Journal of Human Evolution 77 (2014) 132–140

Contents lists available at ScienceDirect

Journal of Human Evolution

journal homepage: www.elsevier.com/locate/jhevol

The appropriation of glucose through primate neurodevelopment

Amy L. Bauernfeind [a, b, *], Courtney C. Babbitt [c]

[a] Department of Anthropology, The George Washington University, Washington, DC 20052, USA
[b] Department of Anatomy & Neurobiology, Washington University School of Medicine, St. Louis, MO 63110, USA
[c] Department of Biology, University of Massachusetts Amherst, Amherst, MA 01003, USA

ARTICLE INFO

Article history:
Received 14 January 2014
Accepted 2 May 2014
Available online 7 August 2014

Keywords:
Aerobic glycolysis
Oxidative phosphorylation
Brain energetics
Development
Human evolution
Comparative genetics

ABSTRACT

The human brain is considerably larger and more energetically costly than that of other primate species. As such, discovering how human ancestors were able to provide sufficient energy to their brains is a central theme in the study of hominin evolution. However, many discussions of metabolism frequently omit the different ways in which energy, primarily glucose, is used once made available to the brain. In this review, we discuss two glucose metabolic pathways, oxidative phosphorylation and aerobic glycolysis, and their respective contributions to the energetic and anabolic budgets of the brain. While oxidative phosphorylation is a more efficient producer of energy, aerobic glycolysis contributes essential molecules for the growth of the brain and maintaining the structure of its cells. Although both pathways occur in the brain throughout the lifetime, aerobic glycolysis is a critical pathway during development, and oxidative phosphorylation is highest during adulthood. We outline how elevated levels of aerobic glycolysis may support the protracted neurodevelopmental sequence of humans compared with other primates. Finally, we review the genetic evidence for differences in metabolic function in the brains of primates and explore genes that may provide insight into how glucose metabolism may differ across species.

Introduction

Although it makes up only 2% of total body mass, the adult modern human brain utilizes about 15–20% of the body's resting metabolic resources (Hofman, 1983). This is far greater than the brains of other primates that consume between 2 and 10% of their body's resting energy expenditure (Mink et al., 1981). The rate of glucose uptake needed to sustain the adult human brain imposes a substantial cost to the body that is thought to be met either by a greater input of energy through increased diet quality or cooking (Gaulin and Kurland, 1976; Leonard and Robertson, 1994; Aiello and Wheeler, 1995; Broadhurst et al., 2002; Fish and Lockwood, 2003; Wrangham, 2009) or by metabolic tradeoff with other organs, including musculature (Leonard et al., 2003) or the size of the digestive tract (Aiello and Wheeler, 1995 but see; Navarrete et al., 2011). It has also been suggested that modern humans coevolved an extended life history and period of childhood to support the growth and metabolic requirements of the brain (Foley and Lee, 1991; Bogin, 1997; Leigh, 2004; Barton and Capellini, 2011).

Although the human brain is very energetically expensive in adulthood, the rate of glucose uptake per gram of tissue reaches twice the adult level around the age of two or three years (Chugani et al., 1987). In contrast, the brain of the macaque monkey obtains its maximum rate of glucose uptake per gram of tissue at birth (Jacobs et al., 1995), which is about one-third greater than the rate of glucose uptake in the adult macaque brain. Therefore, the glucose requirements of the primate brain are dynamic throughout the lifetime, and the trajectory of how glucose uptake rates change over time appears to differ across species. Humans are unique among primates in that the extremely high metabolic costs of growing the large human brain must be sustained over a much longer period of neurodevelopment (Leigh, 2004; Barrickman et al., 2008). Additionally, the increased energy required for the human brain's maturation may not be met by glucose alone but may depend upon additional sources of energy, including ketones (Miller et al., 1982; Nehlig and Pereira de Vasconcelos, 1993). Although it is clear that meeting the metabolic costs imposed by the brain must have been a difficult challenge to meet during human evolution, the precise reasons for this high energetic cost deserve more attention.

All multicellular organisms use adenosine-5'-triphosphate (ATP) as their chief energy source, and it is most typically supplied

Abbreviations: Acetyl-CoA, acetyl coenzyme A; ATP, adenosine-5′-triphosphate; LDH, lactate dehydrogenase; PET, positron emission tomography; PPP, pentose phosphate pathway.

* Corresponding author.
E-mail address: amy81@gwu.edu (A.L. Bauernfeind).

http://dx.doi.org/10.1016/j.jhevol.2014.05.016
0047-2484/

by the metabolic pathway of oxidative phosphorylation (Nelson and Cox, 2008). Oxidative phosphorylation includes the sequential processes of glycolysis, the citric acid cycle, and the electron transport chain, which, together, metabolize glucose into ATP. In this review, we use the definitions put forth by other authors (Pellerin and Magistretti, 1994; Vander Heiden et al., 2009; Vaishnavi et al., 2010) to distinguish between glycolysis and aerobic glycolysis. As described above, glycolysis digests glucose to pyruvate and is an integral step of oxidative phosphorylation. Aerobic glycolysis also refers to the breakdown of glucose to pyruvate but is not followed by the citric acid cycle and the electron transport chain. Despite its name and unlike oxidative phosphorylation, aerobic glycolysis does not consume oxygen and is therefore not an aerobic process. Although both aerobic glycolysis and oxidative phosphorylation produce ATP from glucose, oxidative phosphorylation is a much more efficient producer of energy. In most tissues of the body, aerobic glycolysis is a pathway typically associated with hypoxic conditions (insufficient oxygen availability) or dysfunction of the mitochondria that would prevent oxidative phosphorylation from occurring (Ullah et al., 2006; Soane et al., 2007; Perez de Heredia et al., 2010; Nielsen et al., 2013). However, aerobic glycolysis also occurs in the brain under normal conditions despite the presence of sufficient oxygen for oxidative phosphorylation (Raichle et al., 1970; Wyss et al., 2011). Moreover, some authors have noted the importance of aerobic glycolysis as a contributor of carbon to the anabolic processes that synthesize the constituent molecules of the brain, including lipids, proteins, and nucleotides (Raichle, 2010; Vaishnavi et al., 2010).

We review the contributions of the two major metabolic pathways, aerobic glycolysis and oxidative phosphorylation, toward meeting the developing brain's energy requirements and the necessary contribution of molecules to its biomass. Because protracted development is a hallmark of human brain growth and development (Leigh, 2004), we review how humans may differ from other primates in their reliance of these pathways over time. For more detail regarding the biochemical and neurological basis for these hypotheses, we refer the reader to a recent review by Bauernfeind et al. (2014). Finally, we consider what gene sequence evolution and differential gene expression tell us about how brain glucose metabolism may differ in humans compared with other primates. We discuss the importance of these issues for the development, function, and maintenance of the energetically expensive human brain.

A brief review of metabolic pathways and anabolic processes

When a molecule of glucose enters a cell, the typical outcome is for it to be immediately converted into pyruvate by glycolysis, a process that occurs in the cytoplasm of the cell and generates two molecules of ATP (Nelson and Cox, 2008). Pyruvate can be converted into lactate, for short-term energy storage, or acetyl coenzyme A (acetyl-CoA), which is used in the oxidative phosphorylation pathway. In oxidative phosphorylation, acetyl-CoA enters the mitochondria and is completely metabolized into carbon dioxide and water by the citric acid cycle. The electron transport chain follows and a total of around 36 molecules of ATP are produced per molecule of glucose (Fig. 1). Through aerobic glycolysis, one of the molecules derived from glucose may be used as a precursor to biosynthetic pathways, including the synthesis of fatty acids and other lipids required for myelination (Brown et al., 2001; Tekkök et al., 2005) or the synthesis of amino acids necessary for building the complex proteins that compose the cell's structural and functional elements including enzymes (Nelson and Cox, 2008). Indeed, the synthesis of enzymes by aerobic glycolysis may even be critical to the development and maintenance of the molecules that compose the citric acid cycle, suggesting interdependence between aerobic glycolysis and oxidative phosphorylation (Hovda et al., 1992, 2006). An intermediate molecule of glycolysis, glucose-6-phosphate, may be used by the pentose phosphate pathway (PPP) for the synthesis of nucleotides. Each of these anabolic processes

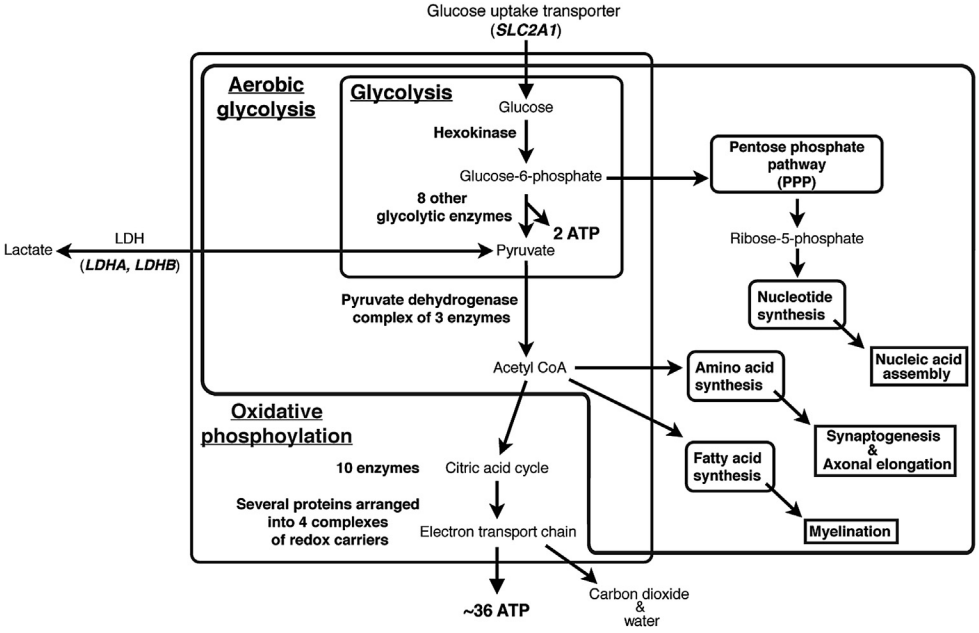

Figure 1. The potential outcomes of glucose entry into a neuron are diagramed. Larger boxes surround several stages of the metabolic pathways and encompass the steps that are referred to by glycolysis, oxidative phosphorylation, and aerobic glycolysis. Although aerobic glycolysis produces only two molecules of ATP, it provides molecules, glucose-6-phosphate and pyruvate, that can be used as substrates for nucleotide, amino acid, and fatty acid synthesis. Oxidative phosphorylation is an efficient producer of ATP, yielding approximately 36 molecules of ATP per molecule of glucose. The major steps within glycolysis and oxidative phosphorylation have the names of the enzymes or transporters next to them or a listing of how many molecules are involved in the process. Importantly, these molecules may be explored as potential targets of gene regulation that may change the kinetics of these glucose metabolism pathways. This figure is reproduced with permission from Bauernfeind et al. (2014).

uses glucose (or a downstream molecule) as a source of carbon for the creation of biomolecules. Consequently, although oxidative phosphorylation is the more efficient producer of energy, aerobic glycolysis contributes precursor molecules for the synthesis of lipids, proteins, and nucleotides that are essential to the structure and function of cells (Vander Heiden et al., 2009, 2010; Raichle, 2010).

Throughout the lifetime, the energetic and anabolic needs of the brain change (Erecinska et al., 2004). Postnatal brain development requires additional lipids and proteins to support the maturational processes of axonal elongation (Jareb and Banker, 1997; Goldberg, 2003; Zivraj et al., 2010), myelination (Baumann and Pham-Dinh, 2001; Lee, 2001; Rinholm et al., 2011), and synaptogenesis (Knott et al., 2006). It appears that in early postnatal brain development the lipid requirements of the rapidly growing brain may be so extensive that the endogenous production of fatty acids from glucose may be supplemented by ketone bodies from the diet (Edmond, 1974; Yeh et al., 1977; Sheaff-Greiner et al., 1996; reviewed in; Cunnane et al., 2003). Once brain maturation is complete, synthesis of lipids, proteins, and nucleotides must continue, albeit at a lower rate, to replace the constituent molecules of the cell, including those that compose the cell membrane, ion channels, neurotransmitter receptors, myelin sheaths, and signal transduction pathways (Star et al., 2002; Ehlers, 2003; Yi and Ehlers, 2005; Marder and Goaillard, 2006; Raichle, 2010; Fünfschilling et al., 2012). Furthermore, dendritic spines and synapses require the addition of lipids and proteins to support the structural modifications that underlie learning (Li et al., 2004; Sheng and Hoogenraad, 2007; Newman et al., 2011; Suzuki et al., 2011). Therefore, glucose taken up by the brain must continually contribute to aerobic glycolysis, and the biosynthetic processes it supports, to meet the anabolic requirements necessary for proper neuronal growth, maturation, and function throughout the lifetime.

Positron emission tomography (PET) tracks the uptake of a radiolabeled molecule, typically glucose, in the brain and has been an immensely informative method as to the biochemical needs of the brain during cognitive tasks and in the resting state (Mintun et al., 2001; Buckner, 2012; Barks et al., 2013). It is widely recognized that the majority of energy in active brain tissue fuels neurotransmission (Magistretti et al., 1999; Attwell and Laughlin, 2001; Harris et al., 2012), but it is important to consider that brain activity invoked by performing a specific cognitive task typically elicits an increase of local energy uptake by only about 5% (Sokoloff et al., 1955). Therefore, the brain uses the vast majority of its glucose to maintain its physiological baseline, including the maintenance of the ion gradient across the neuronal membrane (the neuron's resting membrane potential) (Attwell and Laughlin, 2001; Raichle, 2010). Although the synaptic activity underlying cognitive tasks is an important consideration to brain metabolism, it is not the sole, or even the most significant, metabolic expense. The fact that the brain uses glucose for oxidative phosphorylation and aerobic glycolysis (energetic or anabolic processes, respectively) poses an additional challenge to the interpretation of the PET studies using radiolabeled glucose (Raichle, 2010). By tracking both radiolabeled glucose and oxygen, PET studies are able to decipher how much glucose is allocated to which metabolic pathway because oxidative phosphorylation requires oxygen and aerobic glycolysis does not (Vaishnavi et al., 2010).

Human neurodevelopment and energetics

At birth, the human brain weighs roughly 360 g and comprises about 25% of its adult size (Dobbing and Sands, 1979; Robson and Wood, 2008). Postnatal brain growth continues rapidly for the first few years of life, and around the age of seven, the adult human brain volume is obtained (Dobbing and Sands, 1979). Although neurogenesis (the production of new neurons) occurs in the postnatal primate brain (Gould, 2007), it is limited in scope by how many neurons are produced and is restricted to the olfactory bulb, hippocampus, and a few neocortical regions (Kornack and Rakic, 1999, 2001; Rakic, 2002). Consequently, postnatal brain growth is not the result of the addition of new neurons but the maturation of those already existing. Neuronal maturation is critical for the development of function and includes the processes of axonal elongation, dendritic branching and elaboration, myelination of axons, and the proliferation of synapses and subsequent elimination of superfluous synapses (synaptic pruning) (Goldman-Rakic, 1987; Hensch, 2004).

Human neurodevelopment is characterized by heterogeneity in the timing of neuronal maturational processes across the neocortex. Even from the time of birth, differences in the distribution of dendrites, dendritic spines, and synapses are apparent with primary motor and sensory cortices displaying higher densities of these microstructural elements than regions within the prefrontal cortex (Huttenlocher and Dabholkar, 1997). Associative regions of the neocortex, those that do not have direct connections with sensory or motor function such as the prefrontal cortices, are characterized as being more integrative (containing more connections from other cortical regions) in human adulthood (Elston et al., 2001; Semendeferi et al., 2011; Spocter et al., 2012). Although associative cortices are slower to mature than primary motor and sensory cortices, by the time these regions have reached maturity, they have developed a greater degree of structural complexity, including the length and branching of dendrites and the density of synapses (Huttenlocher and Dabholkar, 1997; Jacobs et al., 1997, 2001; Travis et al., 2005; Petanjek et al., 2011). In parallel with the development of the cytoarchitecture of neurons, the average thickness of the neocortex and volume of gray matter in humans increase to about the age of 10, with associative cortices maturing slightly later than sensory cortices (Giedd et al., 1999; Gogtay et al., 2004; Shaw et al., 2008). Together, these data support the case for asynchrony in the maturation of neuronal microstructure across the human neocortex.

Like the maturation of human brain cytoarchitecture, energy metabolism in the brain also displays a dynamic pattern over the course of development (Chugani and Phelps, 1986, Fig. 2). Positron emission tomography studies have shown that glucose uptake in the human brain increases from birth until it reaches its highest rate per gram of tissue around age two or three, which is twice that of the adult level, and remains elevated throughout childhood (Chugani et al., 1987). This period of elevated glucose uptake in the human brain occurs after regions of the neocortex obtain their peak synaptic densities (Jacobs et al., 2001; Petanjek et al., 2011) but before an initial decrease in the rate of myelination (Miller et al., 2012). Once peak synaptic density is reached in late childhood, synaptic pruning occurs, decreasing the number of synapses and refining cortical circuitry (Huttenlocher, 1990; Glantz et al., 2007). In parallel with the elimination of synapses, the brain's glucose uptake steadily declines until it reaches its adult level (Chugani et al., 1987). Like the pattern of synaptogenesis in the developing brain, peak glucose uptake follows a regional pattern across the neocortex with primary motor and somatosensory cortices reaching their adult levels prior to associative areas (Jacobs et al., 2001; Petanjek et al., 2011). Throughout the human neurodevelopmental sequence, the positive correlation between the rates of glucose uptake and the anabolic processes, synaptogenesis and myelination, emphasizes the importance of the appropriation of glucose to support the addition of biomass (Fig. 2).

Considering the dynamics of the human neurodevelopmental sequence, it would be expected that the human brain would

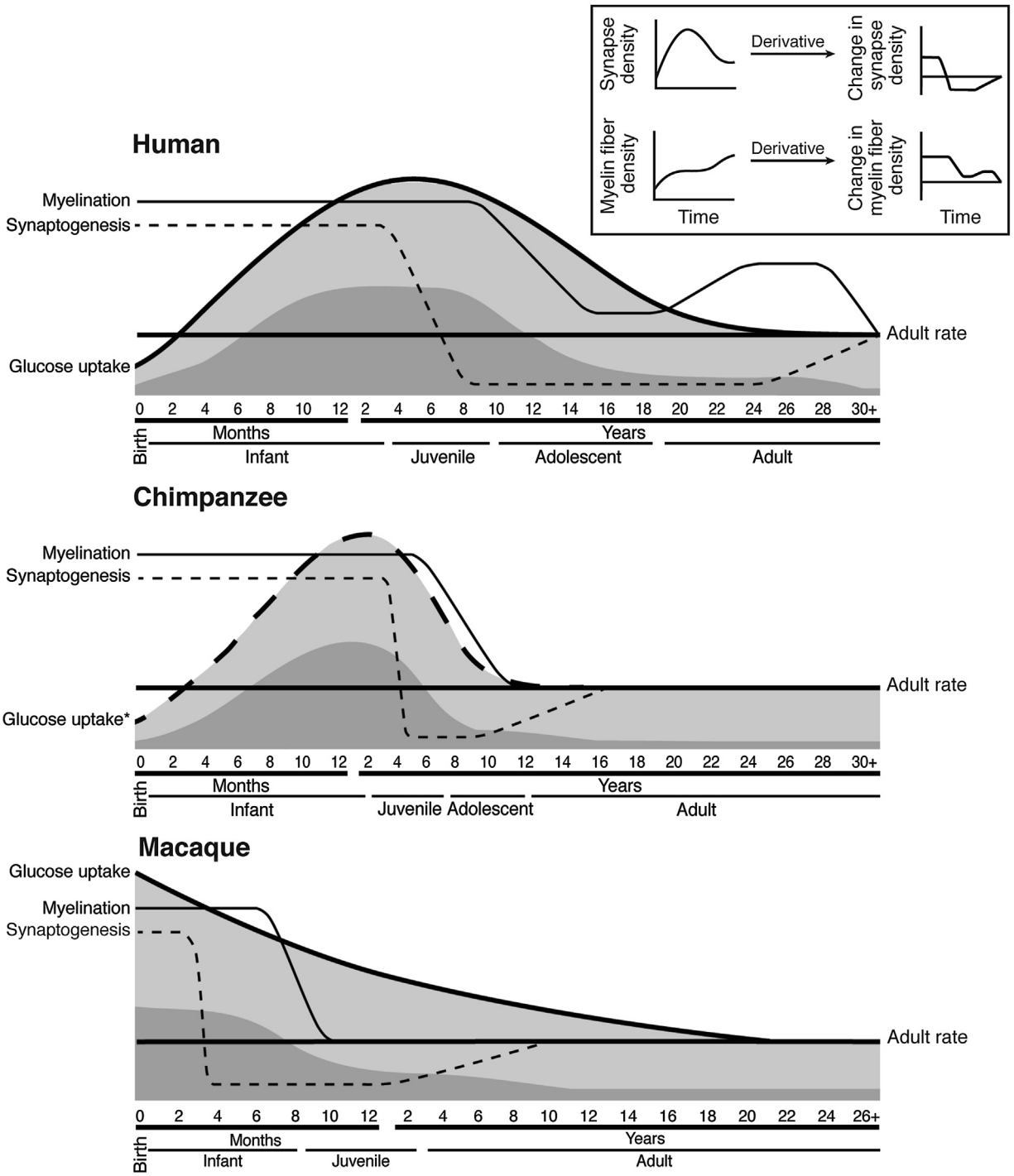

Figure 2. Rates of synaptogenesis, myelination, glucose uptake over the course of development in the human, chimpanzee, and macaque cerebral cortex. Each rate is shown relative to its adult value. Previously published data on the developmental sequence of synapse and myelin fiber densities were then converted into rates of change over the lifetime by estimating the derivative of the curve (see inset) (Gibson, 1970; Rakic et al., 1986; Petanjek et al., 2011; Miller et al., 2012; Bianchi et al., 2013). Rates of glucose uptake are known for humans (Chugani et al., 1987) and macaques (Jacobs et al., 1995), but the rate of glucose uptake over the chimpanzee lifespan (bold dashed line) is estimated based on the maturation of that species' cerebral microstructure. The area under the glucose uptake curve is shaded light gray (estimated proportion of oxidative phosphorylation) or dark gray (estimated proportion of aerobic glycolysis) (Raichle et al., 1970; Settergren et al., 1976; Boyle et al., 1994). The amount of aerobic glycolysis is estimated based on the rate of anabolic processes (synaptogenesis and myelination) occurring at any given time in a species' neurodevelopmental sequence. For each species, the rate of aerobic glycolysis begins at its largest proportion of glucose uptake, remains high to support anabolic processes during neurodevelopment, and then declines to its adult rate. The units on the *x*-axes differ between species to account for their differences in their life histories. This figure is reproduced with permission from Bauernfeind et al. (2014).

appropriate different amounts of glucose to aerobic glycolysis at different times throughout the lifetime. In preterm infants, when the brain is growing at its fastest rate and neurons are proliferating, the brain metabolizes 90% of glucose by aerobic glycolysis (Altman et al., 1993; Powers et al., 1998). Following birth, when there is very little neurogenesis in the brain, 35% of glucose is consumed by aerobic glycolysis (Settergren et al., 1976). In adulthood, the throughput of aerobic glycolysis diminishes to 10–12% of the

glucose available to the brain (Raichle et al., 1970; Boyle et al., 1994). Although there are no direct data on the rate of aerobic glycolysis at other points of development, the rates of anabolic processes allow us to predict the amount of aerobic glycolysis throughout human neurodevelopment (Fig. 2). In early postnatal neurodevelopment, as synaptic connections become more numerous, we would predict the proportion of glucose processed by aerobic glycolysis to remain elevated (around 35%) to support axonal elongation, synaptogenesis, and myelination (Bauernfeind et al., 2014). The rate of aerobic glycolysis would decrease in the later juvenile period as the rates of synaptogenesis and myelination diminish. As anabolic processes and the rate of aerobic glycolysis decline, the proportion of glucose metabolized by oxidative phosphorylation would increase to support the energy demands of synaptic transmission. During human adulthood, aerobic glycolysis continues to metabolize glucose and likely contributes molecules to anabolic processes necessary for biomolecular turnover and experience-dependent learning.

Differences in the neurodevelopmental sequence of primates

Human developmental sequences are protracted compared with other primates (Leigh, 2004), and predictably, the human brain reaches its adult size at a later age compared with other primates (Robson and Wood, 2008; Neubauer et al., 2010; McFarlin et al., 2013). From the perspective of cytoarchitectural development, the human brain displays an extended period of synaptogenesis compared with macaques (Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011). Likewise, an extended time course of myelination of cortical axons exists in the human brain compared with macaques (Yakovlev and Lecours, 1967; Gibson, 1970) and chimpanzees (Miller et al., 2012). Although humans and chimpanzees display a similarly delayed period of synaptogenesis compared with the macaque (Bianchi et al., 2013), protracted myelination and synaptic pruning in humans allows for a longer period of experience-dependent learning to occur prior to the completion of neuronal maturation (Goldman-Rakic, 1987; Miller et al., 2012).

Compared with humans, the maximum rate of glucose uptake in rhesus macaques and vervet monkeys occurs earlier in postnatal life, between the second and sixth months after birth, and occurs synchronously across neocortical regions (Jacobs et al., 1995). The timing of maximum glucose uptake coincides with the timing of the greatest synaptic densities in the macaque, which also displays synchrony across regions (Rakic et al., 1986; Bourgeois et al., 1994). Therefore, like humans, the timing of maximum glucose uptake in the macaque monkey brain occurs concurrently with peak synaptic density. However, humans differ from other primates in that the development of their cytoarchitecture is more protracted and asynchronous across the neocortex. Nothing is known about the glucose uptake in the brains of other primate species over the course of their neurodevelopment.

Because the neurodevelopmental sequence varies across primates, it is anticipated that differences would exist in the duration of elevated aerobic glycolysis to support anabolic processes. As in humans, it appears that the fastest rate of brain growth also occurs in the first few years of neonatal life in other primates (Robson and Wood, 2008; McFarlin et al., 2013), presumably due to the rapid development of neuronal cytoarchitecture. To support the augmentation of brain biomass occurring in these earliest stages of life, aerobic glycolysis is expected to be high across all primates. However, because synaptogenesis and myelination reach their adult levels at a very early age in macaque monkeys, the rate of aerobic glycolysis would be expected to quickly diminish. Although we do not know how glucose uptake in the chimpanzee would compare with other primates, one might predict a trajectory that is intermediary between humans and macaque monkeys due to a period of postnatal synaptogenesis that is similar to that of humans (Bianchi et al., 2013), but with a shorter period of myelination (Miller et al., 2012). Accordingly, elevated aerobic glycolysis in the chimpanzee may extend to a later developmental stage than in the macaque but an earlier absolute age than in humans (Bauernfeind et al., 2014; Fig. 2).

When comparing brain metabolism across primate species, glucose uptake rates should be considered in the context of overall brain size. Kleiber's law states that the amount of energy per gram of tissue required to sustain an organ decreases with increased mass (Kleiber, 1932). A PET study examining the amount of oxygen uptake by the brains of adult mammals and primates, including humans and macaque monkeys, found that larger brains do indeed require less oxygen for each gram of tissue (presumably to support oxidative phosphorylation) than other primates by a scaling rate of 0.75 (Mink et al., 1981; but see; Karbowski, 2007). However, other studies have shown that the rate of glucose uptake per gram of tissue at rest in the human brain (Clarke and Sokoloff, 1999) is indistinguishable from that of the macaque monkey (Kennedy et al., 1978). One interpretation of these data is that humans have more molecules of glucose available at rest for processes other than oxidative phosphorylation than macaque monkeys, which may mean a higher rate of aerobic glycolysis (using glucose and no oxygen) at rest (Bauernfeind et al., 2014). Although this interpretation is speculative, a higher resting throughput of the aerobic glycolysis pathways for anabolic processes in humans compared with other primates would support higher rates of biomolecular turnover and synaptic plasticity (remodeling of synapses) in humans, which could potentially increase the capacity to learn. To our knowledge, a direct comparison of the ratio of glucose and oxygen uptake in the brain by PET has only been performed in adult humans (Vaishnavi et al., 2010). Performing similar studies in other primates would determine if the proportions of glucose contributed to oxidative phosphorylation and aerobic glycolysis differ across primates.

Imprint of changing energy requirements in the human genome

The underlying physiological mechanisms that support glucose metabolism are under the control of the genome and its expression. Therefore, the study of gene sequences or the expression levels of gene transcripts supporting glucose metabolism, and related functions, are crucial to our understanding of how energy may be used in the brain by disparate primate species. Furthermore, because the duration of the neurodevelopmental sequence appears to be of particular importance to the resulting phenotype of the adult primate brain (Leigh, 2004; Barrickman et al., 2008; Barton and Capellini, 2011), the regulation of gene expression over the lifetime is an important consideration. We review what is known about comparative primate brain energetics from the genetic perspective with the goal of appreciating what drives species-specific phenotypic differences.

Several lines of evidence suggest that glucose metabolism, and oxidative phosphorylation in particular, has been a target of natural selection in primate evolution. Lactate dehydrogenase (LDH) is an enzyme that reversibly converts pyruvate into lactate. While the LDH isozyme, LDHA, more rapidly converts pyruvate to lactate, another subtype, LDHB, favors the conversion of lactate to pyruvate (Dawson et al., 1964). Because pyruvate is a necessary molecular substrate for oxidative phosphorylation, the ratio of these LDH subtypes helps to determine the kinetics of glucose metabolism. Although astrocytes, a type of glial cell, contain both LDHA and LDHB, only LDHB is present in neurons (Fig. 3) (Bittar et al., 1996).

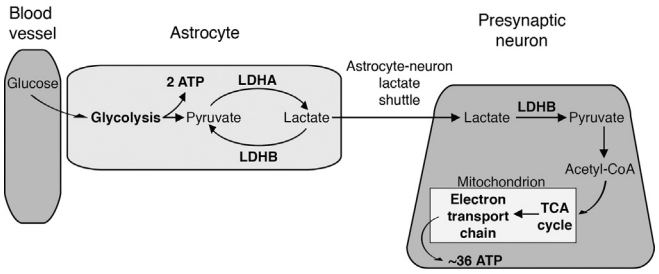

Figure 3. A schematic of the astrocyte-lactate shuttle. An astrocyte uptakes glucose from the blood and metabolizes it into pyruvate by glycolysis. In the astrocyte, LDHA converts pyruvate to lactate, and LDHB can change lactate back into pyruvate (Bittar et al., 1996). The astrocyte-neuron lactate shuttle transports lactate from the astrocyte to a presynaptic neuron (Dienel and Hertz, 2001; Magistretti, 2009). Within the neuron, LDHB converts lactate into pyruvate, which, once converted into acetyl-CoA, is used in oxidative phosphorylation.

Astrocytes have the ability to take up glucose from the blood vessel, metabolize glucose to pyruvate, convert the pyruvate to lactate by LDHA, and provision neurons with lactate to be used as an energy source (Tanaka et al., 2004). This transfer of metabolic substrate from astrocyte to neuron is called the astrocyte-neuron lactate shuttle (Dienel and Hertz, 2001; Magistretti, 2009). Within the neuron, lactate may be retroconverted into pyruvate by LDHB, which is then converted into acetyl-CoA and used in oxidative phosphorylation (Fig. 3). In strepsirrhines, a greater proportion of LDHA is expressed relative to LDHB (Syner and Goodman, 1966; Goodman et al., 1969), while in catarrhines LDHB is more prevalent (Syner and Goodman, 1966; Goodman et al., 1969). The elevated expression of LDHB in catarrhines favors the production of pyruvate and would support a higher rate of oxidative phosphorylation in catarrhines compared with strepsirrhines.

Additional evidence supports evolution in favor of increased oxidative phosphorylation in the primate brain with phylogenetic proximity to humans. Within anthropoids, genes encoding the subunits of cytochrome *c* oxidase, the final component of the electron transport chain, show an accelerated rate of evolution in their sequences compared with any other placental mammals (Grossman et al., 2001; Goldberg et al., 2003; Grossman et al., 2004; Schmidt et al., 2005; Uddin et al., 2008a; Hüttemann et al., 2011). Additionally, the expression of *COX5A*, one of the genes encoding a subunit of cytochrome *c* oxidase, is expressed at a higher level in human neocortex compared with that of other great apes (Uddin et al., 2008a). These genetic changes are indicative of increased control over the mechanisms that process glucose by oxidative phosphorylation within anthropoids (Pierron et al., 2011) and may result in greater levels of ATP availability for synaptic transmission.

Although changes in gene sequence may change the efficiency or function of a gene, the expression level of gene transcripts, dictated by multiple forms of gene regulation, may also affect phenotype (King and Wilson, 1975). For example, the gene encoding the glucose transporter in the brain, *SLC2A1*, has undergone positive selection on regulatory elements within its promoter region in humans but not in chimpanzees (Fedrigo et al., 2011). This change reflects an adaptation for the regulation of glucose uptake that has evolved within the human lineage. Beyond evaluating the expression levels of individual genes, gene enrichment analyses compare the expression of groups of genes that share similar biological functions (Subramanian et al., 2005). Using this method, the expression levels of genes supporting specific biological pathways can be compared for enrichment between species. For instance, there is a consistent pattern of upregulation in the expression of genes involved in glucose metabolism in the human brain compared with that of nonhuman primates, including enrichment for categories such as oxidative phosphorylation, electron transport, and other nuclear encoded genes that function in the mitochondria (Cáceres et al., 2003; Uddin et al., 2004, 2008b; Khaitovich et al., 2006; Oldham et al., 2006; Babbitt et al., 2010). The upregulation of genes in the adult human neocortex that support oxidative metabolism suggests that, per unit mass, the human brain may be more metabolically expensive than the brains of other primates (Preuss et al., 2004; Preuss, 2011). If true, the human brain would violate the physiological principle of greater energetic efficiency with increased size of an organ (Kleiber, 1932).

The adult human brain phenotype results, in part, from the dynamic regulation of gene expression during the neurodevelopmental sequence (Konopka and Geschwind, 2010). Compared to the adult brain, the fetal human brain is enriched in genes related to cell adhesion, and calcium ion binding (Uddin et al., 2008b). Cellular adhesion, including that mediated by cadherins, is crucial to the development of cellular structure and neuronal connectivity (Frank and Kemler, 2002; Junghans et al., 2005). The protracted neurodevelopmental sequence in humans (Fig. 2) is reflected by a shift in gene expression with genes related to synapse development and other gene categories important for neurodevelopment displaying delayed expression in the human brain compared with macaque monkeys and chimpanzees (Somel et al., 2009). Recently, Sterner et al. (2013) performed genetic microarrays on a developmental series of human brain tissue to determine if there are genes whose expression levels are correlated to the temporal changes in glucose uptake. They found that genes supporting nervous system development follow a trajectory similar to that of glucose utilization. Transcriptional neoteny of genes pertaining to neuronal maturation and glucose metabolism could be one of the more important factors for the development of the phenotype of the human brain (Somel et al., 2009, 2011; Liu et al., 2012; Sterner et al., 2013). More thorough examinations of how shifts in gene expression correlate to changes in glucose uptake in the brain throughout development will help clarify the influence of gene expression changes on driving metabolic demand.

Gene regulatory regions in humans also show signs of positive selection in genes related to glucose metabolism (Haygood et al., 2007). In the genomes of humans and chimpanzees, Haygood et al. (2007) compared the rates of sequence evolution in the promoter regions (proximal 5 kilobases) to nearby coding regions. When the sequence of the promoter region evolved more quickly than its associated coding region, positive selection was inferred. They found that humans, compared with chimpanzees, display an excess of change in the promoter regions of genes supporting glucose metabolism. Specific promoter regions that contain high degrees of positive selection in humans are associated with the genes *HK1*, *GCK*, *GPI*, and *PFKFB3*, all of which are involved in glycolysis and the citric acid cycle (Haygood et al., 2007). These results are suggestive of positive selection of the putative regulatory regions in categories supporting carbohydrate metabolism, glycolysis, and other sugar metabolism in humans compared with other primates.

A novel way of studying metabolic pathways between species was performed by Khaitovich et al. (2008). They measured differences in the concentrations of 16 metabolites using ^{1}H nuclear magnetic resonance spectroscopy within the prefrontal cortex of adult humans, chimpanzees, and macaque monkeys and found that several of the metabolites differ in their relative concentrations across species. Metabolites related to energy metabolism (including lactate and creatine), neurotransmission (choline and glycine), and lipid metabolism (acetate, choline, phosphocholine, and glycerophosphocholine) are found in different concentrations in the human brain compared with that of chimpanzees or macaque monkeys. This result is likely due to the human brain using

metabolic pathways in different proportions compared to other primates. An additional study employed gas chromatography coupled with mass spectrometry to investigate other metabolites in the prefrontal cortex and cerebellum of humans, chimpanzees, and macaque monkeys across their developmental sequences while considering the different duration of the stages of life history (Fu et al., 2011). Overall, the small-molecule metabolites in the adult brain of each species differed dramatically from that of the neonate, indicative of a changing metabolic strategy from the earliest stages of life until adulthood. The majority of the metabolites displayed similar changes in concentration across all three primates. However, a greater number of metabolites than predicted in the human prefrontal cortex displayed differences in the trajectories of their concentrations compared to the human cerebellum. The divergent developmental trajectories of metabolites within the human prefrontal cortex may underlie broader differences in the maturation of metabolic pathways across the human brain.

Taken together, the results of these studies are suggestive of adaptive evolution supporting oxidative phosphorylation within the primate lineage, which becomes enhanced with closer phylogenetic proximity to humans. Therefore, the adult human brain may be especially adapted for energy production by the oxidative phosphorylation pathway, but research has not yet fully explored whether these changes in sequence evolution and expression levels have made this pathway more efficient. However, it is reasonable to speculate that genetic changes affecting oxidative phosphorylation may benefit ATP availability for synaptic activity and also regulate the efficiency with which energy is used. Moreover, it appears that temporal changes in gene regulation affecting metabolic pathways are critical to the heterochronous patterns of neurodevelopment within the human brain.

Conclusions

Many questions remain as to how the metabolic and biochemical needs of the brain are met and how these needs may differ across species. First, it is not clear how the brain 'decides' to use oxidative phosphorylation over aerobic glycolysis and vice versa, and the extent to which the balance between metabolic pathways is genetically determined is unknown. Also, the degree of variation in these pathways between humans and other species remains to be explored, particularly as they relate to the differences in the duration of the neurodevelopmental sequence. Understanding how genomic changes, metabolism, cellular physiology, and the brain phenotype relate to one another is important to our understanding of how the human brain develops, how it has evolved to function like it does, and how disregulation of these processes might lead to the onset of disease (Khaitovich et al., 2008). Further explorations into the appropriation of energy in the developing brain are warranted in an attempt to explain why it was important to alter human anatomy, diet, and life history for the sake of the high metabolic demand of the human brain.

Acknowledgments

This work was supported by the National Science Foundation (DGE-0801634) and the Wenner Gren Foundation for Anthropological Research.

References

Aiello, L.C., Wheeler, P., 1995. The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. Curr. Anthropol. 36, 199–221.

Altman, D.I., Perlman, J.M., Volpe, J.J., Powers, W.J., 1993. Cerebral oxygen metabolism in newborns. Pediatrics 92, 99–104.

Attwell, D., Laughlin, S.B., 2001. An energy budget for signaling in the grey matter of the brain. J. Cereb. Blood Flow Metab. 21, 1133–1145.

Babbitt, C.C., Fedrigo, O., Pfefferle, A.D., Boyle, A.P., Horvath, J.E., Furey, T.S., Wray, G.A., 2010. Both noncoding and protein-coding RNAs contribute to gene expression evolution in the primate brain. Genome Biol. Evol. 2, 67–79.

Barks, S.K., Parr, L.A., Rilling, J.K., 2013. The default mode network in chimpanzees (*Pan troglodytes*) is similar to that of humans. Cereb. Cortex http://dx.doi.org/10.1093/cercor/bht253.

Barrickman, N.L., Bastian, M.L., Isler, K., van Schaik, C.P., 2008. Life history costs and benefits of encephalization: a comparative test using data from long-term studies of primates in the wild. J. Hum. Evol. 54, 568–590.

Barton, R.A., Capellini, I., 2011. Maternal investment, life histories, and the costs of brain growth in mammals. Proc. Natl. Acad. Sci. USA 108, 6169–6174.

Bauernfeind, A.L., Barks, S.K., Duka, T., Grossman, L.I., Hof, P.R., Sherwood, C.C., 2014. Aerobic glycolysis in the primate brain: reconsidering the implications for growth and maintenance. Brain Struct. Funct. 219, 1149–1167.

Baumann, N., Pham-Dinh, D., 2001. Biology of oligodendrocyte and myelin in the mammalian central nervous system. Physiol. Rev. 81, 871–925.

Bianchi, S., Stimpson, C.D., Duka, T., Larsen, M.D., Janssen, W.G.M., Collins, Z., Bauernfeind, A.L., Schapiro, S.J., Baze, W.B., McArthur, M.J., Hopkins, W.D., Wildman, D.E., Lipovich, L., Kuzawa, C.W., Jacobs, B., Hof, P.R., Sherwood, C.C., 2013. Synaptogenesis and development of pyramidal neuron dendritic morphology in the chimpanzee neocortex resembles humans. Proc. Natl. Acad. Sci. USA 110, 10395–10401.

Bittar, P.G., Charnay, Y., Pellerin, L., Bouras, C., Magistretti, P.J., 1996. Selective distribution of lactate dehydrogenase isoenzymes in neurons and astrocytes of human brain. J. Cereb. Blood Flow Metab. 16, 1079–1089.

Bogin, B., 1997. Evolutionary hypotheses for human childhood. Yearb. Phys. Anthropol. 40, 63–89.

Bourgeois, J.P., Goldman-Rakic, P.S., Rakic, P., 1994. Synaptogenesis in the prefrontal cortex of rhesus monkeys. Cereb. Cortex 4, 78–96.

Boyle, P.J., Scott, J.C., Krentz, A.J., Nagy, R.J., Comstock, E., Hoffman, C., 1994. Diminished brain glucose metabolism is a significant determinant for falling rates of systemic glucose utilization during sleep in normal humans. J. Clin. Invest. 93, 529–535.

Broadhurst, C.L., Wang, Y., Crawford, M.A., 2002. Brain-specific lipids from marine, lacustrine, or terrestrial food resources: potential impact on early African *Homo sapiens*. Comp. Biochem. Physiol. B 131, 653–673.

Brown, A.M., Wender, R., Ransom, B.R., 2001. Metabolic substrates other than glucose support axon function in central white matter. J. Neurosci. Res. 66, 839–843.

Buckner, R.L., 2012. The serendipitous discovery of the brain's default network. Neuroimage 62, 1137–1145.

Cáceres, M., Lachuer, J., Zapala, M.A., Kudo, L., Geschwind, D.H., Lockhart, D.J., Preuss, T.M., Barlow, C., 2003. Elevated gene expression levels distinguish human from non-human primate brains. Proc. Natl. Acad. Sci. USA 100, 13030–13035.

Chugani, H.T., Phelps, M.E., 1986. Maturational changes in cerebral function in infants determined by ^{18}FDG positron emission tomography. Science 231, 840–843.

Chugani, H.T., Phelps, M.E., Mazziotta, J.C., 1987. Positron emission tomography study of human brain functional development. Ann. Neurol. 22, 487–497.

Clarke, D.D., Sokoloff, L., 1999. Circulation and energy metabolism of the brain. In: Siegel, G.J., Agranoff, B.W., Albers, R.W., Fisher, S.K., Uhler, M.D. (Eds.), Basic Neurochemistry, sixth ed. Lippincott-Raven, Philadelphia, pp. 637–670.

Cunnane, S.C., Ryan, M.A., Nadeau, C.R., Bazinet, R.P., Musa-Veloso, K., McCloy, U., 2003. Why is carbon from some polyunsaturates extensively recycled into lipid synthesis? Lipids 38, 477–484.

Dawson, D.M., Goodfriend, T.L., Kaplan, N.O., 1964. Lactic dehydrogenases: functions of the two types rates of synthesis of the two major forms can be correlated with metabolic differentiation. Science 143, 929–933.

Dienel, G.A., Hertz, L., 2001. Glucose and lactate metabolism during brain activation. J. Neurosci. Res. 66, 824–838.

Dobbing, J., Sands, J., 1979. Comparative aspects of the brain growth spurt. Early Hum. Dev. 311, 79–83.

Edmond, J., 1974. Ketone bodies as precursors of sterols and fatty acids in the developing rat. J. Biol. Chem. 249, 72–80.

Ehlers, M.D., 2003. Activity level controls postsynaptic composition and signaling via the ubiquitin-proteasome system. Nat. Neurosci. 6, 231–242.

Elston, G.N., Benavides-Piccione, R., DeFelipe, J., 2001. The pyramidal cell in cognition: a comparative study in human and monkey. J. Neurosci. 21, RC163.

Erecinska, M., Cherian, S., Silver, I.A., 2004. Energy metabolism in mammalian brain during development. Prog. Neurobiol. 73, 397–445.

Fedrigo, O., Pfefferle, A.D., Babbitt, C.C., Haygood, R., Wall, C.E., Wray, G.A., 2011. A potential role for glucose transporters in the evolution of human brain size. Brain Behav. Evol. 78, 315–326.

Fish, J.L., Lockwood, C.A., 2003. Dietary constraints on encephalization in primates. Am. J. Phys. Anthropol. 120, 171–181.

Foley, R.A., Lee, P.C., 1991. Ecology and energetics of encephalization in hominid evolution. Phil. Trans. R. Soc. B 334, 223–232.

Frank, M., Kemler, R., 2002. Protocadherins. Curr. Opin. Cell Biol. 14, 557–562.

Fu, X., Giavalisco, P., Liu, X., Catchpole, G., Fu, N., Ning, Z.-B., Guo, S., Yan, Z., Somel, M., Pääbo, S., Zeng, R., Willmitzer, L., Khaitovich, P., 2011. Rapid

metabolic evolution in human prefrontal cortex. Proc. Natl. Acad. Sci. USA 108, 6181–6186.
Fünfschilling, U., Supplie, L.M., Mahad, D., Boretius, S., Saab, A.S., Edgar, J., Brinkmann, B.G., Kassmann, C.M., Tzvetanova, I.D., Möbius, W., Diaz, F., Meijer, D., Suter, U., Hamprecht, B., Sereda, M.W., Moraes, C.T., Frahm, J., Goebbels, S., Nave, K.-A., 2012. Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Nature 485, 517–521.
Gaulin, S.J., Kurland, J.A., 1976. Primate predation and bioenergetics. Science 191, 314–317.
Gibson, K.R., 1970. Sequence of myelinization in the brain of *Macaca mulatta*. Ph.D. Dissertation, University of California, Berkeley.
Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nat. Neurosci. 2, 861–863.
Glantz, L.A., Gilmore, J.H., Hamer, R.M., Lieberman, J.A., Jarskog, L.F., 2007. Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. Neuroscience 149, 582–591.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proc. Natl. Acad. Sci. USA 101, 8174–8179.
Goldberg, A., Wildman, D.E., Schmidt, T.R., Huttemann, M., Goodman, M., Weiss, M.L., Grossman, L.I., 2003. Adaptive evolution of cytochrome *c* oxidase subunit VIII in anthropoid primates. Proc. Natl. Acad. Sci. USA 100, 5873–5878.
Goldberg, J.L., 2003. How does an axon grow? Genes Dev. 17, 941–958.
Goldman-Rakic, P.S., 1987. Development of cortical circuitry and cognitive function. Child Dev. 58, 601–622.
Goodman, M., Syner, F.N., Stimson, C.W., Rankin, J.J., 1969. Phylogenetic changes in the proportions of two kinds of lactate dehydrogenase in primate brain regions. Brain Res. 14, 447–459.
Gould, E., 2007. How widespread is adult neurogenesis in mammals? Nat. Rev. Neurosci. 8, 481–488.
Grossman, L.I., Schmidt, T.R., Wildman, D.E., Goodman, M., 2001. Molecular evolution of aerobic energy metabolism in primates. Mol. Phylogenet. Evol. 18, 26–36.
Grossman, L.I., Wildman, D.E., Schmidt, T.R., Goodman, M., 2004. Accelerated evolution of the electron transport chain in anthropoid primates. Trends Genet. 20, 578–585.
Harris, J.J., Jolivet, R., Attwell, D., 2012. Synaptic energy use and supply. Neuron 75, 762–777.
Haygood, R., Fedrigo, O., Hanson, B., Yokoyama, K.-D., Wray, G.A., 2007. Promoter regions of many neural- and nutrition-related genes have experienced positive selection during human evolution. Nat. Genet. 39, 1140–1144.
Hensch, T.K., 2004. Critical period regulation. Annu. Rev. Neurosci. 27, 549–579.
Hofman, M., 1983. Energy metabolism, brain size and longevity in mammals. Q. Rev. Biol. 58, 495–512.
Hovda, D.A., Chugani, H.T., Villablanca, J.R., Badie, B., Sutton, R.L., 1992. Maturation of cerebral oxidative metabolism in the cat: a cytochrome oxidase histochemistry study. J. Cereb. Blood Flow Metab. 12, 1039–1048.
Hovda, D.A., Villablanca, J.R., Chugani, H.T., Barrio, J.R., 2006. Metabolic maturation of the brain: a study of local cerebral protein synthesis in the developing cat. Brain Res. 1113, 54–63.
Hüttemann, M., Helling, S., Sanderson, T.H., Sinkler, C., Samavati, L., Mahapatra, G., Varughese, A., Lu, G., Liu, J., Ramzan, R., Vogt, S., Grossman, L.I., Doan, J.W., Marcus, K., Lee, I., 2011. Regulation of mitochondrial respiration and apoptosis through cell signaling: cytochrome *c* oxidase and cytochrome *c* in ischemia/reperfusion injury and inflammation. Biochim. Biophys. Acta 1817, 598–609.
Huttenlocher, P.R., 1990. Morphometric study of human cerebral cortex development. Neuropsychologia 28, 517–527.
Huttenlocher, P.R., Dabholkar, A.S., 1997. Regional differences in synaptogenesis in human cerebral cortex. J. Comp. Neurol. 387, 167–178.
Jacobs, B., Chugani, H.T., Allada, V., Chen, S., Phelps, M.E., Pollack, D.B., Raleigh, M.J., 1995. Developmental changes in brain metabolism in sedated rhesus macaques and vervet monkeys revealed by positron emission tomography. Cereb. Cortex 5, 222–233.
Jacobs, B., Driscoll, L., Schall, M., 1997. Life-span dendritic and spine changes in areas 10 and 18 of human cortex: a quantitative Golgi study. J. Comp. Neurol. 386, 661–680.
Jacobs, B., Schall, M., Prather, M., Kapler, E., Driscoll, L., Baca, S., Jacobs, J., Ford, K., Wainwright, M., Treml, M., 2001. Regional dendritic and spine variation in human cerebral cortex: a quantitative Golgi study. Cereb. Cortex 11, 558–571.
Jareb, M., Banker, G., 1997. Inhibition of axonal growth by brefeldin A in hippocampal neurons in culture. J. Neurosci. 17, 8955–8963.
Junghans, D., Haas, I.G., Kemler, R., 2005. Mammalian cadherins and protocadherins: about cell death, synapses and processing. Curr. Opin. Cell Biol. 17, 446–452.
Karbowski, J., 2007. Global and regional brain metabolic scaling and its functional consequences. BMC Biol. 5, 18.
Kennedy, C., Sakurada, O., Shinohara, M., Jehle, J., Sokoloff, L., 1978. Local cerebral glucose utilization in the normal conscious macaque monkey. Ann. Neurol. 4, 293–301.
Khaitovich, P., Enard, W., Lachmann, M., Pääbo, S., 2006. Evolution of primate gene expression. Nat. Rev. Genet. 7, 693–702.
Khaitovich, P., Lockstone, H.E., Wayland, M.T., Tsang, T.M., Jayatilaka, S.D., Guo, A.J., Zhou, J., Somel, M., Harris, L.W., Holmes, E., Pääbo, S., Bahn, S., 2008. Metabolic changes in schizophrenia and human brain evolution. Genome Biol. 9, R124.
King, M.C., Wilson, A.C., 1975. Evolution at two levels in humans and chimpanzees. Science 188, 107–116.
Kleiber, M., 1932. Body size and metabolism. Hilgardia 6, 315–353.
Knott, G.W., Holtmaat, A., Wilbrecht, L., Welker, E., Svoboda, K., 2006. Spine growth precedes synapse formation in the adult neocortex *in vivo*. Nat. Neurosci. 9, 1117–1124.
Konopka, G., Geschwind, D.H., 2010. Human brain evolution: harnessing the genomics (r)evolution to link genes, cognition, and behavior. Neuron 68, 231–244.
Kornack, D.R., Rakic, P., 1999. Continuation of neurogenesis in the hippocampus of the adult macaque monkey. Proc. Natl. Acad. Sci. USA 96, 5768–5773.
Kornack, D.R., Rakic, P., 2001. The generation, migration, and differentiation of olfactory neurons in the adult primate brain. Proc. Natl. Acad. Sci. USA 98, 4752–4757.
Lee, A.G., 2001. Myelin: delivery by raft. Curr. Biol. 11, R60–R62.
Leigh, S.R., 2004. Brain growth, life history, and cognition in primate and human evolution. Am. J. Primatol. 62, 139–164.
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., Snodgrass, J.J., Kuzawa, C.W., 2003. Metabolic correlates of hominid brain evolution. Comp. Biochem. Physiol. A 136, 5–15.
Li, Z., Okamoto, K.-I., Hayashi, Y., Sheng, M., 2004. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 119, 873–887.
Liu, X., Somel, M., Tang, L., Yan, Z., Jiang, X., Guo, S., Yuan, Y., He, L., Oleksiak, A., Zhang, Y., Li, N., Hu, Y., Chen, W., Qiu, Z., Pääbo, S., Khaitovich, P., 2012. Extension of cortical synaptic development distinguishes humans from chimpanzees and macaques. Genome Res. 22, 611–622.
Magistretti, P.J., 2009. Role of glutamate in neuron-glia metabolic coupling. Am. J. Clin. Nutr. 90, 875S–880S.
Magistretti, P.J., Pellerin, L., Rothman, D.L., Shulman, R.G., 1999. Energy on demand. Science 283, 496–497.
Marder, E., Goaillard, J.-M., 2006. Variability, compensation and homeostasis in neuron and network function. Nat. Rev. Neurosci. 7, 563–574.
McFarlin, S.C., Barks, S.K., Tocheri, M.W., Massey, J.S., Eriksen, A.B., Fawcett, K.A., Stoinski, T.S., Hof, P.R., Bromage, T.G., Mudakikwa, A., Cranfield, M.R., Sherwood, C.C., 2013. Early brain growth cessation in wild Virunga mountain gorillas (*Gorilla beringei beringei*). Am. J. Primatol. 75, 450–463.
Miller, A.L., Kiney, C.A., Corddry, D.H., Staton, D.M., 1982. Interactions between glucose and ketone body use by the developing brain. Dev. Brain Res. 4, 443–450.
Miller, D.J., Duka, T., Stimpson, C.D., Schapiro, S.J., Baze, W.B., McArthur, M.J., Fobbs, A.J., Sousa, A.M.M., Sestan, N., Wildman, D.E., Lipovich, L., Kuzawa, C.W., Hof, P.R., Sherwood, C.C., 2012. Prolonged myelination in human neocortical evolution. Proc. Natl. Acad. Sci. USA 109, 16480–16485.
Mink, J.W., Blumenschine, R.J., Adams, D.B., 1981. Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. Am. J. Physiol. 241, 203–212.
Mintun, M.A., Lundstrom, B.N., Snyder, A.Z., Vlassenko, A.G., Shulman, G.L., Raichle, M.E., 2001. Blood flow and oxygen delivery to human brain during activity: theoretical modeling and experimental data. Proc. Natl. Acad. Sci. USA 98, 6859–6864.
Navarrete, A., van Schaik, C.P., Isler, K., 2011. Energetics and the evolution of human brain size. Nature 480, 91–93.
Nehlig, A., Pereira de Vasconcelos, A., 1993. Glucose and ketone body utilization by the brain of neonatal rats. Prog. Neurobiol. 40, 163–221.
Nelson, D.L., Cox, M.M., 2008. Lehninger Principles of Biochemistry, fifth ed. W.H. Freeman and Company, New York.
Neubauer, S., Gunz, P., Hublin, J.-J., 2010. Endocranial shape changes during growth in chimpanzees and humans: a morphometric analysis of unique and shared aspects. J. Hum. Evol. 59, 555–566.
Newman, L.A., Korol, D.L., Gold, P.E., 2011. Lactate produced by glycogenolysis in astrocytes regulates memory processing. PloS One 6, e28427.
Nielsen, T.H., Bindslev, T.T., Pedersen, S.M., Toft, P., Olsen, N.V., Nordström, C.H., 2013. Cerebral energy metabolism during induced mitochondrial dysfunction. Acta Anaesth. Scand. 57, 229–235.
Oldham, M.C., Horvath, S., Geschwind, D.H., 2006. Conservation and evolution of gene coexpression networks in human and chimpanzee brains. Proc. Natl. Acad. Sci. USA 103, 17973–17978.
Pellerin, L., Magistretti, P.J., 1994. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. Proc. Natl. Acad. Sci. USA 91, 10625–10629.
Perez de Heredia, F., Wood, I.S., Trayhurn, P., 2010. Hypoxia stimulates lactate release and modulates monocarboxylate transporter (MCT1, MCT2, and MCT4) expression in human adipocytes. Eur. J. Physiol. 459, 509–518.
Petanjek, Z., Judaš, M., Šimic, G., Rasin, M.R., Uylings, H.B.M., Rakic, P., Kostovic, I., 2011. Extraordinary neoteny of synaptic spines in the human prefrontal cortex. Proc. Natl. Acad. Sci. USA 108, 13281–13286.

Pierron, D., Wildman, D.E., Hüttemann, M., Markondapatnaikuni, G.C., Aras, S., Grossman, L.I., 2011. Cytochrome *c* oxidase: Evolution of control via nuclear subunit addition. Biochim. Biophys. Acta 1817, 590–597.
Powers, W.J., Rosenbaum, J.L., Dence, C.S., Markham, J., Videen, T.O., 1998. Cerebral glucose transport and metabolism in preterm human infants. J. Cereb. Blood Flow Metab. 18, 632–638.
Preuss, T.M., 2011. The human brain: rewired and running hot. Ann. N.Y. Acad. Sci. 1225, E182–E191.
Preuss, T.M., Cáceres, M., Oldham, M.C., Geschwind, D.H., 2004. Human brain evolution: insights from microarrays. Nat. Rev. Genet. 5, 850–860.
Raichle, M.E., 2010. Two views of brain function. Trends. Cogn. Sci. 14, 180–190.
Raichle, M.E., Posner, J.B., Plum, F., 1970. Cerebral blood flow during and after hyperventilation. Arch. Neurol. 23, 394–403.
Rakic, P., 2002. Neurogenesis in adult primate neocortex: an evaluation of the evidence. Nat. Rev. Neurosci. 3, 65–71.
Rakic, P., Bourgeois, J.P., Eckenhoff, M.F., Zecevic, N., Goldman-Rakic, P.S., 1986. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 232, 232–235.
Rinholm, J.E., Hamilton, N.B., Kessaris, N., Richardson, W.D., Bergersen, L.H., Attwell, D., 2011. Regulation of oligodendrocyte development and myelination by glucose and lactate. J. Neurosci. 31, 538–548.
Robson, S.L., Wood, B., 2008. Hominin life history: reconstruction and evolution. J. Anat. 212, 394–425.
Schmidt, T.R., Wildman, D.E., Uddin, M., Opazo, J.C., Goodman, M., Grossman, L.I., 2005. Rapid electrostatic evolution at the binding site for cytochrome *c* on cytochrome *c* oxidase in anthropoid primates. Proc. Natl. Acad. Sci. USA 102, 6379–6384.
Semendeferi, K., Teffer, K., Buxhoeveden, D.P., Park, M.S., Bludau, S., Amunts, K., Travis, K., Buckwalter, J., 2011. Spatial organization of neurons in the frontal pole sets humans apart from great apes. Cereb. Cortex 21, 1485–1497.
Settergren, G., Lindblad, B.S., Persson, B., 1976. Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in infants. Acta Paediatr. Scand. 65, 343–353.
Shaw, P., Kabani, N.J., Lerch, J.P., Eckstrand, K., Lenroot, R., Gogtay, N., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., Giedd, J.N., Wise, S.P., 2008. Neurodevelopmental trajectories of the human cerebral cortex. J. Neurosci. 28, 3586–3594.
Sheaff-Greiner, R.C., Zhang, Q., Goodman, K.J., Guissini, D.A., Nathanielsz, P.W., Brenna, J.T., 1996. Linoleate, alpha-linolenate, and docosahexaenoate recycling into saturated and monounsaturated fatty acids is a major pathway in pregnant or lactating adults and fetal or infant rhesus monkeys. J. Lipid Res. 37, 2675–2686.
Sheng, M., Hoogenraad, C.C., 2007. The postsynaptic architecture of excitatory synapses: a more quantitative view. Annu. Rev. Biochem. 76, 823–847.
Soane, L., Kahraman, S., Kristian, T., Fiskum, G., 2007. Mechanisms of impaired mitochondrial energy metabolism in acute and chronic neurodegenerative disorders. J. Neurosci. Res. 85, 3407–3415.
Sokoloff, L., Mangold, R., Wechsler, R.L., Kennedy, C., Kety, S.S., 1955. The effect of mental arithmetic on cerebral circulation and metabolism. J. Clin. Invest. 34, 1101–1108.
Somel, M., Franz, H., Yan, Z., Lorenc, A., Guo, S., Giger, T., Kelso, J., Nickel, B., Dannemann, M., Bahn, S., Webster, M.J., Weickert, C.S., Lachmann, M., Pääbo, S., Khaitovich, P., 2009. Transcriptional neoteny in the human brain. Proc. Natl. Acad. Sci. USA 106, 5743–5748.
Somel, M., Liu, X., Tang, L., Yan, Z., Hu, H., Guo, S., Jiang, X., Zhang, X., Xu, G., Xie, G., Li, N., Hu, Y., Chen, W., Pääbo, S., Khaitovich, P., 2011. MicroRNA-driven developmental remodeling in the brain distinguishes humans from other primates. PLoS Biol. 9, e1001214.
Spocter, M.A., Hopkins, W.D., Barks, S.K., Bianchi, S., Hehmeyer, A.E., Anderson, S.M., Stimpson, C.D., Fobbs, A.J., Hof, P.R., Sherwood, C.C., 2012. Neuropil distribution in the cerebral cortex differs between humans and chimpanzees. J. Comp. Neurol. 520, 2917–2929.
Star, E.N., Kwiatkowski, D.J., Murthy, V.N., 2002. Rapid turnover of actin in dendritic spines and its regulation by activity. Nat. Neurosci. 5, 239–246.
Sterner, K.N., McGowen, M.R., Chugani, H.T., Tarca, A.L., Sherwood, C.C., Hof, P.R., Kuzawa, C.W., Boddy, A.M., Raaum, R.L., Weckle, A., Lipovich, L., Grossman, L.I., Uddin, M., Goodman, M., Wildman, D.E., 2013. Characterization of human cortical gene expression in relation to glucose utilization. Am. J. Hum. Biol. 25, 418–430.
Subramanian, A., Tamayo, P., Mootha, V.K., Mukherjee, S., Ebert, B.L., Gillette, M.A., Paulovich, A., Pomeroy, S.L., Golub, T.R., Lander, E.S., Mesirov, J.P., 2005. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. Proc. Natl. Acad. Sci. USA 102, 15545–15550.
Suzuki, A., Stern, S.A., Bozdagi, O., Huntley, G.W., Walker, R.H., Magistretti, P.J., Alberini, C.M., 2011. Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 144, 810–823.
Syner, F.N., Goodman, M., 1966. Differences in the lactic dehydrogenases of primate brains. Nature 209, 426–428.
Tanaka, M., Nakamura, F., Mizokawa, S., Matsumura, A., Matsumura, K., Murata, T., Shigematsu, M., Kageyama, K., Ochi, H., Watanabe, Y., 2004. Role of lactate in the brain energy metabolism: revealed by bioradiography. Neurosci. Res. 48, 13–20.
Tekkök, S.B., Brown, A.M., Westenbroek, R., Pellerin, L., Ransom, B.R., 2005. Transfer of glycogen-derived lactate from astrocytes to axons via specific monocarboxylate transporters supports mouse optic nerve activity. J. Neurosci. Res. 81, 644–652.
Travis, K., Ford, K., Jacobs, B., 2005. Regional dendritic variation in neonatal human cortex: a quantitative Golgi study. Dev. Neurosci. 27, 277–287.
Uddin, M., Wildman, D.E., Liu, G., Xu, W., Johnson, R.M., Hof, P.R., Kapatos, G., Grossman, L.I., Goodman, M., 2004. Sister grouping of chimpanzees and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles. Proc. Natl. Acad. Sci. USA 101, 2957–2962.
Uddin, M., Opazo, J.C., Wildman, D.E., Sherwood, C.C., Hof, P.R., Goodman, M., Grossman, L.I., 2008a. Molecular evolution of the cytochrome *c* oxidase subunit 5A gene in primates. BMC Evol. Biol. 8, 8.
Uddin, M., Goodman, M., Erez, O., Romero, R., Liu, G., Islam, M., Opazo, J.C., Sherwood, C.C., Grossman, L.I., Wildman, D.E., 2008b. Distinct genomic signatures of adaptation in pre- and postnatal environments during human evolution. Proc. Natl. Acad. Sci. USA 105, 3215–3220.
Ullah, M.S., Davies, A.J., Halestrap, A.P., 2006. The plasma membrane lactate transporter MCT4, but not MCT1, is up-regulated by hypoxia through a HIF-1alpha-dependent mechanism. J. Biol. Chem. 281, 9030–9037.
Vaishnavi, S.N., Vlassenko, A.G., Rundle, M.M., Snyder, A.Z., Mintun, M.A., Raichle, M.E., 2010. Regional aerobic glycolysis in the human brain. Proc. Natl. Acad. Sci. USA 107, 17757–17762.
Vander Heiden, M.G., Cantley, L.C., Thompson, C.B., 2009. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science 324, 1029–1033.
Vander Heiden, M.G., Locasale, J.W., Swanson, K.D., Sharfi, H., 2010. Evidence for an alternative glycolytic pathway in rapidly proliferating cells. Science 329, 1492–1499.
Wrangham, R.W., 2009. Catching Fire: How Cooking Made Us Human. Basic Books, New York.
Wyss, M.T., Jolivet, R., Buck, A., Magistretti, P.J., Weber, B., 2011. *In vivo* evidence for lactate as a neuronal energy source. J. Neurosci. 31, 7477–7485.
Yakovlev, P.I., Lecours, A., 1967. The myelogenetic cycles of regional maturation of the brain. In: Minkowski, A. (Ed.), Regional Development of the Brain in Early Life. Blackwell Science, Oxford, pp. 3–70.
Yeh, Y.-Y., Streuli, V.L., Zee, P., 1977. Ketone bodies serve as important precursors of brain lipids in the developing rat. Lipids 12, 957–964.
Yi, J.J., Ehlers, M.D., 2005. Ubiquitin and protein turnover in synapse function. Neuron 47, 629–632.
Zivraj, K.H., Tung, Y.C.L., Piper, M., Gumy, L., Fawcett, J.W., Yeo, G.S.H., Holt, C.E., 2010. Subcellular profiling reveals distinct and developmentally regulated repertoire of growth cone mRNAs. J. Neurosci. 30, 15464–15478.