2014). Seaweeds are, however, along with microalgae, the source of vital fatty acids and other nutrients for the animals that eat and accumulate them. The brain-essential nutrients highlighted in this review are all present in seaweeds in amounts adequate to fulfill the definition of food for early *Homo*, if eaten as part of a staple diet. This statement holds true for all the other brain-essential nutrients not discussed herein as well, such as iron, copper, choline, and selenium for examples (Anantharaman et al. 2010; Mohamed et al. 2012; Cornish et al. 2015).

As such, it is not difficult to speculate that the expansion of the human brain in form and function was largely influenced by a consistent, high-fiber, high-protein, nutritionally enriched, shore-based diet. Highly fluctuating sea levels (Rohling et al. 2014) and the readiness with which seaweeds completely disintegrate over time are strong factors against finding conclusive fossil evidence of seaweeds used as food, making it easy to overlook their significance in the brain development of *H. sapiens*. However, their ready availability and ease of preservation (drying) means they could have easily supplemented a brain-essential diet of fish, crustaceans, and other shore-based organisms, particularly for prenatal women and young children. Indeed, more recent archeological evidence (i.e., ~14,600 years ago) documented seaweed usage in a settlement located several kilometers inland from the coast of Chile, suggested that inhabitants were familiar with the utilization of this food resource (Dillehay et al. 2008).

PUFAs and taurine in seaweeds

The nutritional composition of seaweeds varies depending on the seasons and with the environment in which they grow and reproduce (Holdt and Kraan 2011; Miyashita et al. 2013). A study by Dawczynski et al. (2007) analyzing 34 edible, commercial seaweed products showed all samples contained all the essential amino acids and the polyunsaturated fatty acids existed in the nutritionally optimum n-6/n-3 FA ratio. As much as 50 % of the FA component was predominantly EPA (n-3). The red seaweeds (*Pyropia* spp. formerly genus *Porphyra*) analyzed in this study featured uniquely high concentrations of taurine (i.e., 2.4–4.3 g/16 g N) relative to the brown seaweeds *Undaria pinnatifida* (Harvey) Suringar, *Laminaria* sp., and *Hizikia fusiforme* (Harvey) Okamura with 0.1, 0.3, and 0.6 g/16 g N, respectively. Laycock and Craigie (1977) reported on the seasonal variation of taurine in samples of *Chondrus crispus* Stackhouse (Irish Moss), as it increased over the winter months and became much depleted by October (in the Northern Hemisphere). Other researchers identified various concentrations of taurine in a number of macroalgal species, including reds, browns, and the green alga *Codium fragile* (Suringar) Hariot (Harnedy and FitzGerald 2011; Mohibullah et al. 2015). Taurine is present in humans in large amounts in the central nervous system and in the retina. The highest concentrations occur in the developing brain; interestingly, its nutritional availability from members of the plant kingdom is negligible (Huxtable 1992; Froger et al. 2012).

Magnesium in seaweeds

Magnesium plays a critical role in synaptic plasticity, important for the ability to store new information in neural networks, thereby impacting cognitive skills such as memory and learning (Nowak et al. 1984; Harrison and Simmonds 1985; Collingridge et al. 2013). Mg is an essential mineral found in legumes, pumpkin and squash seeds, nuts, some fish, and most macroalgae (MacArtain et al. 2007; Dietitians of Canada 2014; USDA, United States Department of Agriculture 2016). Similarly to other nutritional elements found in seaweeds, the magnesium concentration can vary based upon season, species, and environmental conditions. In an analysis of several different seaweeds collected off the southeast coast of India, Anantharaman et al. (2010) detected a range of magnesium content from 39.91 to 181.5 ppm. Bae et al. (2011) investigated the bioavailability of seaweed-derived magnesium and calcium extract in rats and determined this to be a more effective source of these micro-minerals as compared to supplementation with calcium carbonate and magnesium oxide. Numerous seaweeds are a ubiquitous source of many minerals, and significant levels of magnesium have been detected in the browns *Ascophyllum nodosum* (Linnaeus) Le

Jolis, *Laminaria digitata* (Hudson) J.V. Lamouroux, *Saccharina (Laminaria) japonica* (Areschoug) C.E. Lane, C. Mayes, Druehl & G.W. Saunders, the reds *Pyropia (Porphyra)* spp., *C. crispus*, *Kappaphycus alvarezii* (Doty) Doty ex Silva, *Gloiopeltis furcata* (Postels & Ruprecht) J. Agardh, and the greens *Ulva* (Enteromorpha) spp., *Caulerpa lentillifera* J. Agardh to name a few (see also Ratana-arporn and Chirapart 2006; MacArtain et al. 2007; Nakamura et al. 2012; Yong et al. 2015).

Zinc in seaweeds

Zinc is also critical for human cognitive development. It is a transition metal with a rapid turnover rate within the plasma pool, such that a stable intake is required to support important aspects of brain function and development (Frederickson et al. 2000; Rink and Gabriel 2000; Bonnaventura et al. 2015). Zinc is abundant in the liver and various other cuts of meat, crustaceans, especially molluscs such as oysters, and many species of seaweed. Zn is also present, albeit in smaller amounts, in nuts and seeds, but very little would have been present in the grasses and sedges early hominins may have eaten (MacArtain et al. 2007; Dietitians of Canada 2014; USDA, United States Department of Agriculture 2016). Seaweeds typically reflect the mineral status of the seawater in which they grow, and while modern analyses may be indicative of anthropogenic activities, dissolved solids and chemical weathering of rocks would have contributed to the oceanic zinc pool of 2 mya. In an extensive analysis of marine, black shale samples from North America, Africa, Australia, Asia, and Europe, dated 2.7 billion to 580 mya, Scott et al. (2013) determined there was high seawater zinc availability in the early oceans. In a study on edible seaweeds, MacArtain et al. (2007) detected zinc levels of $1.6 \mu\text{g g}^{-1}$ wet weight in *L. digitata* and $1.7 \mu\text{g g}^{-1}$ wet weight in *Himanthalia elongata* (Linnaeus) Gray, while others have also reported zinc in a variety of other macroalgal species. In an analysis of 19 species, Stengel et al. (2004) found that concentrations ranged from 15 to $115 \mu\text{g g}^{-1}$ dry weight. Misheer et al. (2006) recorded a range of 100–400 ppb in several samples of *Gelidium abbottiorum* R.E. Norris, and Astorga-España et al. (2007) reported a range of 14.9–79.0 $\mu\text{g g}^{-1}$ dry weight for several algal species sampled off the coast of Chile. However, the amount of zinc present in ancient seaweeds could have been much different, depending on the concentration of this mineral in the early oceans. The current recommended dietary allowance (RDA) for adults is 12–15 mg day^{-1} (NRC Food and Nutrition Board 1989).

Vitamin B₁₂ in seaweeds

An adequate supply of vitamin B₁₂ is essential for normal blood formation and for neurological function, and fetal and

maternal B₁₂ serum concentrations are strongly correlated. The RDA for pregnancy is $2.6 \mu\text{g day}^{-1}$ and for lactation increasing slightly to $2.8 \mu\text{g day}^{-1}$ (Otten et al. 2006; Health Canada 2010). Meat, fish, eggs, and some seaweeds are natural sources. Prokaryotes are the only organisms that synthesize B₁₂ and B₁₂-dependent macroalgae enter into mutualistic, symbiotic relationships with bacteria, providing fixed carbon in exchange for the vitamin (Kazamia et al. 2012). Vitamin auxotrophy in seaweeds is highly variable, and over 50 % of the 306 algal species surveyed required vitamin B₁₂, although this included many microalgae as well (see Croft et al. 2006). Obviously, there is a requirement for further investigations into this area regarding B₁₂-dependent macroalgae such as *Pyropia* sp., which contains substantial amounts of vitamin B₁₂ ($\sim 133.8 \text{ ng g}^{-1}$ dry weight) (Watanabe et al. 2014).

In a study to examine the vitamin B₁₂ status of long-term adherents of a strict, uncooked vegan diet, Rauma et al. (1995) showed that vegans ($n = 16$) consuming *Pyropia* sp. and/or *Chlorella* sp. had serum B₁₂ concentrations twice as high as those not eating algae ($n = 5$). Results of a study by Kwak et al. (2010) to investigate the influence of traditional foods, seaweeds, kimchi, and soybean-fermented foods on the B₁₂ status of very elderly Korean women ($n = 127$) led to the conclusion that these foods were significant sources of B₁₂. *Pyropia* spp. are found in temperate waters worldwide and belong to the order Bangiales, which is one of the most primitive groups of seaweeds (De Clerck et al. 2012). This genus is often considered the ancient precursor to the red algal clade. Scientists continue to question the processes underlying how species become dependent on an external source of essential micronutrients and the prevailing theory is that vitamin availability drives selection for vitamin dependence. Such a process invariably links an organism's metabolism to its environment (Helliwell et al. 2015), and it is reasonable that *Pyropia* species would have been readily available to coastal dwellers over 2–3 mya. The natural habitat of this red seaweed species is located among the highest in the intertidal zone.

Iodine in seaweeds

There is no question that iodine is a critical element for healthy, neurological brain development and the recommended intake of $220\text{--}290 \mu\text{g day}^{-1}$ for pregnant or breastfeeding women (WHO 2002; Otten et al. 2006; WHO 2007; Health Canada 2010) would be a challenge to obtain for early *Homo* species. Of the food sources containing iodine that would have been available over 2 mya to human ancestors might be some species of fish, such as cod or haddock, which may contain around 87 μg . Eggs might be especially abundant during nesting seasons and these may contain approximately 25–30 μg iodine (Dietitians of Canada 2014). However, these food sources would be neither stable over the long term nor would they be adequate to effectively meet the demands of a

developing brain equipped with any degree of cognitive sophistication.

The 1811 discovery of iodine in seaweed ash led to the utilization of burned seaweed (“kelp”) for the supply of iodine for medicinal purposes for many decades (Teas et al. 2004; Guiry and Morrison 2013). Iodine content in seaweeds is widely known, so much so, that it is sometimes referred to in precautionary terms, with respect to potential toxicity that could result from excessive consumption of certain species, particularly browns. However, concentrations of iodine differ among thallus parts, as reported by Nitschke and Stengel (2015) that developed a simple and reliable technique to accurately quantify iodine levels. All 19 seaweed species they analyzed demonstrated iodine content, with the highest amounts present in various portions of the Laminariales (i.e., 359–1920 $\mu\text{g g}^{-1}$ FW) and the lowest amounts in the Ulvophyceae (i.e., 3–14 $\mu\text{g g}^{-1}$ FW). The iodine content in the red seaweeds analyzed ranged between 9 and 174 $\mu\text{g g}^{-1}$ FW.

To investigate the potential for low-level seaweed supplementation to improve the iodine status of healthy, but iodine-insufficient women, Combat et al. (2014) conducted a cross-over iodine bioavailability study and a 2-week seaweed supplementation study. These authors tested commercially available encapsulated *A. nodosum* in 2×0.5 g daily servings with an iodine content approximating 712 μg (in the bioavailability study) and half that dosage in the supplementation study. Results suggested only a modest bioavailability at 33 (interquartile range (IQR), 28–46 %) of the ingested dose compared to 59 (IQR 46–74 %) from the potassium iodide (KI) supplement, possibly attributable to factors associated with the seaweed matrix. Daily ingestion of 0.5 g of the seaweed for 2 weeks significantly increased urinary iodine excretion and the concentrations of thyroid-stimulating hormone from 1.5 (IQR 1.2–2.2) to 2.1 (IQR 1.3–2.9). The authors concluded that with adequate analytical testing, the inclusion of seaweed in staple foods would serve as an effective alternative to fortification with salt or KI as a means to combat iodine deficiency.

Of particular significance with respect to the impact of seaweeds in early *H. sapiens* brain development, an issue related to the importance of iodine (particularly for women during pregnancy in terms of fetal supply and subsequent infant nutrition) may pertain to iodovolatilization. Iodovolatilization is a process where molecular iodine and a wide range of volatile organic iodine compounds are released into the atmosphere in coastal areas where brown seaweeds are abundant (Chance et al. 2009).

It is possible, perhaps even probable, that the relatively small group of hominins who became direct modern-day human ancestors took up residence in a coastal environment rich in seaweeds, shellfish, and marine life. Indeed, recent studies showed that urine samples from 45.6 % of schoolchildren living in coastal seaweed-rich environments had iodine values

>150 $\mu\text{g L}^{-1}$ as compared to only 3.6 % of children living in coastal areas without any seaweed beds present (Smyth et al. 2011).

Antioxidants in seaweeds

The robust antioxidant capacities attributed to seaweeds cannot be ignored in any discussion related to human health and wellness, as ROS underlie the pathologies associated with all forms of systemic duress. The human brain is particularly prone to oxidative stress, in part as a result of its high O_2 consumption. This effect of O_2 amount per unit of tissue mass is even more pronounced in young children with smaller bodies but not proportionately smaller brains (Halliwell and Gutteridge 2007). Inflammation is a common feature of human health disorders, and its associated ROS overproduction is particularly influential in the nervous system, contributing to neurodegenerative diseases and irregularities in brain function (Modgil et al. 2014; Jo et al. 2015, Kiecolt-Glaser et al. 2015).

Nutritional imbalances can also contribute to oxidative damage, although specific cause and effects are difficult to establish definitively due to the multitude of influential variables and cellular dynamics (Halliwell and Gutteridge 2007). However, numerous studies have demonstrated anti-inflammatory and neuroprotective effects based on the antioxidant properties of various seaweed extracts (Table 1). The stress-coping mechanisms of intertidal macroalgae are diverse and include antioxidant production and free radical scavenging activities, making them potent food sources for not only balancing nutrition but for providing avenues for cellular homeostasis (Cornish and Garbary 2010; Chojnacka et al. 2012).

The human “second brain”

The microbiota–gut–brain axis

A thorough discussion is beyond the scope of this review, but the rapidly expanding study of the microbiota–gut–brain axis cannot be ignored in a research appraisal involving nutrition and brain health and development. It is clear that dietary diversity is one of the most crucial factors impacting the human gut microbiota from birth, even possibly as early as the prenatal period, to old age (Oriach et al. 2016). More than an organ that processes, transports, and absorbs food, the human gut contains between 50 and 100 million nerve cells and several trillion microbes with a large species variety. This intricate system has often been referred to as the “second brain,” based upon its size, complexity, and its similarities in neurotransmitters and signaling molecules with the human brain (Mayer 2011). The bidirectional communication pathway between the brain and the gut microbes and the signals or metabolites that they

Table 1 Examples of macroalgal species (and/or extracts) associated with brain health and protection

Species	Purported mechanism(s)	Anticipated neurological effect(s)	Test organism	References
<i>Agarum clathratum</i> subsp. <i>yakishiriense</i> Yamada ex G.H. Boo & P.C. Silva	Attenuation of microglia activation	Neuronal protection from ischemic injury	Gerbils	Kim et al. (2014)
<i>Chondrus crispus</i> Stackhouse	Alleviates oxidative stress/upregulates stress response genes	Neuroprotection against Parkinson's disease	Transgenic <i>Caenorhabditis elegans</i>	Liu et al. (2015)
<i>Cystoseira tamariscifolia</i> (Hudson) Papenfuss; <i>Cystoseira nodicaulis</i> (Withering) M. Roberts	Acetylcholinesterase inhibition, oxidative stress reduction	Neuronal protection	In vitro laboratory analyses	Custódio et al. (2015)
<i>Ecklonia maxima</i> (Osbeck) Papenfuss	Acetylcholinesterase inhibition	Manage neurodegenerative disorders	In vitro laboratory analyses	Kannan et al. (2013)
<i>Ecklonia cava</i> Kjellman	Antioxidant activity	Neuronal protection	Hippocampus cell line	Kang et al. (2012)
	Acetylcholinesterase inhibition, phlorotannins	Memory enhancement	Mice	Myung et al. (2005)
<i>Eisenia bicyclis</i> (Kjellman) Setchell	Antioxidant activity	Protection from retinal neuronal death	Rats, retinal ganglion cells	Kim et al. (2012)
<i>Gelidium acerosa</i> (Forskåll) Feldmann & G. Hame	Antioxidant activity, phlorotannins	Neuroprotection, anti-Alzheimer's	Pheochromocytoma cells (rat)	Ahn et al. (2012)
<i>Gelidium amansii</i> (J.V. Lamouroux) J.V. Lamouroux	Antioxidants (terpenoids) Acetylcholinesterase inhibition Not determined	Neuroprotection, anti-Alzheimer's Neurogenesis (synaptogenesis promotion)	In vitro laboratory analyses Rat hippocampal neurons	Syad et al. (2012, 2016) Hannan et al. (2013), Hannan et al. (2014a, b)
<i>Gracilariaopsis chorda</i> (Holmes) Ohmi	Antioxidant, arachidonic acid	Neuroprotection	Rat hippocampal neurons	Mohibbullah et al. (2015)
<i>Hypnea valentiae</i> (Turner) Montagne	Acetylcholinesterase inhibition	Neuroprotection	In vitro laboratory analyses	Suganthy et al. (2010)
<i>Ishige okamurai</i> Yendo	Antioxidant, phlorotannin	Neuroprotection	Rat hippocampal neurons	Heo et al. (2012)
<i>Kappaphycus alvarezii</i> (Doty) Doty ex P.C. Silva	Not determined	Neurite outgrowth-promoting activity	Rat hippocampal neurons	Tirtawijaya et al. (2016)
<i>Laurencia undulata</i> Yamada	Antioxidant (floridoside), nitric oxide inhibition	Protects against neuroinflammation	BV-2 microglia cells	Kim et al. (2013)
<i>Porphyra yezoensis</i> f. <i>kinositae</i> Y. Yamada & T. Tanaka	Antioxidant activity, taurine	Neurogenesis, neuroprotection	Rat hippocampal neurons	Mohibbullah et al. (2016)
<i>Saccharina japonica</i> Areschoug	Not determined	Neurogenesis, neuroprotection	Rat hippocampal neurons	Hannan et al. (2014a, b)
<i>Sargassum fuvellum</i> (Turner) C. Agardh	Not determined	Neurogenesis, neuroprotection	Rat hippocampal neurons	Hannan et al. (2012)
<i>Sargassum fusiform</i> (Harvey) Setchell	Fucoidan (specific mechanism not determined)	Enhanced cognitive ability	Mice	Hu et al. (2016)
<i>Sargassum horneri</i> (Turner) C. Agardh	Sterols increased noradrenaline/serotonin signalling in CNS	Antidepressant effects	Mice	Zhao et al. (2016)
<i>Turbinaria decurrens</i> Bory	Antioxidant activity, increased dopamine level	Neuroprotection (Parkinson's)	Parkinsonic mice	Meenakshi et al. (2016)
<i>Undaria pinnatifida</i> (Harvey) Suringar	Not determined Antioxidant activity	Neurogenesis, neuroprotection Anti-inflammatory, anti-Alzheimer's	Rat hippocampal neurons Rat hippocampal neurons	Hannan et al. (2014a, b), Bhuiyan et al. (2015), Rafiqzaman et al. (2015)
<i>Ulva reticulata</i> Forskåll	Acetylcholinesterase inhibition	Neuroprotection	In vitro laboratory analyses	Suganthy et al. (2010)

produce significantly influences both physical and psychological health. Potentially, it impacts even on emotional and cognitive function, as clearly exhibited in rodents, which therefore has become an area of currently active and exciting research (Li et al. 2009; Heijtz et al. 2011; Al-Asmakh et al. 2012; Cryan and Dinan 2012; Marques et al. 2013).

Essential to brain health and its development, in the context of gut microbiota-mediated, metabolic reactions, are the short-chain fatty acids (SCFA). These are produced by microbial fermentation in the large bowel where they are ultimately absorbed. SCFA are produced from dietary carbohydrates such as polysaccharides/oligosaccharides that are not absorbed nor digested in the small intestine; they include acetate, propionate, and butyrate (Tan and O'Toole 2015; Ríos-Covián et al. 2016). Food components that are selectively fermented and result in specific changes in the composition and/or activity of the gastrointestinal microbiota as to confer health benefits to the host are called “prebiotics” (Gibson et al. 2010).

A schematic illustration of microbiota–gut–brain axis and its relation to seaweeds as will be discussed below is shown in Fig. 1.

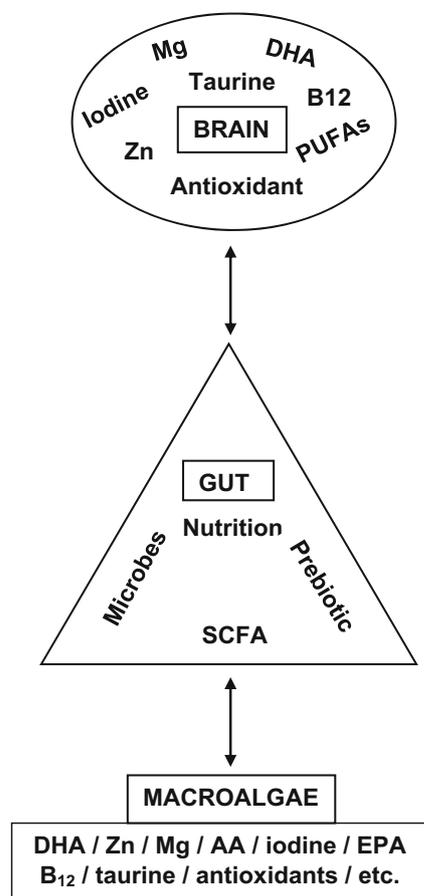


Fig. 1 Schematic illustration of the microbiota–gut–brain axis and how the essential brain nutritional elements and antioxidants are related to the contents of seaweeds as discussed in the present paper

Seaweeds and the microbiota–gut–brain axis

An increasing volume of research on the fermentable characteristics of the components of seaweeds lends extensive support to the validity of dietary macroalgae as a robust source of prebiotics. Algal-derived, marine oligosaccharides are broadly classified into different groups depending upon their chemical diversity, namely chitosan-, laminarin-, alginate-, fucoidan(s)-, carrageenan(s)-, and ulvan-oligosaccharides (Jutur et al. 2016). While the health benefits associated with the fermentation of many of these algal carbohydrates in the lower gut have been demonstrated, relatively few studies have been carried out on seaweed prebiotics and their effects specific to brain health. Therefore, neural health benefits at this time can only be implied, based upon existing empirical evidence mostly from animal studies. One obvious aspect of this inference, however, is related to evidence for increased surface area related to gut morphology and changes in the intestinal pH, as brought about by seaweed prebiotics, providing conditions conducive to enhanced mineral absorption. Increases in total SCFA production and significantly higher numbers of gut bacteria which are widely considered to be beneficial are also key indicators of the purported health benefits associated with dietary prebiotics originating from seaweeds (Zaporozhets et al. 2014; Cian et al. 2015; Raposo et al. 2016).

For example, Kulshreshtha et al. (2014) compared the effects of powdered red seaweeds (i.e., *C. crispus* and *Sarcodiotheca gaudichaudii* (Montagne) P.W. Gabrielson) incorporated into chicken feed on such production parameters as egg quality, intestinal histomorphology, and cecal SCFA content. In contrast to the control, the seaweed-treated hens had significantly ($P < 0.05$) greater villus height and surface area and a marked increase in the abundance of beneficial bacteria. These results corresponded to similar, significant outcomes in other research studies utilizing seaweeds or seaweed extracts in animals such as rats (Wang et al. 2006), pigs (Reilly et al. 2008; Heim et al. 2014) and in vitro fermentation systems (Ramnani et al. 2012; Charoensiddhi et al. 2016).

As researchers continue to delve into the complex realm of microbes and how they influence human health and behavior, fascinating evidence of coevolution comes to light. It has been determined that while many genes are homologs of bacterial genes, derived primarily by descent, some genes have been acquired by gene transfer from bacteria (McFall-Ngai et al. 2013). A classic example of this is the discovery of a porphyran/agar degradation locus transferred from an ancestral marine *Bacteroidetes* to the human gut isolate, *Bacteroides plebeius* (Hehemann et al. 2010). Porphyran and agar are polysaccharides unique to certain seaweeds, and with these specialized degradation enzymes, *B. plebeius* is able to utilize these seaweeds as a carbon source. Interestingly, these bacterial enzymes are only found in Japanese and Spanish

populations, where the consumption of porphyran and agar-producing seaweeds is common. They are absent in the guts of North Americans (Thomas et al. 2011).

The idea that multicellular organisms never act in isolation but instead function as a complex community has never been more evident than in the context of the cloud of microbes associated with the human organism, which influence every biological activity. In an intriguing review, Shapiro (2016) presented evidence for how microbiota affect and contribute to host evolution, either by evolving along with the host or by stepping in at critical moments to help the host adapt to a new environmental change. With respect to cognitive capacities and brain development, human microbiota have been shown to play fundamental roles in such areas as emotion, social interaction, stress management, motor control, and anxiety (Heijtz et al. 2011; Prado and Dewey 2014; Dinan et al. 2015; Oriach et al. 2016). Nutritional quality and availability are clearly the impetus for microbial diversity and positive influence, and dietary seaweeds offer an enormous number of opportunities to this effect.

The fascinating pathway from single cells, to multi-cellularity, to the progressive development of functionally integrated systems resulting in a mortal being is clearly indicative that physical health, psychological wellness, and human consciousness must be treated as a whole. Food is an essential component of this developmental process, and it not only directly impacts growth, vital processes, and energy requirements, it also significantly influences gut microbial populations. These in turn impact health, psychological wellness, and metabolic function and are possibly the most important targets for nutritional elements. While it is prudent to acknowledge that specific food-stuffs do not constitute a panacea, macroalgae were an ancient resource highly compatible with human development, and they remain so today. Recent review articles highlight research regarding the neuroprotective activities of macroalgae (Pangestuti and Kim 2011; Barbosa et al. 2014; Alghazwi et al. 2016), adding to the extensive volume of published research related to human nutrition, antioxidant effects, and cardiovascular health (Cornish and Garbary 2010; Gómez-Ordóñez et al. 2010; Holdt and Kraan 2011; Cornish et al. 2015). In addition, certain brown macroalgae have been reported to play a constructive role in human sexual function, purportedly as an effect of specific radical scavenging activity (Kang et al. 2003; Sansalone et al. 2014). The human sexual response cycle is primarily a neurologically based function, impacted by both brain (psychologic and neurologic) and vascular health (Feifer and Carrier 2008; Menezes et al. 2011; Georgiadis and Kringelbach 2012). Interestingly, oral administration of L-arginine and L-citrulline has been shown to improve erectile function in rat models (Toque and Caldwell 2014), and these free amino compounds are also found in many seaweeds (Laycock and Craigie 1977; Laycock et al. 1981; Broberg et al. 1998). However, it does not appear that any serious

investigations into this potential association and application of dietary seaweeds have been reported in the public forum.

Conclusions

Modern-day *H. sapiens* requires a specific portfolio of nutrients to sustain growth, repair, and vital processes, as well as to provide energy, but the variety of foods available today is vastly different from what would have been available to early hominins. Compelled to forage for sustenance, it seems likely that to acquire a steady supply of brain-essential nutrients, human ancestors would have had most success by exploiting shore-based marine resources.

Although impossible to prove, seaweeds could have been a logical and perhaps necessary addition to a diet of oysters, mussels, crustaceans, and occasional fish and mammal carcasses, thereby extending the conventional theory of marine food sources being essential for human brain evolution and development (Cunnane and Crawford 2014). Today, neurodegenerative diseases are on the rise (Hibbeln 2007; Olesen et al. 2012), and poor nutritional regimes are leading to serious health pathologies triggered by widespread and chronic risk factors such as obesity, diabetes, inflammation, and hypertension (Ezatti et al. 2002; Mouritsen 2016). Perhaps, it would be wise to carefully consider what may have stimulated the early development and cognitive sophistication of the human brain, such that humans became differentiated from our closest relatives, the chimpanzees. In the extensive collection of research reports on which the present review is based, the necessary brain nutritional elements and their sources become surprisingly obvious, although not all were discussed in detail. Some examples of macroalgal species associated with brain health and protection are provided in Table 1. Obviously, bio-availability of the various nutrients and the effectiveness of antioxidants are factors requiring more research (Wells et al. 2016). However, seaweeds produced under controlled conditions offer boundless opportunities to satisfy the known requirements for brain health and could readily play important roles in improving overall human health and well-being.

Acknowledgements The work by O.G.M. is supported by Lundbeckfonden (re: R95-A10447) as well as Nordea-fonden (via a center grant to Taste for Life).

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