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Energetic and nutritional constraints on infant brain development: Implications for brain expansion during human evolution

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ABSTRACT

The human brain confronts two major challenges during its development: (i) meeting a very high energy requirement, and (ii) reliably accessing an adequate dietary source of specific brain selective nutrients needed for its structure and function. Implicitly, these energetic and nutritional constraints to normal brain development today would also have been constraints on human brain evolution. The energetic constraint was solved in large measure by the evolution in hominins of a unique and significant layer of body fat on the fetus starting during the third trimester of gestation. By providing fatty acids for ketone production that are needed as brain fuel, this fat layer supports the brain's high energy needs well into childhood. This fat layer also contains an important reserve of the brain selective omega-3 fatty acid, docosahexaenoic acid (DHA), not available in other primates. Foremost amongst the brain selective minerals are iodine and iron, with zinc, copper and selenium also being important. A shore-based diet, i.e., fish, molluscs, crustaceans, frogs, bird's eggs and aquatic plants, provides the richest known dietary sources of brain selective nutrients. Regular access to these foods by the early hominin lineage that evolved into humans would therefore have helped free the nutritional constraint on primate brain development and function. Inadequate dietary supply of brain selective nutrients still has a deleterious impact on human brain development on a global scale today, demonstrating the brain's ongoing vulnerability. The core of the shore-based paradigm of human brain evolution proposes that sustained access by certain groups of early *Homo* to freshwater and marine food resources would have helped surmount both the nutritional as well as the energetic constraints on mammalian brain development.

Introduction

The adult human brain weighs about 1350 g or about three pounds (Allen et al., 2002), which is about three times more than in either *Australopithecus afarensis* or large apes today (Table 1). The human brain is large not only in absolute size but, at ~2% of adult body weight, is also large in proportion to body size. The hominin fossil record provides few clues to explain how and why the brain of *Homo sapiens* evolved to become so much larger and so much more cognitively developed than in non-human primates.

Normal brain development in the infant is a prerequisite for optimal brain function in the adult so potential constraints on brain development have implicit significance for understanding constraints on evolving higher functionality of the primate brain. The brain in newborn humans represents about 13% of lean body weight, which is about 30% more than for the newborn chimpanzee (Table 1). It also has a very high energy requirement, greatly exceeding that of the rest of the body combined (Fig. 1). This remarkable situation provides insight into the uniqueness of human brain evolution: how did so much energy metabolism get focused on the neonatal brain when it is not really able to contribute to survival until the child is at least five to six years old, i.e., long after the age at which other primates are semi- if not totally autonomous?

To expand three-fold over the past two to three million years, the early hominin brain had to overcome at least two constraints: (i) an energetic constraint: increasing energy requirements as the brain size increased, and (ii) a nutritional constraint: increasing requirements for nutrients that play a specific role in mammalian brain structure, development and function. The energetic constraint is synonymous with the 'metabolic' constraint described in earlier publications (Cunnane, 2010) but 'energetic' is perhaps the more appropriate term given that it refers exclusively to

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Table 1
Brain and body weights of several species of australopithecine (A.) and *Homo (H.)*, compared with *Pan troglodytes* (revised from Cunnane, 2010).

	Brain weight (g)	Brain/body (%)
A. afarensis (3.6–2.8 Ma)	455	1.7
A. africanus (3.0–2.2 Ma)	450	1.0
H. habilis (1.9–1.5 Ma)	600	1.7
H. erectus (1.8–0.3 Ma)	940	1.6
H. heidelbergensis (600–200 ka)	1200	1.8
H. neanderthalensis (200–40 ka)	1450	1.9
H. sapiens (100–10 ka)	1490	2.4
H. sapiens (present day)		
Adult male	1350	2.3 (2.7[a])
Newborn	380	10.9 (13.1[a])
Pan troglodytes		
Adult male	400	0.9
Newborn	160	10.0

Ma – millions of years ago, ka – thousand of years ago.
[a] Corrected to lean body weight since present-day primates have very low body fat content, a condition also presumed to have existed in australopithecines and early *Homo*.

meeting energy requirements. Similarly, the nutritional constraint is synonymous with the 'structural' constraint described elsewhere because the nutrients tend to be needed for cellular structure and function. Nevertheless, the distinction between these two constraints is imperfect because they have a certain degree of overlap with each other, especially during infancy. Either constraint alone can delay and/or permanently foreshorten cognitive development in infants today, so it is important to emphasise that surmounting just one of these two constraints alone would not have been sufficient to push human brain evolution forwards. Therefore, the path towards hominin brain expansion involved a long period of investment in overcoming the energetic and nutritional vulnerability of the brain during infant development, a vulnerability that is greater in humans than other species and remains with us to the present day.

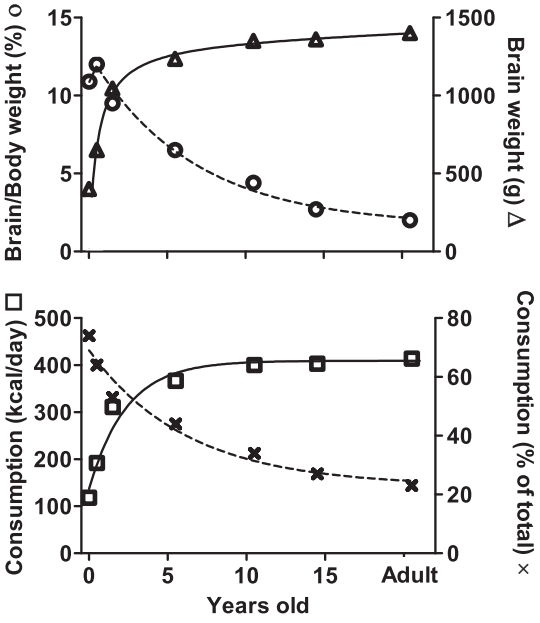

Figure 1. Brain size and energy consumption in the human from birth to adulthood (modified from Holliday, 1971). Normal infant brain development is a prerequisite for optimal brain function in the adult so the challenge is to explain how the disproportionate brain size and energy consumption evolved in the human infant.

The shore-based paradigm of human brain evolution proposes that hominins destined to become humans surmounted the brain's developmental vulnerability by exploiting shore-based habitats that provided abundant and sustained access to a wide selection of foods rich in brain selective nutrients. This paradigm also proposes that occupying the shore-based habitat was associated the evolution of neonatal body fat reserves, which were just as important for optimal human brain development. Deposits of subcutaneous body fat are not unusual in adult mammals but, with the exception of humans, are not present in the neonates of non-human primates. The particularly high energy needs of the developing human brain suggest that fuel stored as body fat in the newborn plays a critical role in early brain development. By providing access to an enriched dietary source of brain selective nutrients and by permitting evolution of body fat, a shore-based habitat masked the neurodevelopmental vulnerability that is still a hallmark of human infants today. Together, these two developments in early hominins led eventually to evolution of the modern human brain.

Vulnerability of the developing brain

Brain development passes through a series of processes that, in essence, starts with overproduction of neurons, followed by their migration to specific layers within the brain, then pruning of excess neurons, followed by myelination. This highly regulated and complex process involves a sequence of critical periods in brain development such that successful completion of a given period depends on (and is therefore vulnerable to) the successful completion of the preceding period. Deficits and distortions in brain maturation can occur both within specific regions of the brain and also in the brain as a whole compared with the rest of the body (Dobbing, 1985). These disruptions can arise because genetic or environmental circumstances block the completion of a critical period at the moment or in the sequence prescribed. The problem can be at one or more levels, including the migration of a certain cell type, or the maturation of a neural network, or region of the brain. When this maturation process is disrupted, optimal brain function is frequently not achieved in the adult. Brain selective nutrients are key players in this step-wise process.

There are two strategies to reduce this neurodevelopmental vulnerability: (i) restrict brain size and cognitive potential, or (ii) assure a richer and more reliable supply of fuel and brain selective nutrients. Thus, it would have been advantageous if the human brain could have evolved without needing a higher fuel requirement. However, the cost of a lower fuel requirement would be less development of the metabolically expensive process of establishing and maintaining advanced connectivity between neurons, which is the hallmark of cognitive capacity in humans. The hominin solution to this trade-off was to evolve a better brain fuel reserve in the form of body fat stores that start to form in the fetus during the last third of gestation. Compared with all other non-human primates or terrestrial animals in general, the fat store in human neonates provides a far more significant reserve not only of fuel but also of certain key fatty acids needed for the structural integrity of the brain. Without having evolved a specialized fuel reserve to support the developing brain, non-human primates were restricted to a lower cognitive development and functionality. However, compared with humans, they retained the key advantage of lower brain vulnerability during early development.

Challenging aspects of brain energy metabolism

Several challenges for brain energy metabolism arose in mammals and became more acute in species with larger brains. First is the brain's high metabolic rate, i.e., its high energy needs (Table 2).

In order to regenerate its cellular fuel, adenosine triphosphate, the brain has to process glucose through the tricarboxylic cycle. In addition, the amino acid, glutamate, is a key neurotransmitter but it can also trigger undesirable signals if its concentration in the brain rises too much. A large part of the brain's energy expenditure is used to keep molecules like glutamate accessible to certain neurons but also appropriately compartmentalised through a sophisticated system of selective transport and compartmentalisation (Magistretti, 2004).

Second is the blood brain barrier, which essentially seals off the brain from large molecules that circulate in the blood. Large, complex molecules, including many different proteins, can dock at receptors on the capillaries of the brain but the blood brain barrier blocks their direct access to the brain. Specific transporters have evolved for the brain to take up smaller molecules like glucose. This selective filtering process is critical to brain integrity but is also metabolically extremely costly (Pardridge, 1991). Hence, not only is brain function itself metabolically expensive but so is the maintenance of the blood brain barrier.

Third, unlike in other tissues, brain glucose uptake is mostly independent of whether blood glucose or insulin is high or low. This relative insensitivity to insulin is important for maintaining a steady rate of brain glucose utilisation by preventing wide swings in brain glucose uptake as blood glucose and insulin change after each meal. The challenge is that when blood glucose decreases for more than a few hours, the brain rapidly needs to be supplied with a different fuel. Most tissues use long chain fatty acids (16 and 18 carbon fatty acids such as palmitic, stearic and oleic acids) as the back-up to glucose but this was not an option for the brain. The brain was unique in coming to depend on ketone bodies (ketones) instead of fatty acids as the back-up to glucose (see Ketones: The key to brain fuel security, below).

Fourth, in muscle and liver tissue, a significant amount of glucose can be stored as glycogen, but storage of glycogen requires three to four grams of water for each gram of glycogen produced, making this form of glucose reserve physically very bulky. This is not a problem for liver or muscle tissue, which is not encased by bone but cannot be accommodated by the inflexible cranial space that is fully occupied by the brain. The brain does contain a supply of glycogen that could last for a few minutes but this small (though possibly important) energy reserve is not able to serve as a long-term fuel reserve. Hence, despite its high energy needs, the brain could neither store glucose nor exploit the fuel alternatives to glucose available to other tissues (fatty acids); a different solution was needed.

High brain energy requirement: the first key constraint

The brain's energy requirement is essentially constant regardless of the cognitive effort being expended at any particular moment (Magistretti, 2004). On a normal pattern of food intake (three meals per day), the brain runs almost exclusively on the six carbon sugar: glucose. The adult human brain consumes ~3–4 mg of glucose per 100 g of brain tissue per minute or about 100 g (a quarter pound) of glucose per day. Thus, the adult brain's energy requirement is equivalent to about 20–23% of the body's daily energy intake. In the newborn human brain, the value is a remarkable 74% (Fig. 1).

Blood glucose is derived mostly from dietary carbohydrates, i.e., starches and sugars. When blood glucose declines after more than two to three hours of fasting, glucose can be made by gluconeogenesis from other molecules such as glycerol, which is produced during fat metabolism, or from amino acids in tissue protein. However, both routes are very short-term solutions that are not adequate to supply the brain's energy needs for even a few days. Other tissues use long chain fatty acids stored in body fat to replace glucose as a fuel but this is not an option for the brain because fatty acids cross the blood brain barrier too slowly.

Ketones: the key to brain fuel security

To provide longer-term back-up fuel insurance for a large and expanding brain, a different energy substrate not involving glucose or tissue breakdown was needed. Ketones (beta-hydroxybutyrate, acetoacetate, and acetone) became the alternative fuel backing up glucose for the adult human brain. Ketones are small molecules derived from fatty acid oxidation, principally in the liver (Fig. 2). Brain uptake of ketones increases in direct proportion to ketone levels in the blood (Cunnane et al., 2011). Thus, when fasting starts, the initial rate of brain ketone uptake is relatively slow because plasma ketone concentrations are low and because the monocarboxylic acid transporters are still not fully activated for ketone transport. If fasting goes beyond four to six hours, the normal stimulation of insulin production by carbohydrate intake decreases markedly, thereby permitting release of free fatty acids from fat stores into the blood. Free fatty acids replace glucose for most organs and drive ketone production in the liver, allowing brain uptake of ketones to become fully activated.

The amounts and activities of the enzymes in the brain needed to metabolise ketones always exceed what is necessary to supply the brain's fuel needs, even during fasting or starvation (Fukao et al., 2004). Hence, ketone utilization is a constitutive feature of the brain and not an adaptive response, i.e., the brain is used to metabolising ketone bodies and is always prepared to use them as soon as they are available (Cunnane et al., 2011). Ketones can seamlessly replace an inadequate supply of glucose to meet up to two-thirds of the adult brain's energy needs (Owen et al., 1967).

There are three key advantages to having ketone bodies as the main alternative fuel for the adult human brain. First, humans

Table 2
Challenges to expanding brain energy requirements and brain size.

1. Maintaining the electric potential of neurons and the activity of synapses consumes a lot of energy.
2. Restricted access to the brain of potentially suitable energy substrates to replace glucose. Despite the brain's ability to oxidize fatty acids, they are largely inaccessible to the brain.
3. Unlike in other tissues, brain glucose uptake is driven by neuronal activity and is largely insensitive to insulin, the principle hormone controlling glucose uptake in other tissues.
4. Glycogen is an important fuel reserve in muscle and liver but only a minor fuel reserve for the brain. This is mainly because storage of glycogen requires a lot of water, which takes up a lot of physical space that is not available within the confined limits of the cranium.

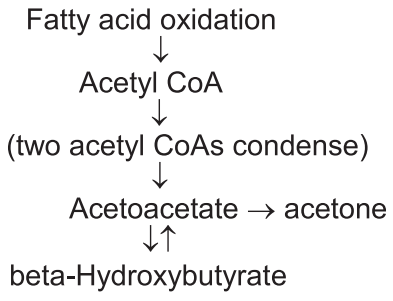

Figure 2. Ketone body synthesis. Two-way arrows indicate reversibility of the step. Acetoacetate and beta-hydroxybutyrate both have four carbons. Acetone has three carbons and is formed by the spontaneous decarboxylation of acetoacetate (modified from Cunnane, 2005).

normally have significant body fat stores so the supply of fatty acids needed to make ketones is more than adequate. Second, using ketones for up to two-thirds of the brain's energy requirement greatly reduces the risk of detrimental muscle breakdown or compromised function of organs, the protein from which would be needed to make glucose if fasting lasts more than a few hours. Third, by using ketones, the brain competes less with cells that have no choice but to use glucose, i.e., red blood cells.

Unlike in the adult brain where ketones are an alternative fuel when glucose is not sufficiently available, in the neonate, ketones are an essential brain fuel because glucose alone cannot meet the developing brain's energy needs (Adam et al., 1975; Robinson and Williamson, 1980; Cremer, 1982). Ketone body uptake by the brain is four to five times faster in newborns and older infants compared with adults, so the developing brain appears equipped to exploit ketones in proportion to its higher energy needs. The lower dependence on ketones of the adult compared with the infant brain implies that the former is a vestige of the latter; ketones became optional for the adult brain but remained essential fuels for the infant brain.

Ketones are also the main source of carbon to make cholesterol and some long chain fatty acids (palmitic, stearic, oleic acids) that are important structural lipids in the developing brain. These lipids constitute about 45–50% of the solid matter of the human brain and are crucial components of neuronal membranes. Interruption of brain cholesterol synthesis has catastrophic consequences for brain development in all mammalian species. The majority of brain cholesterol is made within the brain itself from carbon supplied mostly from ketones (Edmond, 1974; Jurevics and Morell, 1995; Cunnane et al., 1999). Hence, whether cholesterol or saturated fatty acids are high or low in the diet has no bearing on their uptake by the brain; the brain can only meet its needs for these important lipids by endogenous synthesis, in large measure from carbon provided by ketones.

Mammalian milk contains short- and medium-chain fatty acids (4–14 carbons in length), which are particularly ketogenic, i.e., they are the best ketone precursors. These ketogenic fatty acids represent up to 23% of all fatty acids in ruminant milk while in human milk they account for about 15–17% (Sarda et al., 1987). An important feature of ketone production in the mammalian neonate is that, once in the gut, absorption of short and medium-chain fatty acids in milk follows a different path from that of long chain fatty acids (see Changes in other organ systems facilitated brain evolution, below). During lactation, the brains of most neonatal mammals probably use ketones to some extent. Once lactation ceases in mammals other than humans, there is no longer an incoming supply of these ketogenic medium chain fatty acids found in milk. In contrast, with their stores of body fat that accumulate some medium chain fatty acids, human infants have access to ketones well beyond weaning. Because there is so little body fat in other mammalian neonates, there is also almost no reserve of long chain fatty acids to make ketones, even during starvation.

The ability of the adult brain to switch to ketones to replace glucose is not unique to humans but seems to be much better developed in humans than in other omnivorous mammals (Robinson and Williamson, 1980). Adult carnivores like dogs achieve negligible ketogenesis during fasting but also have smaller brains and markedly lower brain energy needs. Hibernating mammals like bears are believed to meet their brain energy requirements from fat breakdown, which liberates sufficient glycerol to compliment/replace glucose without the need to produce large amounts of ketones. The brain is also proportionally smaller in other animals than in humans so meeting its energy requirement is therefore less dependent on an alternative to glucose (Robinson and Williamson, 1980).

Body fat: the infant brain's unique energy reserve

Most mammals acquire a layer of fat as they mature or if they are domesticated or become more sedentary (Pond, 1992). However, amongst primates, body fat in the near-term fetus and neonate is unique to humans (Kuzawa, 1998; Cunnane, 2005). During the first two-thirds of gestation, the human fetus is very lean like the fetuses of other mammals but at 25–26 weeks gestation, subcutaneous fat cells begin develop and accumulate fats. This process leads to body fat doubling in the fetus during the next six to seven weeks and more than tripling by the end of a term pregnancy (39–40 weeks). As a result, 500–600 g of fat will normally be present in the human fetus if it is born at term (Widdowson, 1974; Harrington et al., 2002). Babies born five weeks prematurely have about 50% less fat than they should, while those born ten weeks early have about 85% less fat than they should.

Human baby fat is different from adult body fat in several ways. (i) Body fat in the infant is about 25% water and 70% stored fat, whereas in adults it is about 10–12% water and >85% stored fat. (ii) Unlike adults, baby fat is almost all directly under the skin (subcutaneous fat) and next to none is present as visceral fat surrounding the abdominal organs (Harrington et al., 2002). (iii) Of the fatty acids in newborn body fat, greater than 90% are saturated or monounsaturated. Correspondingly, there are very low amounts of the two primary dietary polyunsaturated fatty acids, the omega-6 fatty acid, linoleic acid, and the omega-3 fatty acid, alpha-linolenic acid (Hirsch et al., 1960; Sarda et al., 1987). Linoleic and alpha-linolenic acids are typically found at a total of 10–15% in adult body fat, an amount corresponding to their consumption from vegetable oils in the diet. (iv) Compared with adults, baby fat contains three to four times more arachidonic acid and docosahexaenoic acid (DHA; 22:6ω3), both of which are extremely important for brain development (Farquharson et al., 1992). Neither arachidonic acid nor DHA are very easily beta-oxidized to CO_2, i.e., they are much less important as fuels than palmitate, stearate, oleate or linoleate. In contrast, of all the long chain fatty acids, arachidonic acid and DHA are the most easily released from adipose tissue stores (Raclot and Groscolas, 1993). Arachidonic acid and DHA are stored in infant body fat strictly as a reserve for structural purposes, especially in the developing brain, rather than as fuels (see Baby fat: The brain's DHA and fuel reserve, below). Thus fetal body fat is different in composition and serves a function that differs somewhat from adult fat, which is simply an energy store mirroring the composition of dietary fat.

Nutrients for brain structure and function: the second key constraint

Certain nutrients must be present in the diet to assure optimal mammalian development, maturation and reproduction. These nutrients include a number of amino acids, vitamins, minerals and fatty acids. 'Brain selective nutrients' is a term that was coined to signify those nutrients that are needed for optimal brain development and that would therefore have facilitated human brain evolution (Cunnane and Crawford, 2003). Of course, it does not imply that these nutrients exist only in the brain or that they have no role in other organs. Brain selective nutrients can be divided into three groups: (i) brain selective minerals, (ii) brain selective fatty acids, and (iii) brain selective vitamins. There are at least five brain selective minerals: iodine, iron, zinc, copper and selenium. There is probably only one brain selective fatty acid: DHA. The brain selective vitamins are less well studied but there are probably at least two: vitamins A and D. At present, none of the indispensable (essential) amino acids are known to be a brain selective nutrient.

Three features characterise brain selective nutrients (Cunnane, 2010):

(i) A minimum amount of each brain selective nutrient is required in the diet on a regular basis to permit normal development of the human brain. If these nutrients are not present in the diet in sufficient amounts, brain development will be suboptimal in proportion to the degree of their dietary deficiency.
(ii) There is a cluster of brain selective nutrients, each with a separate and distinct role in brain development and function. Inadequate intake of any one brain selective nutrient results in specific symptoms regardless of the sufficiency of the others. Severity of the symptoms of deficiency of a brain selective nutrient depends on the body's ability to conserve it in the face of its deficient intake. The best known brain selective nutrients are DHA, iodine and iron, so, for the moment, they form the nucleus of this nutrient cluster. Iodine and iron both control different aspect of energy metabolism (see Iodine and iron: The two main brain selective nutrients, below). Docosahexaenoic acid is important in neuron-to-neuron communication (see Docosahexaenoic acid: The brain selective omega-3 fatty acid, below) and its synthesis is iron-dependent.
(iii) A generous supply of brain selective nutrients supported, indeed, was probably essential for, hominin brain expansion. The corollary is that inadequate intake of the cluster of brain selective nutrients would have been a significant impediment to human brain evolution.

Inadequate intake of brain-selective nutrients is more severe in some geographical regions than others but, on a global scale, it is a massive public health problem. Low intake of brain selective nutrients is much less prevalent in populations regularly consuming fish and shellfish, a point crucial for the link between brain selective nutrients, shore-based diets and human brain evolution (Crawford et al., 1997; Crawford, 2010; Cunnane, 2010). The extensive prevalence of suboptimal brain development in humans subsisting on diets providing inadequate amounts of brain selective nutrients underlies the ongoing developmental vulnerability of the human brain; this vulnerability was clearly not eliminated but rather probably increased as the brain expanded during its evolution.

Iodine and iron: the two main brain selective minerals

At least a billion people today have deficient intake of iodine and iron, making these two minerals the two main brain selective minerals. Indeed, without the use of iodized table salt for nearly a century now, the problem of suboptimal brain development and occasional clinical cretinism due to dietary iodine deficiency would be far worse than it actually is today. The importance of iodine for normal fetal and post-natal brain development is principally due to its role in thyroid hormone production. Thyroid hormones, thyroxine and triiodothyronine, control body energy metabolism and, hence, body temperature (Pharoah et al., 1971; Dussault and Ruel, 1987). They are also important for the normal development of the nervous system.

The legal requirement that iodine be added to certain foods, particularly table salt, demonstrates the ongoing severity and global scale of the public health problem of iodine deficiency. Iodine deficiency is most prevalent in mountainous and/or inland areas (Venturi et al., 2000; Cunnane, 2005; Venturi and Bégin, 2010) and is contributing to an increasing risk of hypothyroidism in women of child-bearing age in many developed regions including Australia, Europe and the United States (Cunnane, 2010). Iodine deficiency arises when fish, shellfish or other coastal plants are not consumed and is exacerbated by the intake of goiterogens in plants such as cassava. Fish, shellfish and coastal plants, particularly algae and seaweed, are the richest and most bioavailable food sources not only of iodine but of all the brain selective nutrients (Cunnane, 2010).

Dietary iron deficiency is an important cause of suboptimal neurodevelopment on a global scale equivalent to that of iodine deficiency (Ramkrishnan, 2002). Iron deficiency compromises several components of brain and behavioural development including visual attention, concept acquisition, verbal scores, and school achievement (Pollitt, 1993). Like iodine deficiency, iron deficiency is associated with poorer performance on cognitive tests (Lozoff and Brittenham, 1986; Pollitt and Metallinos-Katsaras, 1990; Pollitt, 1993). Iron deficiency is almost always present where the population is poor (whether rural or urban) and where diets are cereal-based, i.e., when meat or fish are rarely or never consumed.

Docosahexaenoic acid: the brain selective omega-3 fatty acid

Docosahexaenoic acid is an integral part of membrane phospholipids of neurons throughout the brain. Synapses, the contact points between neurons, are particularly enriched in DHA. It is in this structural role that DHA participates in processes linked to learning and memory, but the specific molecular mechanism by which this occurs is still poorly understood. Learning and memory are almost always compromised under clinical or experimental conditions causing lower brain DHA. These conditions may be genetic in origin, i.e., low DHA synthesis in Zellweger Syndrome, or may be induced by experimental dietary depletion of omega-3 fatty acids. All stages of the life cycle seem to be affected, though more so during vulnerable periods such as infancy and old age.

There are three reasons why DHA is probably the only brain selective fatty acid:

(i) A specific and irreplaceable lipid component: The unique specificity of DHA in photoreceptor function is well known throughout the animal kingdom. No other polyunsaturated fatty acid, not even DHA's two closest homologues, the omega-3 and the omega-6 docosapentaenoic acids (22:5n-3 and 22:5n-6, respectively), can replace DHA in the highly specialized photoreceptor membrane (Crawford, 2010). The specific requirement for DHA is best known in the photoreceptor but the analogous situation occurs in the neuronal synapse.
(ii) DHA synthesis is insufficient: Humans possess functional forms of the enzymes used to make DHA from shorter chain omega-3 fatty acids so in theory can make some DHA endogenously. However, numerous studies show that humans are capable of converting less than 0.5% of the precursor omega-3 fatty acids, alpha-linolenic acid or eicosapentaenoic acid, to DHA (reviewed by Plourde and Cunnane, 2007). Infants are reportedly better able to synthesize DHA from its omega-3 precursors than adults, but the brain of a six month old infant not consuming pre-formed DHA still accumulates about 50% less DHA than the brain of a breast-fed infant (Farquharson et al., 1992; Makrides et al., 1994; Cunnane et al., 2000, Fig. 3). Since the brain of human infants accumulates so much less DHA if pre-formed DHA is not provided in the diet (or milk), the synthesis route alone is clearly not able to meet the brain's DHA requirement. Thus, the developing human brain unequivocally needs to be provided with pre-formed DHA or it will not be able to optimally accumulate DHA.

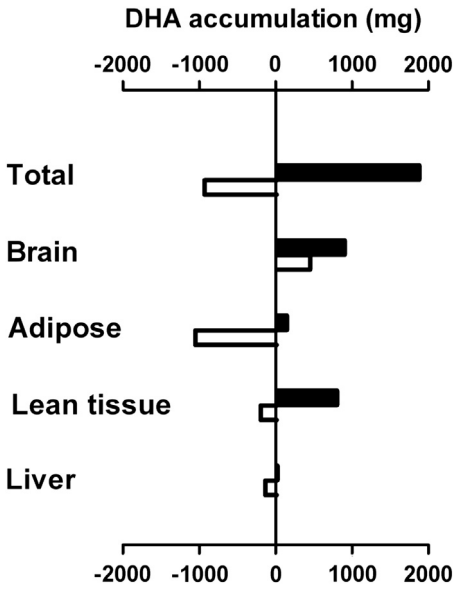

Figure 3. Docosahexaenoic (DHA) acid accumulation in the first six months of life depending on whether the infant was breast-fed (■) or formula-fed a milk containing no DHA (□). In the formula-fed infant, the brain accumulates about 50% of the DHA accumulated by the brain of the breast-fed infant, while the rest of the body loses DHA (from Farquharson et al., 1992; Makrides et al., 1994; Cunnane et al., 2000). The interpretation is that without incoming, pre-formed DHA, brain DHA accumulation in the infant is suboptimal, irrespective of some capacity of the infant to synthesize DHA.

(iii) A complicated route to DHA synthesis: DHA synthesis depends on an alternating series of desaturation and chain elongation of enzymes that are catalysed by a number of different cofactor nutrients, including iron, zinc, vitamin B_6, and magnesium (Plourde and Cunnane, 2007). As a result, in all mammals (not just humans), DHA synthesis depends on the nutritional adequacy of these cofactors as well as on the amount of precursor omega-3 fatty acid in the diet. As explained in point 2 above, assuming for the sake of argument that the low rate of DHA synthesis (0.5%) was adequate to meet the DHA requirements of the adult, the dependence of this pathway on multiple nutrient cofactors still makes DHA synthesis a much less reliable way to get DHA into the body than consuming it directly. The need for iron in this pathway combined with the extremely widespread prevalence of iron deficiency in the world today makes it even less plausible that the increasing requirement for DHA for the evolving human brain would have been provided by its synthesis route as opposed to obtaining it pre-formed in the diet.

Baby fat: the brain's DHA and fuel reserve

At birth, body fat contains very low amounts of polyunsaturated fatty acids; at most 1–2% of all the fatty acids present (Farquharson et al., 1992). However, this small depot includes significant amounts of DHA, which, when multiplied by the 500–600 g of fat normally present at birth, represents a reserve of about 1000 mg of DHA (Fig. 3). Docosahexaenoic acid accumulation in the brain during the first six months of life occurs at a rate of about 10 mg per day, and in the whole body at about 20 mg per day. Hence, pre-formed DHA in body fat at birth represents a supply for the infant that could last for at least 50 days in the absence of any other source of DHA (Cunnane et al., 2000). Some DHA synthesis occurs in the infant and, if breast-fed, maternal milk is also a major source of pre-formed DHA. This redundancy in the availability of DHA (in fat stores, milk and some synthesis) serves to virtually assure sufficient DHA accumulation by the developing brain. Premature or low birth weight infants have a much lower reserve of pre-formed DHA because they have much less body fat at birth, which contributes to their risk of neurodevelopmental delay. Chimpanzee infants have no body fat and hence no known reserve of pre-formed DHA.

The classical paradigm

Classically, hominin brain expansion has been linked to the development of the skills needed to efficiently make stone tools and use them for scavenging or hunting. The fresh meat thus acquired would have provided a better quality diet than in other primates. Stone tool making is generally acknowledged to have been common about two million years ago in *Homo habilis*. For some time now, it has also been generally understood that the brain has a high energy requirement, and that brain expansion during human brain evolution would require a diet that was more digestible, thereby providing higher energy density than is available from a plant-based diet (Mace et al., 1981; Martin, 1981, 1996). Human brain evolution is therefore generally explained as a process by which the gradual refinement of stone tools permitted early *Homo* to hunt for and/or efficiently scavenge fresh meat, which would have provided higher dietary energy density than from a plant-based diet.

Despite the important insight that an expanding brain would have a higher fuel requirement (Teaford and Ungar, 2000), this energetic constraint has generally been regarded as something to be accommodated after human brain expansion was well on its way, i.e., once the hominin brain had expanded enough to learn how to make and use stone tools, a higher quality diet would have been needed because now the bigger brain had a higher energy requirement (Leonard and Robertson, 1994, 1996; Aeillo and Wheeler, 1995; Leonard, 2002). Meat does contain creatine, which potentially increases energy generation within the brain. Meat is also a good source of several vitamins and minerals, but neither of these two points were part of the classical paradigm until very recently (Pfefferle et al., 2011).

Shortcomings of the classical paradigm

Additional meat intake unquestionably increases the nutrient density of the diet, but the classical paradigm still has several important short-comings:

(i) Cart before the horse: A bigger brain clearly does need a better supply of dietary energy but something had to start the ball rolling; something must have permitted a degree of hominin brain expansion before (as well as after) the development of stone tools and hunting. What stimulated brain expansion enough to permit the conceptualisation of tools and weapons made from stone? What fuelled the small increments in brain size during hundreds of thousands of years before the emergence of *H. habilis* and functional stone tools?

(ii) More meat does not solve the brain fuel problem: The classical paradigm rightly focuses on the challenging issue of providing more energy to the expanding hominin brain, but more meat intake is actually not a solution to this problem. Meat does have higher energy density than plants but the brain cannot use amino acids in protein as an energy source. Some amino acids can be converted to glucose but this is a stop-gap process that would furnish the brain with no more

than a few hours' worth of energy (see previous section: High brain energy requirements: The first key constraint), so meat was not really a long term solution to obtaining more glucose compared to digesting complex carbohydrates and plant fibre. Wild terrestrial animals are also extremely lean so eating meat did not even indirectly provide enough incremental fat intake to supply ketones to meet the increasing energy requirements of the developing brain. Furthermore, excessive dependence on high protein intake from meat can cause metabolic problems and can damage the kidneys (Cordain et al., 2005).

(iii) Lack of prediction: The classical paradigm makes no specific prediction about human brain development, function or evolution. If meat-eating was the solution to permit continued brain hominin expansion, why is the developing human brain still so vulnerable to micronutrient deficiencies? Why is iodine supplementation necessary throughout the world today even in meat eaters? Some 'Westernized' populations eat more meat today than ever before but disorders of brain development and function have never been more prevalent (Crawford, 2010).

(iv) The developing brain: The classical paradigm does not make any attempt to account for the important energetic or nutrient challenges facing the developing brain in the human pre-weaning infant (see previous sections: Challenging aspects of brain energy metabolism, High brain energy requirements: The first key constraint).

Some might argue that this portrayal of the 'classical' paradigm places too much emphasis on the role of hunting and meat intake and not enough on the wide interest in the 'gatherer' part of hunter-gatherer subsistence. As explained in the next section, the 'shore-based paradigm' fully accepts that the hominins destined to become humans probably obtained much of what they ate by gathering, but gathering foods found mostly on or near the shores rather than fruits, vegetables, grains and tubers as commonly suggested. Foods gathered on the shores included not only aquatic and marsh plants but also fish, shellfish, amphibians, crustaceans, eggs, etc.

The new paradigm: a shore-based habitat and diet

The shore-based paradigm proposes that one or more australopithecine populations in eastern and southern Africa came to occupy a habitat and consume a diet that provided solutions to both the energetic and nutritional constraints on primate brain size and function. This paradigm has four principal features:

(i) Ketones and ketogenesis: Increasing energy and structural lipid (e.g., cholesterol) requirements of the expanding brain were met in large part by ketones (see previous section: Ketones: The key to brain fuel security).

(ii) Subcutaneous fat: The evolution of neonatal body fat probably occurred before evolution of the bigger brain (see previous section: Body fat: The infant brain's unique energy reserve). Subcutaneous fat not only supplies the fatty acids that are substrates for ketone production but also stores key structural fatty acids for the developing brain, particularly DHA.

(iii) Brain selective nutrients: A diet providing a richer and more reliable source of brain selective nutrients was needed for optimum brain development and function in adult life. These nutrients include not only DHA but also several brain selective minerals and vitamins (see previous sections: Nutrients for brain structure and function, Iodine and iron, Docosahexaenoic acid).

(iv) Shore-based habitat and diet: A shore-based habitat and diet provided a secure and abundant food supply richer in brain selective nutrients than any other diet (Cunnane, 2005). Sustained access to a shore-based diet occurred before significant brain expansion and tool-making started. Access to a reliable food supply also provided an opportunity to develop more fixed habitats in which fat deposition could gradually evolve in the human fetus and neonate.

Some brain selective nutrients contributed to relieving the metabolic (energetic) constraint on the developing brain, i.e., iodine and iron. Others helped relieve the nutritional constraint, i.e., DHA, zinc, copper and selenium. Some brain selective nutrients played both roles, i.e., iron and copper, which are essential structural components of enzymes needed for efficient energy metabolism (Fig. 4). Evolution of neonatal body fat also contributed to relieving both of these constraints. It provided a reserve of DHA for neuronal membrane structure but also other saturated and monounsaturated fatty acids that are good ketone precursors, which could be used both for the synthesis of other brain lipids and as an alternative brain fuel to glucose.

For 40 years now, attention has been drawn to the importance of DHA in human brain development and evolution (Crawford and Sinclair, 1972; Crawford and Marsh, 1989). Indeed, the idea that DHA is a brain selective nutrient is now widely endorsed. Notwithstanding the fact that DHA is the poster nutrient for successful brain development and function throughout the life cycle, it alone could not have stimulated brain evolution in hominins without a concomitant increase in availability of either the full cluster of brain selective nutrients or a way to reliably ramp up brain fuel supply as the brain expanded.

Previous skepticism about the plausibility of the shore-based paradigm has focused on two points: First, weak evidence that hominins were consuming shore-based foods, especially fish and/or shellfish, before about 120,000 years ago. The implication is that consumption of shore-based foods by hominins was a late development in human evolution that occurred after rather than before substantial brain expansion. In fact, detailed fossil evidence of frequent consumption of catfish and tilapia by *H. habilis* in East Africa has been available for nearly 20 years (Stewart, 1994; see ;

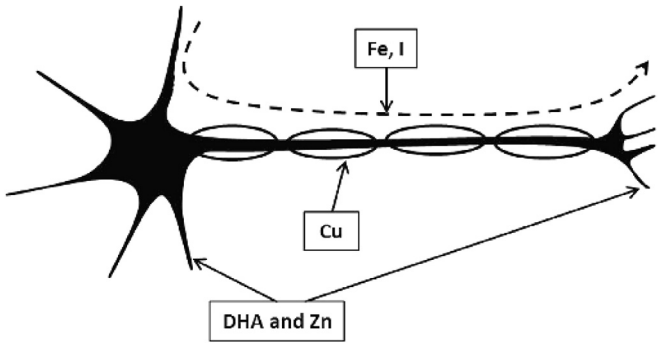

Figure 4. Schematic overview of some functions of brain selective nutrients in the brain. Docosahexaenoic acid (DHA) and zinc (Zn) are intimately involved in chemical neurotransmission at the synapses between neurons. Copper (Cu) is needed for normal myelination to insulate the axon and successfully deliver the electrical message from one end of the neuron to the other. Iron (Fe) and iodine (I) are key components of the ATP-generating system that fuels neuronal activity, i.e., transmission from synapses receiving incoming signals to those transmitting them to other neurons (the dotted arrow). Other brain selective nutrients (selenium, vitamin A and vitamin D) are not shown.

Stewart, 2014) and has been strengthened recently (Braun et al., 2010; Stewart, 2010; see also; Archer et al., 2014; Kappelman et al., 2014). It is therefore no longer credible to claim that there is no fossil evidence of early hominins eating fish.

Second, humans can synthesize some DHA from shorter chain omega-3 fatty acids, thereby supposedly avoiding the need for pre-formed dietary DHA. Two independent studies of infant brain fatty acid composition in the first six months of life make it clear, however, that this capacity is insufficient to permit brain DHA accumulation at a normal rate, i.e., equivalent to that seen in breast-fed infants that receive pre-formed DHA in maternal milk (Farquharson et al., 1992; Makrides et al., 1994; see previous section: Docosahexaenoic acid; Fig. 3). It is therefore not tenable to argue that DHA synthesis alone can meet the DHA requirements of the developing human brain.

Neither an abundant supply of meat nor a rich supply of minerals and vitamins in a plant-based diet could solve the constraint of the increasing energy requirement of an expanding brain. In fact, neither provided an adequate supply of DHA or iodine either, which made accessing shore-based foods all the more important.

Brain selective nutrients in the shore-based diet

A shore-based diet provided a richer supply of brain selective nutrients and thus helped relieve the nutritional constraint on hominin brain expansion because foods available on or near shores are generally excellent sources of DHA, iodine, iron, zinc, copper, selenium, vitamin A, and vitamin D. Shore-based foods include a large variety of nutritious plants, shallow freshwater fish such as catfish, crustaceans, shellfish, amphibians, and eggs of birds nesting on or near shorelines. Most shore-based foods can be obtained without needing either highly developed cognitive and manual skills or manufacture of cutting stone implements or other fishing technology.

Most if not all nutrients known to be important for the developing brain are present in higher amounts in foods found on freshwater and marine shores than in foods not associated with lakes, marshes or waterways. The daily requirements for brain selective minerals can therefore be met by less shellfish or fish than by any other food groups, including pulses, fruits, vegetables, nuts, or meat (Cunnane, 2005). Thus, any amount of fish and/or shellfish contributes very significantly to meeting the dietary needs of humans for brain selective nutrients (Broadhurst et al., 1998; Cunnane, 2005, 2010). Conversely, the less one eats foods found along the shores, the harder it is to get sufficient intake of iodine, selenium, iron and DHA.

Shore-based habitat in the hominin fossil record

Starting at least two million years ago in East Africa, the fossil record shows that hominins destined to evolve larger brains on their way to becoming humans started to occupy shore-based habitats along freshwater lakes, marshes, rivers, estuaries and possibly some sea coasts (Cunnane and Stewart, 2010). Further examples of early hominins subsisting on shore-based foods, particularly freshwater fish and shellfish, are emerging from the work of several experienced groups of palaeoanthropologists examining early hominin fossil sites (Stewart, 1994; Braun et al., 2010; Erlandson, 2010; Parkington, 2010; Stewart, 2010, 2014; Archer et al., 2014).

In addition to enhanced availability of brain selective nutrients, a shore-based habitat would have permitted a lifestyle that was less preoccupied by a nomadic search for food or haphazard success with hunting while competing with other more efficient scavengers. In turn, access to a secure and reliable food supply permitted more time to be invested in the development of manual, social and cognitive skills that led to language, social organisation, tool-making and, eventually, hunting. Genetic changes that presumably contributed to some aspects of human brain evolution were dependent on an enriched dietary supply of brain selective nutrients and a more secure brain fuel supply.

Changes in other organ systems facilitated brain evolution

The hominin brain did not evolve in isolation from the rest of the body. Indeed, at least four other physiologic and/or metabolic changes helped pave the way for the modern human brain. First was the evolution of neonatal subcutaneous body fat, which was a crucial development before human brain evolution was possible (see previous section: Body fat: The infant brain's unique energy reserve). Amongst primates, fetal/neonatal body fat is unique to humans so, of these changes favouring brain evolution, it seems likely that evolution of neonatal subcutaneous body fat in hominins occurred most recently.

Second was prolongation of gestation. Primates have longer gestation than most other mammals of a similar size, which favours brain development during the third trimester. In humans, longer gestation favours both brain and adipose tissue development in fetus. Fetal fat development during the third trimester of pregnancy is in large measure a function of gestational length (Battaglia and Meschia, 1973; Kuzawa, 1998), so, in turn, longer gestation in hominins probably evolved before fetal fat development (Fig. 5).

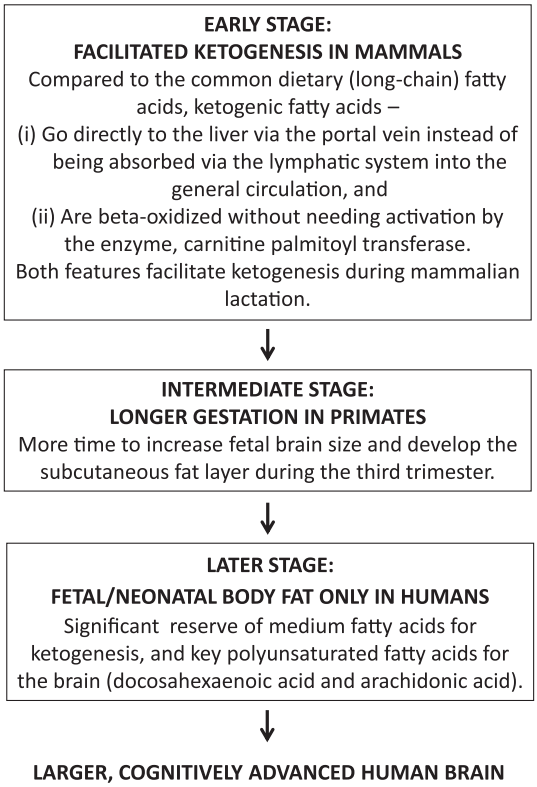

Figure 5. Physiological changes in three distinct processes or organ systems apart from the brain, each of which preceded and facilitated expansion of the hominin brain. All three of these changes were cumulative and were probably obligatory for human brain evolution. The early stage (facilitated ketogenesis) is present in many mammals and permitted more fuel to be available to the infant but during lactation only. The intermediate stage (longer gestation) was common to primates and permitted longer fetal development. Amongst primates, the later stage (fetal/neonatal body fat) is unique to humans and extended brain fuel insurance well beyond the end of lactation.

Third was distinctly different gastrointestinal absorption of ketogenic short- and medium-chain fatty acids compared with long-chain fatty acids. Like most nutrients, short- and medium-chain fatty acids are absorbed directly from the stomach and small intestine into the portal blood leading to the liver. This route of absorption differs markedly from the absorption of dietary long chain fatty acids (greater than 14 carbons in length), which occurs via formation of chylomicrons that are transferred from the intestine to the general circulation via the lymphatic system. Therefore, the evolution of these two separate routes of fatty acid absorption is probably older than the evolution of longer gestation and fetal/neonatal body fat.

In non-human mammals, more rapid absorption of short- and medium-chain fatty acids is presumably important only during lactation because these fatty acids are very rare in nature outside of mammalian milk (Sarda et al., 1987). Unlike long chain fatty acids, only small amounts of medium-chain (and no short-chain) fatty acids are stored in fat because they are highly ketogenic and used rapidly as a fuel source. The importance of short- and medium-chain fatty acids during lactation is that, as the main precursors to ketones, they complement glucose in helping newborn mammals become autonomous, thereby increasing their chances of survival. To a greater extent than in other mammals and despite the intake of ketogenic fatty acids, the human neonate is still heavily dependent on the mother after weaning because the brain is not sufficiently developed. Also unlike other mammals, the human neonate has its own fat stores containing 8–10% short- and medium-chain fatty acids (Sarda et al., 1987), which prolong ketogenesis well beyond weaning.

Fourth, the beta-oxidation of ketogenic fatty acids for energy involves a biochemical process that is simpler and more direct than for long chain fatty acids. The common long chain fatty acids (16 and 18 carbons) making up most of dietary fat need to be 'activated' by the enzyme carnitine palmitoyl transferase (CPT) before they can be beta-oxidized or burned as fuels. This extra step in the conversion of long chain fatty acids into energy is not required for those fatty acids under 14 carbons in length, which are all more ketogenic than long chain fatty acids. The infant consuming maternal milk is therefore more easily able to sustain mild ketosis from the short- and medium-chain fatty acids in milk than can the adult whose only source of fatty acids for ketogenesis is the long chain fatty acids in the diet or in body fat stores that need to be activated by CPT before yielding ketones. Therefore, not only does the storage of medium chain fatty acids in infant fat extend ketogenesis but the biochemical process involved in oxidizing fatty acids to make ketones is easier for medium-chain than long-chain fatty acids. Hence, a combination of evolving subcutaneous fat in the human fetus and neonate with simpler absorption and oxidation of ketogenic fatty acids were key elements in permitting ketogenesis from stored medium chain fatty acids to be extended beyond weaning. These processes were key components in breaking through the energetic constraint on brain expansion.

Discussion

Expansion of the hominin brain came at the cost of increasing neurodevelopmental vulnerability. Without evolving a way to mask or circumvent the increasing vulnerability of the developing hominin brain as it expanded, its evolution might have started but would not have been sustainable. The hominin fossil record shows that at least two million years ago, some populations of *H. habilis* were living around the big lakes and other water bodies of East Africa and frequently eating fish and shellfish (Stewart, 1994, 2010; Braun et al., 2010; Stewart, 2014; Archer et al., 2014). Hence, environmental and nutritional circumstances favouring brain evolution were present in at least one hominin lineage prior to truly significant brain expansion.

Ketones are the back-up fuel to glucose in the human adult but in the neonate they are the predominant brain fuel. During mammalian evolution, the presence of medium chain fatty acids in milk allowed the developing brain to exploit ketones as a compliment to glucose. However, in all mammals except humans, that fuel advantage terminates at the end of lactation. Hominin infants were also acquiring abundant body fat stores, which prolonged the supply of medium chain fatty acids used to make ketones well beyond the end of lactation; this was the game changer for human brain evolution. Evolution of other organ systems that laid the groundwork for expanding the brain and adipose tissue included longer gestation in primates and the presence of a separate, more direct route for absorbing ketogenic fatty acids from the gut and burning them without needing the additional step of fatty acid activation through CPT. Human brain evolution became a possibility because of the evolution of metabolically efficient use of ketones made possible by these other changes as well.

Though necessary, by itself, more fuel (whether glucose or ketones) for the brain was not sufficient to stimulate human brain evolution. This energetic constraint was accompanied by a nutritional constraint affecting the structure and performance of neurons and their networks (Fig. 6). Enhanced brain performance involves enhanced connectivity between neurons, which is the

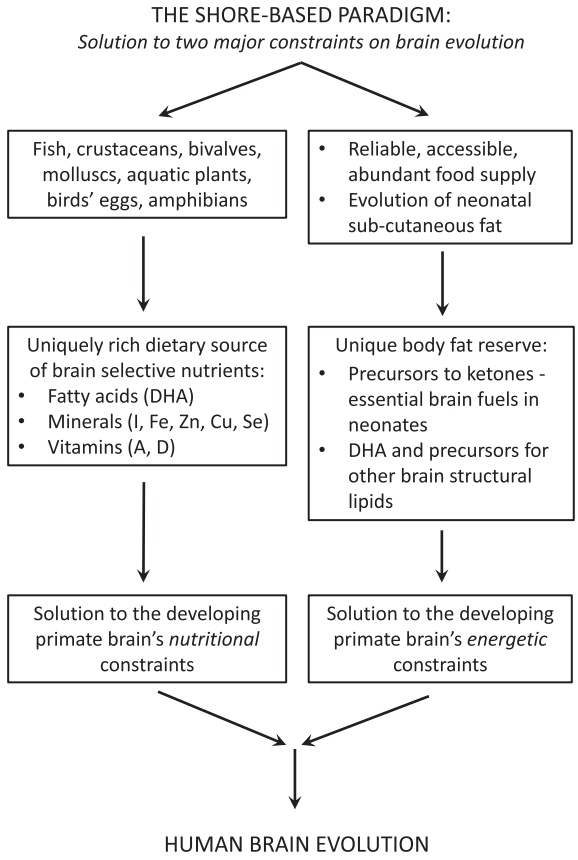

Figure 6. Schematic representation of the shore-based paradigm of human brain evolution (modified from Cunnane, 2010). Nutritional and energetic constraints are not necessarily strictly separate in a biological sense. For instance, in neurons, the two are intimately linked. They are shown separately to emphasise the point that brain evolution depended on surmounting both types of constraints; providing the brain with more energy alone or providing it with one or more of the key structural nutrients such as docosahexaenoic acid (DHA) alone would not have been sufficient to drive human brain evolution.

defining characteristic of human versus non-human primate cognitive capacity. Improving connectivity depended on greater dietary availability of brain selective nutrients and, hence, a shore-based habitat. Beyond supplying brain selective nutrients, an accessible and abundant shore-based diet and habitat would have allowed time to be committed to nascent technological and cultural development, including stone knapping, language, music and art. Hence, survival of the individual is not what drove human brain evolution (Tattersall, 1998); if survival had been the issue, the human brain would not have evolved as it did because not only its development but also its function, i.e., neuronal connectivity, in adults is suboptimal when the intake of one or more brain selective nutrients is low (Horrobin, 2001; Freeman et al., 2006; Cunnane et al., 2009; Crawford, 2010).

Human brain size is frequently argued to have waxed and waned over the last two million years, or at least to have been static for long periods. The shore-based paradigm acknowledges that optimal brain development depends absolutely on environmental circumstances providing a favourable diet and that over time the hominin brain could have expanded and contracted accordingly. Indeed, average adult brain size is actually somewhat smaller now than in the earliest anatomically modern humans (Table 1). It is unclear whether this decrease is transitory or could be the beginning of a long-term trend.

If hominin occupation of a shore-based habitat was crucial to promote and sustain human brain evolution, moving away from a shore-based habitat would be predicted to threaten optimal brain development and function. A billion iodine and iron-deficient people in the world today, living mostly inland and consuming no fish or shellfish, show that moving away from a diet enriched in brain selective minerals has serious and long-lasting risks for human brain development and function in the adult. Hence, the high vulnerability of the human brain shows that we have not yet evolved beyond dependence on a shore-based diet.

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The ideas expressed here are our own, particularly the aspects linking human brain evolution to brain energetics, ketone metabolism and neonatal body fat. We coined the term ‘brain selective nutrients,’ but this aspect, especially in relation to DHA, is more interwoven with concepts discussed and distilled on many occasions with others. Continued support from Leo Standing (Bishop’s University, Lennoxville, Quebec) has been most encouraging. Numerous students, collaborators and colleagues around the world have challenged and helped refine some of these concepts. It has been a pleasure and honour to work with Kathy Stewart and Ian Tattersall on this thematic issue of the Journal of Human Evolution. The Natural Sciences and Engineering Research Council of Canada (3606-2008) is thanked for financial support.

References

Adam, P.A.J., Raiha, N., Rahiala, E.L., Kekomaki, E.L., 1975. Oxidation of glucose and D-beta-hydroxybutyrate by the early human fetal brain. Acta Paediatr. Scan. 64, 17–24.
Aeillo, L.C., Wheeler, P., 1995. The expensive-tissue hypothesis. The brain and digestive system in human and primate evolution. Curr. Anthropol. 36, 199–221.
Allen, J.S., Damasio, H., Grabowski, T.J., 2002. Normal neuroanatomical variation in the human brain. An MRI-volumetric study. Am. J. Phys. Anthropol. 118, 341–358.
Archer, W., Braun, D.R., Harris, J.W.K., McCoy, J.T., Richmond, B.G., 2014. Early Pleistocene aquatic resource use in the Turkana Basin. J. Hum. Evol. 77, 74–87.
Battaglia, F.C., Meschia, G., 1973. Fetal and Neonatal Physiology. Cambridge University Press, Cambridge.
Braun, D.R., Harris, J.W.K., Levin, N.E., McCoy, J.T., Herries, A.I.R., Bamford, M.K., Bishop, L.C., Richmond, B.G., Kibunjia, M., 2010. Early hominin diet included diverse terrestrial and aquatic animals 1.95 Ma in East Turkana, Kenya. Proc. Natl. Acad. Sci. 107, 10002–10007.
Broadhurst, C.L., Cunnane, S.C., Crawford, M.A., 1998. Rift Valley lake fish and shellfish provided brain-specific nutrition for early *Homo*. Brit. J. Nutr. 79, 3–21.
Cordain, L., Eaton, S.B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B.A., O’Keefe, J.H., Brand-Miller, J., 2005. Origins and evolution of the Western diet: health implications for the 21st century. Am. J. Clin. Nutr. 81, 341–354.
Crawford, M.A., 2010. Long-chain polyunsaturated fatty acids in human brain evolution. In: Cunnane, S.C., Stewart, K.M. (Eds.), Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken, pp. 13–32.
Crawford, M.A., Marsh, D., 1989. The Driving Force: Food in Evolution and the Future. William Heinemann, London.
Crawford, M.A., Sinclair, A.J., 1972. Nutritional influences in the evolution of the mammalian brain. In: Eliot, K., Knight, J. (Eds.), Lipids, Malnutrition and the Developing Brain, A Ciba Foundation Symposium. Elsevier, Amsterdam, pp. 267–292.
Crawford, M.A., Costeloe, K., Ghebremeskel, K., 1997. Are deficits of arachidonic and docosahexaenoic acids responsible for the neural and vascular complications of preterm babies? Am. J. Clin. Nutr. S66, 1032S–1041S.
Cremer, J.E., 1982. Substrate utilization and brain development. J. Cerebral Blood Flow Metab. 2, 394–407.
Cunnane, S.C., 2005. Survival of the Fattest. World Scientific, Hackensack.
Cunnane, S.C., 2010. Human brain evolution: A question of solving key nutritional and metabolic constraints on mammalian brain development. In: Cunnane, S.C., Stewart, K.M. (Eds.), Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken, pp. 33–64.
Cunnane, S.C., Crawford, M.A., 2003. Survival of the fattest: Fat babies were the key to evolution of the large human brain. Comp. Biochem. Physiol. 136A, 17–26.
Cunnane, S.C., Stewart, K.M. (Eds.), 2010. Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken.
Cunnane, S.C., Menard, C.R., Likhodii, S.S., Brenna, J.T., Crawford, M.A., 1999. Carbon recycling into *de novo* lipogenesis is a major pathway in neonatal metabolism of linoleate and alpha-linolenate. Prostag. Leukotr. Ess. 60, 387–392.
Cunnane, S.C., Francescutti, V., Brenna, J.T., Crawford, M.A., 2000. Breast-fed infants achieve a higher rate of brain and whole body docosahexaenoate accumulation than formula-fed infants not consuming dietary docosahexaenoate. Lipids 35, 105–111.
Cunnane, S.C., Plourde, M., Pifferi, F., Bégin, M.E., Féart, C., Barberger-Gateau, P., 2009. Fish, docosahexaenoic acid and Alzheimer’s disease. Progr. Lipid Res. 48, 239–256.
Cunnane, S.C., Nugent, S., Roy, M., Coutchesne-Loyer, A., Croteau, E., Tremblay, S., Castellano, C.C., Pifferi, F., Bocti, C., Paquet, N., Begdouri, H., Bentourkia, M., Turcotte, E., Allard, M., Barberger-Gateau, P., Fulop, T., Rapoport, S.I., 2011. Brain fuel metabolism, aging, and Alzheimer’s disease. Nutrition 27, 3–20.
Dobbing, J., 1985. Infant nutrition and later development. Am. J. Clin. Nutr. 41 (S2), 477–484.
Dussault, J.H., Ruel, J., 1987. Thyroid hormones and brain development. A. Rev. Physiol. 49, 321–334.
Edmond, J., 1974. Ketone bodies serve as important precursors of brain lipids in the developing rat. J. Biol. Chem. 249, 72–80.
Erlandson, J.M., 2010. Food for thought: The role of coastlines and aquatic resources in human evolution. In: Cunnane, S.C., Stewart, K.M. (Eds.), Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken, pp. 125–136.
Farquharson, J., Cockburn, F., Patrick, W.A., Jamieson, E.C., Logan, R.W., 1992. Infant cerebral cortex fatty acid composition and diet. Lancet 340, 810–813.
Freeman, M.P., Hibbeln, J.R., Wisner, K.L., Davis, J.M., Mischoulon, D., Peet, M., Keck Jr., P.E., Marangell, L.B., Richardson, A.J., Lake, J., Stoll, A.L., 2006. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. J. Clin. Psychiatr. 67, 1954–1967.
Fukao, T., Lopaschuk, G.D., Mitchell, G.A., 2004. Pathways and control of ketone metabolism: on the fringe of lipid biochemistry. Prostagl. Leukotr. Ess. 70, 243–251.
Harrington, T.A., Thomas, E.L., Modi, N., 2002. Fast and reproducible method for the direct quantitation of adipose tissue in newborn infants. Lipids 37, 95–100.
Hirsch, J., Farquhar, J.W., Ahrens Jr., E.H., 1960. Studies of adipose tissue in man. Am. J. Clin. Nutr. 8, 499–511.
Holliday, M., 1971. Metabolic rate and organ size during growth from infancy to maturity and during late gestation and early infancy. Pediatrics 47, 169–172.
Horrobin, D.F., 2001. The Madness of Adam and Eve. Bantam, London.
Jurevics, H., Morell, P., 1995. Cholesterol for synthesis of myelin is made locally, not imported into the brain. J. Neurochem. 64, 895–901.
Kappelman, J., Nachman, B., Tewabe, D., Todd, L., 2014. Another unique river: a consideration of some of the characteristics of the trunk tributaries of the Nile River in northwestern Ethiopia in relationship to their aquatic resources. J. Hum. Evol. 77, 117–131.
Kuzawa, C.W., 1998. Adipose tissue in human infancy and childhood: an evolutionary perspective. Am. J. Phys. Anthropol. S27, 177–209.
Leonard, W.R., 2002. Food for thought. Dietary change was a driving force in human evolution. Sci. Am. 287, 106–115.
Leonard, W.R., Robertson, M.L., 1994. Evolutionary perspectives on human nutrition. The influence of brain and body size on diet and metabolism. Am. J. Hum. Biol. 6, 77–88.
Leonard, W.R., Robertson, M.L., 1996. On diet, energy metabolism, and brain size in human evolution. Curr. Anthropol. 37, 125–129.

Lozoff, B., Brittenham, G.M., 1986. Behavioural aspects of iron deficiency. Progr. Hematol. 14, 23–53.
Mace, G.M., Harvey, P.H., Clutton-Brock, T.H., 1981. Brain size and ecology in small mammals. J. Zool. 193, 333–354.
Magistretti, P.J., 2004. Brain energy metabolism. In: Byrne, J.H., Roberts, J.L. (Eds.), An Introduction to Cellular and Molecular Neuroscience. J.L. Academic, Hong Kong, pp. 67–90.
Makrides, M., Neumann, M.A., Byard, R.W., Simmer, K., Gibson, R.A., 1994. Fatty acid composition of brain, retina and erythrocytes in breast- and formula-fed infants. Am. J. Clin. Nutr. 60, 189–194.
Martin, R.D., 1981. Relative brain size and basal metabolite rate in terrestrial vertebrates. Nature 293, 57–60.
Martin, R.D., 1996. Scaling of the mammalian brain: the maternal energy hypothesis. News Physiol. Sci. 11, 149–156.
Owen, O.E., Morgan, A.P., Kemp, H.G., Sullivan, J.M., Herrera, M.G., Cahill Jr., G.F., 1967. Brain metabolism during fasting. J. Clin. Invest. 46, 1589–1595.
Pardridge, W.M., 1991. Blood-brain barrier transport of glucose, free fatty acids, and ketone bodies. In: Vranic, M., Efendic, S., Hollenberg, C.H. (Eds.), Fuel Homeostasis and the Nervous System. Plenum Press, New York, pp. 43–53.
Parkington, J., 2010. Coastal diet, encephalization, and innovative behaviours in the late Middle Stone Age of southern Africa. In: Cunnane, S.C., Stewart, K.M. (Eds.), Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken, pp. 189–203.
Pfefferle, A.D., Warner, L.R., Wang, C.W., Nielsen, W.J., Babbitt, C.C., Fedrigo, O., Wray, G.A., 2011. Comparative expression analysis of the phosphocreatine circuit in extant primates: implications for human brain evolution. J. Hum. Evol. 60, 205–212.
Pharoah, P.O.D., Buttfield, I.H., Hetzel, B.S., 1971. Neurological damage to the fetus resulting from severe iodine deficiency during pregnancy. Lancet 13, 308–310.
Plourde, M., Cunnane, S.C., 2007. Extremely limited conversion of long chain omega-3 polyunsaturates in adults: implications for their dietary essentiality and use as supplements. Appl. Physiol. Nutr. Metab. 32, 619–634.
Pollitt, E., 1993. Iron deficiency and cognitive function. A. Rev. Nutr. 13, 521–537.
Pollitt, E., Metallinos-Katsaras, E., 1990. Iron deficiency and behaviour. Constructs, methods, and validity of the findings. Nutr. Brain 8, 101–148.
Pond, C.M., 1992. An evolutionary and functional view of mammalian adipose tissue. Proc. Nutr. Soc. 51, 366–377.
Raclot, T., Groslocas, R., 1993. Differential mobilization of white adipose tissue fatty acids according to chain length, unsaturation and positional isomerization. J. Lipid Res. 34, 1515–1526.
Ramkrishnan, U., 2002. Prevalence of micronutrient malnutrition worldwide. Nutr. Rev. 60, S45–S52.
Robinson, A.M., Williamson, D.H., 1980. Biological roles of ketone bodies as substrates and signals in mammalian tissues. Physiol. Rev. 60, 143–187.
Sarda, P., Lepage, G., Roy, C.C., Chessex, P., 1987. Storage of medium-chain triglyceride in adipose tissue of orally fed infants. Am. J. Clin. Nutr. 45, 399–405.
Stewart, K.M., 1994. Early hominid utilisation of fish resources and implications for seasonality and behaviour. J. Hum. Evol. 27, 229–245.
Stewart, K.M., 2010. The case for exploitation of wetlands environments and foods by pre-sapiens hominins. In: Cunnane, S.C., Stewart, K.M. (Eds.), Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken, pp. 137–172.
Stewart, K.M., 2014. Early hominin use of freshwater environments and resources as a buffer against environmental instability. J. Hum. Evol. 77, 74–87.
Tattersall, I., 1998. Becoming Human: Evolution and Human Uniqueness. Harcourt, Brace and Company, New York.
Teaford, M.F., Ungar, P.S., 2000. Diet and the evolution of the earliest human ancestors. Proc. Natl. Acad. Sci. 97, 13506–13511.
Venturi, S., Bégin, M.E., 2010. Thyroid hormone, iodine and human brain evolution. In: Cunnane, S.C., Stewart, K.M. (Eds.), Human Brain Evolution: The Influence of Freshwater and Marine Food Resources. Wiley, Hoboken, pp. 105–124.
Venturi, S., Donati, F.M., Venturi, M., 2000. Environmental iodine deficiency. A challenge to the evolution of terrestrial life. Thyroid 10, 727–729.
Widdowson, E.M., 1974. Changes in body proportion and composition during growth. In: Davies, J.A., Dobbing, J. (Eds.), Scientific Foundations of Pediatrics. Heinemann, London, pp. 153–163.