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REVIEW

Aerobic glycolysis in the primate brain: reconsidering the implications for growth and maintenance

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Abstract Glucose metabolism produces, by oxidative phosphorylation, more than 15 times the amount of energy generated by aerobic glycolysis. Nonetheless, aerobic glycolysis remains a prevalent metabolic pathway in the brain. Here we review evidence suggesting that this pathway contributes essential molecules to the biomass of the brain. Aerobic metabolism is the dominant metabolic pathway during early postnatal development when lipids and proteins are needed for the processes of axonal elongation, synaptogenesis, and myelination. Furthermore, aerobic metabolism may continue into adulthood to supply biomolecules for activity-related changes at the synapse and turnover of constituent structural components of neurons. Conversely, oxidative phosphorylation appears to be the main metabolic support for synaptic transmission, and, therefore, this pathway seems to be more dominant in brain structures and at time points in the lifespan that are characterized by increased synaptic density. We present the case for differing relationships between aerobic glycolysis and oxidative phosphorylation across primates in association with species-specific variation in neurodevelopmental trajectories. In doing so, we provide an alternative interpretation for the assessment of radiolabeled glucose positron emission tomography studies that regularly attribute increases in glucose uptake to neural activity alone, and propose a new model for the contribution of metabolic pathways for energetic demand and neural tissue growth. We conclude that comparative studies of metabolic appropriation in the brain may contribute to the discussion of human cognitive evolution and to the understanding of human-specific aging and the etiology of neuropsychiatric diseases.

Keywords Aerobic gycolysis · Oxidative phosphorylation · Brain energetics · Default mode network · Evolution

Abbreviations

Acetyl-CoA	Acetyl coenzyme A
AD	Alzheimer's disease
AMP	Adenosine-5′-monophosphate
ATP	Adenosine-5′-triphosphate
DMN	Default mode network
DMPFC	Dorsomedial prefrontal cortex
LDH	Lactate dehydrogenase
NADH	Nicotinamide adenine dinucleotide (NAD^+), reduced state
NFT	Neurofibrillary tangle
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PiB	Pittsburgh compound B
PPP	Pentose phosphate pathway
ROS	Reactive oxygen species
VMPFC	Ventromedial prefrontal cortex

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Introduction

Cells in the central nervous system have minimal energy reserves and, therefore, operate within a small margin of metabolic safety (Ames 2000). Furthermore, energetically expensive processes of the brain, including growth, biomolecular turnover, and synaptic activity, require a delicate balance of interconnected biological pathways to meet the metabolic and molecular requirements of the tissue (Brooks 2009; Erecinska et al. 2004). In multicellular organisms, adenosine-5′-triphosphate (ATP), the major energy source for all cells in the body, is predominantly supplied by the metabolic pathway of oxidative phosphorylation (Nelson and Cox 2008). Oxidative phosphorylation uses glucose to produce ATP through a series of steps including glycolysis, the citric acid cycle, and the electron transport chain. In the central nervous system, the traditional view of cell metabolism is that oxidative phosphorylation occurs exclusively unless aerobic respiration is prevented from occurring following a perturbation to the supply of oxygen (hypoxic or anoxic conditions) or the impairment of mitochondria (Nielsen et al. 2013; Perez de Heredia et al. 2010; Soane et al. 2007; Ullah et al. 2006). Under these abnormal conditions, glycolysis may be used as a fallback mechanism for meeting the tissue's ATP requirements (Ames 1992). However, data suggest that glycolysis also takes place in the brain under normal conditions despite enough oxygen being present for aerobic respiration to proceed (Raichle et al. 1970; Wyss et al. 2011). Aerobic glycolysis is the term that has been designated for glycolysis that occurs despite the presence of sufficient oxygen to support oxidative phosphorylation.

Otto Warburg, an early investigator of the pathogenesis of cancer cells, discovered that most of the glucose taken up by cancer cells is predominantly converted to ATP by glycolysis, rather than oxidative phosphorylation, a process typically thought of as anaerobic fermentation (Warburg et al. 1924, 1927). It had long been thought that this switch from aerobic to anaerobic metabolic pathways, termed the 'Warburg effect,' occurred because insufficient oxygen was supplied to cancerous cells to meet the energetic needs by the aerobic process of oxidative phosphorylation (Gatenby and Gillies 2004; Warburg 1956). Recently, this topic has been revisited by scientists who suggested an alternative explanation, noting that under certain conditions glycolysis may be the preferred pathway for energy production in rapidly proliferating cells despite the availability of a sufficient oxygen supply (Locasale and Cantley 2011; Vander Heiden et al. 2009, 2010). Aerobic glycolysis occurs when glucose is incompletely metabolized to carbon dioxide and water, so that the intermediate molecule, pyruvate, can be used in other biological processes or can easily be converted to lactate by isoforms of lactate dehydrogenase (LDH) (Syner and Goodman 1966). Indeed, it seems surprising that aerobic glycolysis would be used in any tissue supplied with sufficient oxygen to produce ATP via oxidative phosphorylation; aerobic glycolysis is a much less efficient producer of energy compared to oxidative phosphorylation. So what is the benefit of adopting the metabolic strategy of aerobic glycolysis when oxygen is in abundant supply? This metabolic pathway is likely to be utilized because, aside from its limited energy production capacity, it also contributes to the synthesis of molecules that are critical for the production of biomass (Fig. 1). Furthermore, it has recently been revealed that adopting the metabolic strategy of aerobic glycolysis can be a regulatory switch to initiate biosynthesis (De Bock et al. 2013).

Because the major energetic expenditure of neuronal activity is synaptic transmission (Attwell and Laughlin 2001; Harris et al. 2012; Magistretti et al. 1999), the traditional perspective of glucose metabolism is that most ATP produced in the brain should support this function. However, some authors have noted that glycolysis in the brain may have important functional roles other than metabolic support of neural transmission (Fox et al. 1988), including induction of vasodilation (Gordon et al. 2008; Vlassenko et al. 2006), regulation of the redox state affecting cell survival (Brooks 2009; Vaughn and Deshmukh 2008), fast axonal transport of vesicles (Zala et al. 2013), and contribution of molecules to anabolic processes (Bufill et al. 2011; Raichle 2010; Vaishnavi et al. 2010). Although the efficiency of energy production by oxidative phosphorylation appears to be best suited to support the high metabolic costs of synaptic transmission, we embrace the perspective of Vander Heiden et al. (2009, 2010; also Raichle 2010) that aerobic glycolysis contributes to anabolic pathways for the production of biomass, and we apply this model to the development of the brain. During postnatal brain development, however, the matter is not one of neuronal proliferation as in cancer cells, but rather the processes of axonal elongation, myelination, and synaptogenesis that also require the addition of molecules to the biomass (Baumann and Pham-Dinh 2001; Jareb and Banker 1997; Knott et al. 2006; Lee 2001). In adulthood, proteins, lipids, and amino acids are continuously synthesized to replace constituent molecules and to support the molecular modifications that underlie plasticity of dendritic spines and synapses (Ehlers 2003; Star et al. 2002; Yi and Ehlers 2005). Aerobic glycolysis may persist into adulthood to contribute to these anabolic processes.

Determining the relative demand of aerobic glycolysis as a proportion of the total amount of energetic consumption through brain development is particularly important from the perspective of human evolution. The extraordinarily high metabolic costs of growing a large brain are sustained over a longer period of development in humans

compared to other primates (Barrickman et al. 2008). It has been proposed that such metabolic costs may be offset through a combination of interspecific differences in growth pattern, body composition, and foraging and reproductive strategies (Aiello and Wheeler 1995; Barton and Capellini 2011; Foley and Lee 1991; Kuzawa 1998, 2007; Leonard and Robertson 1994; Navarrete et al. 2011). Fully understanding the end-results of glucose uptake in the brains of humans and other species will better equip us for answering questions about metabolic appropriation and the tradeoffs associated with energetic provisioning of the brain. To what extent does aerobic glycolysis affect the maturation of cytoarchitecture, including axonal elongation, synaptogenesis, and myelination? Do species differences exist in the timing of a switch between an early postnatal brain metabolism that is highly reliant on glycolysis and one that predominantly depends upon aerobic metabolism? If so, what is the effect on brain growth and neuronal maturation? Recognizing that glucose may be used for different purposes as the energetic and biomolecular demands of the nervous system changes through neural development is a critical first step in understanding the appropriation of energy in the brain.

In this review, we discuss the importance of two metabolic pathways, aerobic glycolysis and oxidative phosphorylation, in light of current evidence about the metabolic and anabolic demands of the human brain through development and into adulthood. We compare the maturational schedule of the human brain to that of other primates and hypothesize that aerobic glycolysis may be prolonged in humans to support protracted neurodevelopment. Finally, we stress the importance of considering aerobic glycolysis in the context of human-specific brain disorders and aging.

Review of metabolic pathways

Upon entering a cell, glucose is typically metabolized into pyruvate through glycolysis, which generates only about two molecules of ATP (Nelson and Cox 2008). Pyruvate, the end-product of glycolysis, can be converted to lactate, transported to the mitochondria for aerobic respiration, or used as a carbon substrate for other biological pathways (Fig. 1) (Purves et al. 2001). As sources of carbon, pyruvate and lactate can serve as substrates in biosynthetic processes once converted into acetyl coenzyme A (acetyl-CoA). Acetyl-CoA is a precursor for the fatty acid synthesis mandatory for myelination (Brown et al. 2001; Tekkök et al. 2005). Also, nucleotides are created via the pentose phosphate pathway (PPP), which uses glucose-6-phosphate, an intermediate molecule in glycolysis, as a precursor to ribose found in nucleotides. Additionally, glycolytic byproducts or pyruvate itself can be used as a

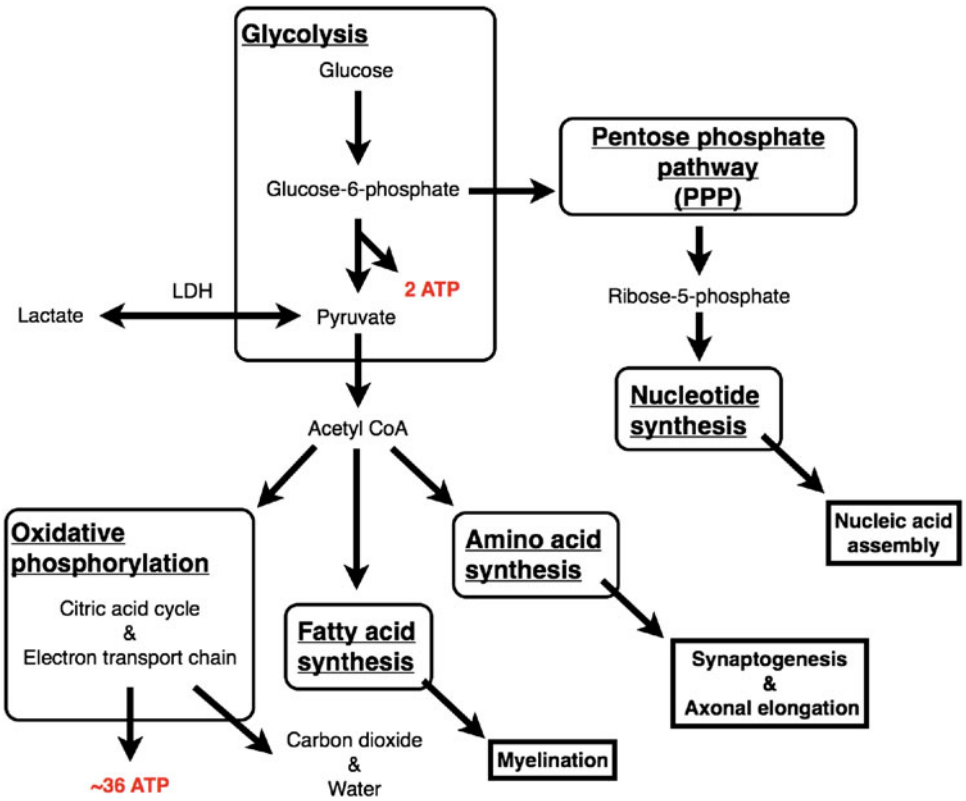


Fig. 1 This schematic summarizes how glucose is metabolized into ATP by either oxidative phosphorylation (resulting in ~30 molecules of ATP) or by aerobic glycolysis (resulting in 2 molecules of ATP). Aerobic glycolysis produces acetyl-CoA, which can be used as substrate for fatty acid or amino acid synthesis. Alternatively, incomplete conversion of glucose into pyruvate may yield a byproduct, glucose-6-phosphate, which can be used in nucleotide synthesis via the PPP. For a more detailed review of the pathways that contribute to biomass, the reader is referred to Vander Heiden et al. (2009)

source of carbon for amino acid synthesis prior to the formation of larger, more complex proteins that may form constituent molecules of the cell's architecture (Nelson and Cox 2008). Therefore, in addition to producing energy for the cell, there is an array of potential anabolic results from glucose entering the glycolytic pathway. Because positron emission tomography (PET) studies using radiolabeled glucose cannot by themselves distinguish the fate of a glucose molecule from energy producing aerobic glycolysis or any of the anabolic pathways listed above (Raichle 2010), we use the term aerobic glycolysis to refer to any one of these outcomes.

For oxidative phosphorylation to occur, pyruvate must enter the matrix of the mitochondria and go through a series of oxidative chemical reactions known as the citric acid cycle by which NADH (reduced nicotinamide adenine dinucleotide, NAD^+) and carbon dioxide are produced. The electron transport chain follows, whereby NADH donates electrons to establish a gradient across the intermembrane space of the mitochondria, creating a source of potential energy. ATP synthase, a protein complex of the inner mitochondrial membrane, allows protons to flow through the membrane, down the electrical gradient, producing ATP as a consequence. In contrast to glycolysis, oxidative phosphorylation is an efficient producer of energy, generating a net of roughly 36 molecules of ATP (Nelson and Cox 2008).

Although it remains unclear whether aerobic glycolysis contributes significant energy to fuel synaptic transmission (see Dienel and Hertz 2001; Hall et al. 2012; Harris et al. 2012; Hertz 2004; Magistretti 2009; Magistretti et al. 1999; Pellerin and Magistretti 1994, 2003), it is not our intention to discuss the relative contributions of oxidative phosphorylation and glycolysis to the ATP energy budget. Instead, we turn our attention to metabolic provisioning on a larger scale as assessed by PET. The motivation for this review is to lend an alternative interpretation for the assessment of radiolabeled glucose PET studies that generally attribute increases in glucose uptake to neural activity alone. While the neural energy budget allocates most glucose uptake to the support of activity at the synapse (Attwell and Laughlin 2001), it is important to remember that in response to brain activity local energy uptake typically increases by only about 5 % (Sokoloff et al. 1955). This is consistent with the notion that the majority of energy use in the brain is not a result of task-evoked neural activity, but rather of a high intrinsic cost of the brain attributed to upkeep and baseline states (Raichle 2010).

When discerning the contributions of oxidative phosphorylation and aerobic glycolysis to the brain or any other organ by PET, one must know the relative amounts of oxygen and glucose used. When the aerobic process of oxidative phosphorylation exists to the exclusion of aerobic glycolysis, the molar ratio of oxygen to glucose uptake is 6, but when aerobic glycolysis is present, the ratio of oxygen to glucose uptake is lower by an amount inversely proportional to the amount of aerobic glycolysis present (Vaishnavi et al. 2010). Therefore, tracking oxygen uptake alone can be seen as a proxy for oxidative phosphorylation but neglects ATP production by aerobic glycolysis. Alternatively, PET studies that utilize glucose uptake follow glucose utilized by the oxidative phosphorylation and aerobic glycolysis indiscriminately. Given the presence of aerobic glycolysis in the brain during postnatal neurodevelopment and adulthood, caution is required when interpreting data from radiolabeled glucose PET scans without complementary radiolabeled oxygen data.

Aerobic glycolysis in the brain contributes to biomass

It is well known that glutamatergic synaptic transmission is the most metabolically expensive function of active neural tissue (Attwell and Laughlin 2001; Harris et al. 2012; Magistretti et al. 1999), and as such it has been assumed that most glucose used by the brain supports activity at the synapse. Because the metabolic and molecular needs of neural tissue changes through development and adulthood (Erecinska et al. 2004), it is plausible that the metabolic appropriation of glucose uptake may change as a consequence of a dynamic relationship between the pathways of oxidative phosphorylation and aerobic glycolysis. With this in mind, we propose a new model for the contribution of metabolic pathways for metabolic demand and neural tissue growth. While oxidative phosphorylation may be most important for synaptic activity throughout development and adulthood, aerobic glycolysis may support the proliferation of proteins, nucleotides, and lipids, which are critical components for the neuronal growth and maturation (Fig. 2a–c). We theorize that during in utero development of the brain, aerobic glycolysis is the predominant metabolic pathway because it is used to support the molecular demands of neuronal proliferation (Fig. 2a). Later during postnatal development, aerobic glycolysis may persist to support the maturational changes of neurons, including axonal elongation, synaptogenesis, and myelination (Fig. 2b). We speculate that the synthesis of biomolecules resulting from aerobic glycolysis would continue throughout adulthood for the purposes of (1) activity-related changes at the synapse that accompany learning, and (2) turnover of neuronal constituent molecules (Fig. 2c).

There are several lines of evidence that corroborate the contribution of aerobic glycolysis to the biomass of the brain:

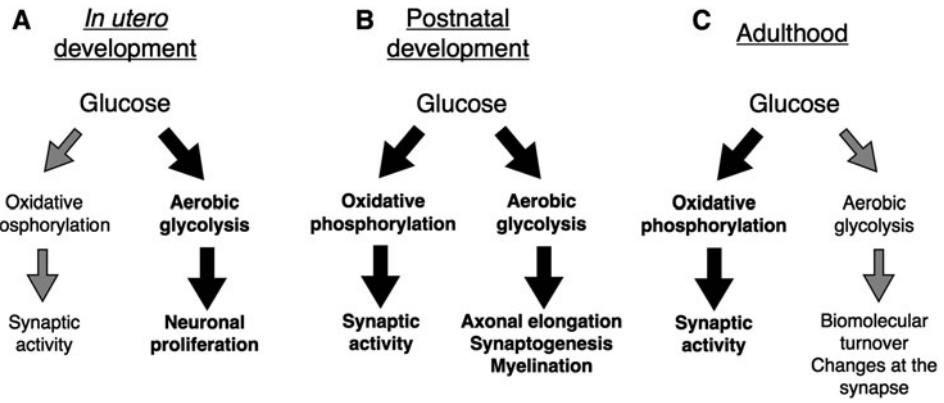


Fig. 2 Model of the dynamic relationship between aerobic glycolysis and oxidative phosphorylation through in utero development (**a**), early postnatal development (**b**), and adulthood (**c**). *Large bold arrows* signify a higher throughput of a pathway, while *smaller arrows* represent a reduced reliance on the pathway. The utility of aerobic glycolysis changes throughout the lifespan as the biomolecular needs of neurons change. Through development and adulthood, oxidative phosphorylation persists to support synaptic transmission

1. *Timing of neurodevelopment and aerobic glycolysis* The idea that aerobic metabolism can be used to contribute to building biomass of the brain is underscored by the variable amount of glucose allocated to this pathway at different time points of the lifespan in humans. In preterm infants, the vast majority of glucose uptake by the brain (90 %) is allocated to the metabolically inefficient pathway of aerobic glycolysis (Altman et al. 1993; Powers et al. 1998), during which time, proteins, lipids, and nucleotides are important for neuronal cell proliferation (Fig. 2a). Because there is little neurogenesis after birth, aerobic glycolysis accounts for roughly 35 % of the glucose consumption of the neonatal brain (Settergren et al. 1976) (Fig. 2b). By adulthood, the amount of glucose metabolized by aerobic glycolysis decreases to 10–12 % (Boyle et al. 1994; Raichle et al. 1970). Although not constituting direct evidence for the contribution of aerobic glycolysis to increasing biomass of the brain, it is notable that the amount of glucose allocated to this pathway is highest when demands for protein and lipids are greatest and may be concordant with rapid postnatal increases in dendritic spines (Huttenlocher and Dabholkar 1997) and growing white matter volume (Giedd et al. 1999; Paus et al. 1999).
2. *Amino acid synthesis* It is also worth noting that the process of oxidative phosphorylation itself uses a large number of proteins that need to be synthesized before it can be an effective mechanism for producing energy (Hevner and Wong-Riley 1991). Glycolysis early in development may be necessary to manufacture proteins necessary for aerobic metabolism. In the rat, the number of mitochondria in neurons increases after birth (Gregson and Williams 1969; Pysh 1970), despite there being similar numbers of neurons as in the adult brain. In cats, the peak level of protein synthesis occurs earlier in development than peak oxygen utilization (Hovda et al. 2006). As in the neocortex of most mammals, aerobic glycolysis accounts for most of the brain's glucose usage in the neonate despite the spike in oxidative phosphorylation later in life (Hovda et al. 1992). These facts are consistent with the notion that aerobic glycolysis contributes to biomass of the developing brain in the earliest stages of life.
3. *Axonal elongation* Laser capture microdissection has been used to isolate the axonal growth cones of retinal ganglion cells in the mouse (Zivraj et al. 2010). Subsequent mRNA analysis revealed that genes coding for protein synthesis and metabolic functions, including glycolysis, are among classes of functional gene categories whose expression is enhanced in the growth cone compared to the axon. Upregulation of genes related to glycolysis could potentially support the protein and lipid synthesis necessary for the integrity of the elongating neuronal membrane (Goldberg 2003). Furthermore, it was recently found that aerobic glycolysis is necessary and sufficient for the fast axonal transport along the length of the axon to nerve terminals, suggesting that aerobic glycolysis is also important as an energy source for the delivery of molecules necessary for axonal elongation (Zala et al. 2013).
4. *Synaptogenesis and experience-dependent modification* Because mitochondria are usually absent in dendritic spines (Li et al. 2004; Sheng and Hoogenraad 2007), glycolysis, which occurs in the cytoplasm, may be an important source of energy at the synapse. It was recently discovered that blocking the transport of lactate between astrocytes and neurons disrupts the

formation of long-term memories and experience-dependent modifications in CA1 of the hippocampus of the rat (Newman et al. 2011; Suzuki et al. 2011). Blocking the transport of lactate into the neuron prevented the induction of molecules, including cAMP response element-binding protein and cofilin, and the translation of the gene Arc, which are necessary for the dynamic changes in the cytoskeleton supporting the creation and modification of dendritic spines that underlie long-term memory formation (Suzuki et al. 2011). These findings are consistent with an increase of aerobic glycolysis following focused task-induced activity (Fox et al. 1988), which persists for nearly an hour (Lund Madsen et al. 1995).

5. *Myelination* In $Cox10^{flox/flox}$ mutant mice, a key component of the electron transport chain, cytochrome *c* oxidase, does not properly assemble (Antonicka et al. 2003; Diaz 2005). Although the mutation prevents glucose metabolism by oxidative phosphorylation, it does not cause glial cell death, demyelination, or degeneration of cortical axons, indicating that glycolysis alone is sufficient to maintain myelin in adulthood (Fünfschilling et al. 2012). Additionally, hypoglycemia in the developing mouse cerebral cortex results in a reduction of oligodendrocyte lineage cells and myelination, but the deficiencies can be overcome when exogenous L-lactate is supplied, meaning that glycolytic products are necessary for the production of myelin during development (Rinholm et al. 2011). Considering that aerobic glycolysis is higher in white matter than in gray matter of adults (Leveille et al. 1980) and may be particularly elevated in oligodendrocytes compared to neurons or astrocytes (Sánchez-Abarca et al. 2001), aerobic glycolysis' contribution to the production and maintenance of myelin sheaths may outweigh its contribution to other anabolic processes.

Metabolic and biomolecular costs of the brain through development and adulthood

Human neurodevelopment

The newborn human brain is only ~25 % of its adult volume, and rapid brain growth continues for the first two years postnatally, slowing down until the mature volume is reached around the age of seven (Dobbing and Sands 1979; Robson and Wood 2008). The average peak cortical thickness and cortical gray matter volume in humans occurs at approximately 10 years of age, with a relative delay in higher-order association cortices compared to somatosensory areas (Giedd et al. 1999; Gogtay et al. 2004; Shaw et al. 2008). A similar pattern also characterizes changes in the relative surface area of the cortical mantle in the developing human brain (Hill et al. 2010). Such changes in the thickness, volume, and surface area of neocortical gray matter reflect underlying neuronal maturation, not postnatal neurogenesis. Although neurogenesis occurs in the postnatal mammalian brain (Gould 2007), the distribution is limited to a few regions, including the olfactory bulb, hippocampus, and a few regions of the neocortex, and does not significantly contribute to adult neuron number (Kornack and Rakic 1999, 2001; Rakic 2002). Therefore, postnatal brain growth occurs through the maturation of preexisting neurons. Maturational processes, including axonal elongation, increasing dendritic branching and elaboration, proliferation of synapses, and myelination of subcortical axons account for postnatal growth of the brain and are crucial for the development of function (Hensch 2004).

Even from the time of birth, the human neocortex displays a heterogenous distribution of dendrites, spines, and synapses; in neonates there are higher densities of these structural components in primary sensory and motor regions compared to prefrontal cortex (Huttenlocher and Dabholkar 1997; Travis et al. 2005). High-order association cortices, including prefrontal cortex, reach peak synaptic densities and dendritic branching later than primary motor and somatosensory cortices, and upon reaching their respective peaks, synaptic pruning and refinement of neuronal circuitry occurs (Huttenlocher and Dabholkar 1997; Jacobs et al. 1997, 2001; Travis et al. 2005). Development of neuronal cytoarchitecture may continue, particularly in prefrontal cortex, into early adulthood (Giedd et al. 1999; Huttenlocher 1990; Paus et al. 1999; Petanjek et al. 2011). The delayed pattern of maturation seen in the circuitry of prefrontal cortex, and likely other associative cortical regions with dense corticocortical connections, may allow increasing complexity of processing circuits that become more integrative during postnatal development (Chugani 1998; Goldman-Rakic 1987). As synaptic connections become more numerous in a highly integrative region, such as prefrontal cortex (Elston et al. 2001; Semendeferi et al. 2011; Spocter et al. 2012), metabolic demand is expected to increase (see Jacobs et al. 2001).

Given the data supporting asynchronous regional development of neurons in the human cerebral cortex, it is notable that brain energetics display a similarly dynamic pattern. Indeed, PET studies in humans have found that the mass-specific glucose consumption by cortical gray matter increases from birth to the age of 2 or 3 years, remains almost twice the adult level throughout most of childhood, and declines to reach the adult level of glucose metabolism in the twenties (Chugani et al. 1987) (Fig. 3). The period of peak glucose consumption occurs slightly after

synaptogenesis begins to decline in rate (Jacobs et al. 2001; Petanjek et al. 2011), but before the initial decrease in the rate of myelination (Miller et al. 2012). Upon reaching peak synaptic density, synaptic pruning and refinement of neuronal circuitry occurs, and rate of myelination declines to a lower rate through adolescence. Accordingly, glucose uptake by the brain declines until an adult level of glucose uptake is observed (Chugani et al. 1987), presumably because less glucose is needed to support these anabolic processes. These developmental data demonstrate the close temporal relationship between glucose consumption and anabolic processes and emphasize differing metabolic appropriation of glucose through neurodevelopment.

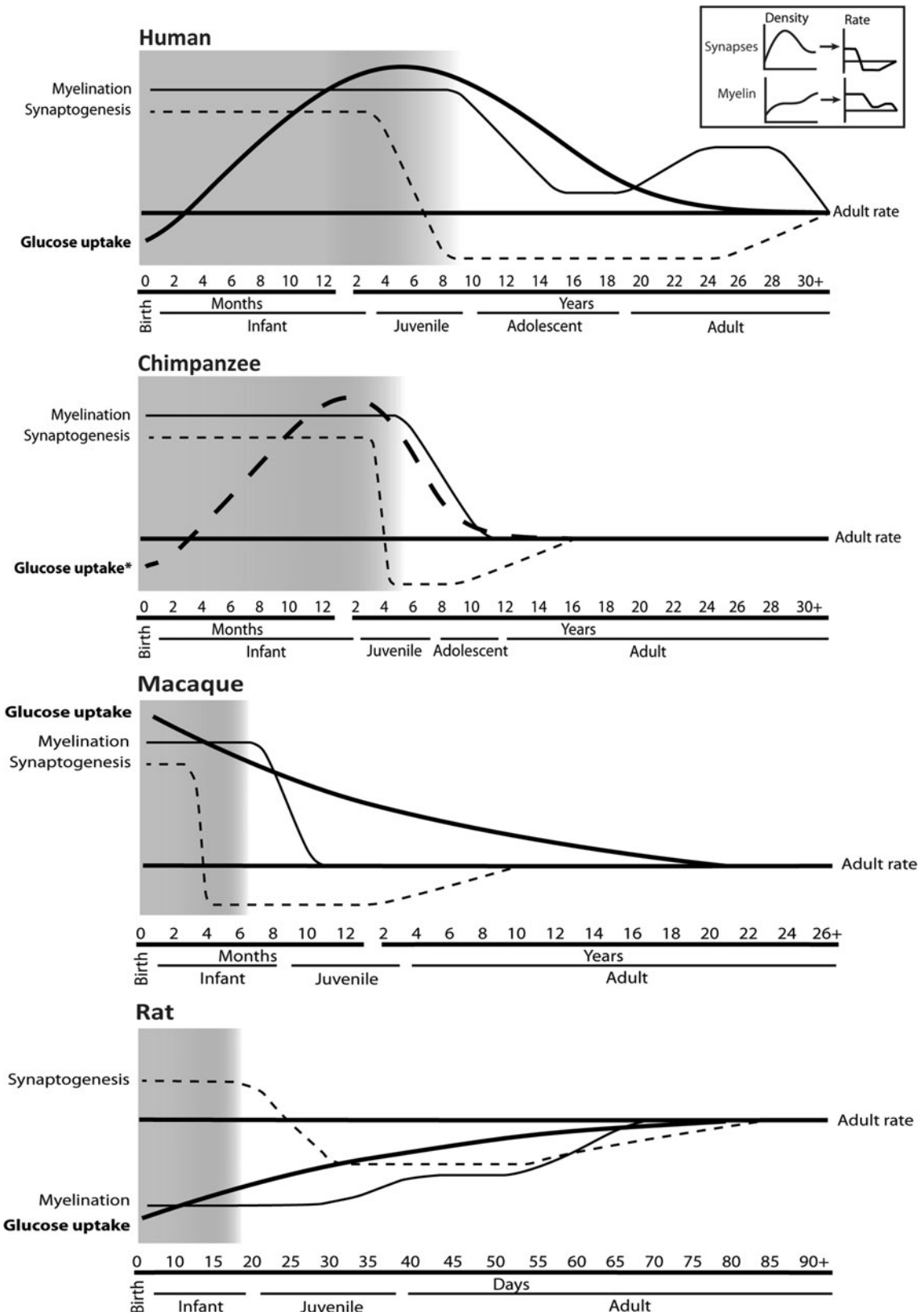
The fraction of glucose metabolized via aerobic glycolysis versus oxidative phosphorylation changes during postnatal neurodevelopment. At birth, around 30 % of the brain's glucose consumption is metabolized by aerobic glycolysis (Settergren et al. 1976) but declines to one-third of that value in adulthood (Boyle et al. 1994; Raichle et al. 1970). As of yet, it is not known whether the percentage of glucose allocated to aerobic glycolysis increases during childhood, when metabolic demand to support synaptogenesis is at its highest. It is likely that during postnatal development aerobic glycolysis increases to support the addition of biomass. After peak synaptogenesis is reached in the gray matter and myelination is completed in the white matter, the amount of aerobic glycolysis may decrease to a lower level in adulthood for cellular repair and molecular turnover. Concomitantly, oxidative phosphorylation would gradually increase with the proliferation of synapses and decrease to adult levels following synaptic pruning. Therefore, peak glucose uptake during childhood may result from a combination of high rates of both aerobic glycolysis (supporting anabolic processes) and oxidative phosphorylation (supporting synaptic transmission) (Fig. 2b).

Interspecific differences in neurodevelopment

Even after overall brain size has been obtained in development, the microstructure of the human brain continues to mature, refining connections and circuitry, even beyond the time of sexual maturity (Giedd et al. 1999; Sowell et al. 2003). Such a prolonged developmental schedule may result from a relatively delayed shift in gene expression related to synapse development and other gene ontology categories for neurodevelopment in the human brain compared to macaque monkeys as well as chimpanzees, the closest living relatives of humans (along with bonobos) (Somel et al. 2009). While the maximum glucose uptake of neocortex displays a delayed trajectory in human development (Chugani et al. 1987) compared to that of macaques (Jacobs et al. 1995), a similarly prolonged trajectory of expression has been found in a subset of human genes that support neurodevelopment, synaptic function, and glucose metabolism (Sterner et al. 2013). Morphologically, the delay in maturation of the human brain is manifest by extended periods of synapse development compared to macaques (Huttenlocher and Dabholkar 1997; Petanjek et al. 2011). Similarly, an extended time-course exists in the myelination of axons in humans, which is uniquely protracted compared to macaques (Gibson 1970; Yakovlev and Lecours 1967) and chimpanzees (Miller et al. 2012). Although it was recently found that synaptogenesis is delayed in chimpanzees similarly to humans (Bianchi et al. 2013), the postponement of other markers of neuronal maturation may be a key component underlying the evolution of human cognition and social learning by permitting greater opportunity for these networks to be influenced by experience (Miller et al. 2012).

As assessed by PET, maximum glucose metabolism in rhesus macaques and vervet monkeys has been shown to occur between the second and sixth months of postnatal life with synchrony across neocortical regions (Jacobs et al. 1995) (Fig. 3). The developmental cerebral glucose consumption curve in macaques is temporally coincident with changes in the overproduction and subsequent pruning of dendritic spines (Bourgeois et al. 1994; Rakic et al. 1986). Therefore, peak glucose metabolism in brains of these Old World monkey species reaches adult levels relatively early in development and synchronously across the neocortex, which differs from the more prolonged and asynchronous pattern of glucose uptake in the developing human brain. Chimpanzees are intermediate, showing a human-like pattern of extended postnatal synaptogenesis (Bianchi et al. 2013), but a shorter interval of myelination than in humans (Miller et al. 2012).

As previously noted, peak glucose uptake in the human brain occurs in early childhood (ages 4–5) and likely results from a combination of both high levels of aerobic glycolysis and oxidative phosphorylation. Therefore, peak glucose metabolism may be seen as a transitional point of development when a switch occurs from the high levels of aerobic glycolysis early in infancy to higher levels of oxidative phosphorylation later in childhood and adolescent development (Fig. 2c). Because the human developmental sequence is protracted relative to other primates (Bogin 1997), this metabolic transition in humans will occur at a later absolute age compared to other apes, such as chimpanzees, and a later developmental stage relative to other primates, such as macaques (Fig. 3). Additionally, the metabolic switch between aerobic glycolysis and oxidative phosphorylation may occur in primary sensory and motor cortices earlier than in higher order cortices that contain more integrative connections, mirroring the asynchronous pattern of neurodevelopment in the human brain (Jacobs et al. 2001).


Human
Density
Rate
Synapses
Myelin
Myelination
Synaptogenesis
Glucose uptake
Adult rate
0 2 4 6 8 10 12 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30+
Birth
Months
Years
Infant
Juvenile
Adolescent
Adult
Chimpanzee
Myelination
Synaptogenesis
Glucose uptake*
Adult rate
0 2 4 6 8 10 12 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30+
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Macaque
Glucose uptake
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Synaptogenesis
Adult rate
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Birth
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Years
Infant
Juvenile
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Rat
Synaptogenesis
Adult rate
Myelination
Glucose uptake
0 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90+
Birth
Days
Infant
Juvenile
Adult

◀**Fig. 3** A depiction of the time course of synaptogenesis and myelination relative to glucose uptake in humans, chimpanzees, macaques, and rats. The *three lines* on each *graph* (glucose uptake, myelination, and synaptogenesis in the cerebral cortex) are rates, depicting degree of change over time. Rates of synaptogenesis and myelination are converted from synaptic spine and myelin fiber densities by estimating the derivative of the line (see *inset*) over the course of development for each of the three primate species (Bianchi et al. 2013; Gibson 1970; Miller et al. 2012; Petanjek et al. 2011; Rakic et al. 1986) and rats (Markus and Petit 1987; Smith 1973). Rates of glucose uptake over development are previously published in humans (Chugani et al. 1987), macaques (Jacobs et al. 1995), and rats (Nehlig et al. 1988; Nehlig and Pereira de Vasconcelos 1993). The glucose uptake line for the chimpanzee (bold dashed line) is estimated based on the maturation of the structural parameters. The gray-shaded area behind the graphs approximates the duration through which aerobic glycolysis is estimated to remain elevated to support anabolic processes. It is important to consider the units on the *X* axes for these species, which account for differences in length of life histories. Modified from Teffer and Semendeferi (2012) and Sterner et al. (2013)

Data from rats highlights the protracted primate neurodevelopmental sequence relative to rodents. Unlike primates, rats begin postnatal life with a relatively small rate of glucose uptake in the cerebral cortex that increases until adulthood (Fig. 3) (Nehlig et al. 1988; Nehlig and Pereira de Vasconcelos 1993). A high rate of synaptogenesis occurs during infancy in rats, and pruning of synapses begins during the juvenile stage (Markus and Petit 1987). Notably, the neonatal rat has roughly 130 percent more myelin than during adulthood; thus the total lipid content of the rat brain decreases throughout development (Smith 1973). Based on the rates of synaptogenesis and myelination through development, it appears that rats may transition to higher levels of oxidative phosphorylation during infancy (Fig. 3).

Interspecific differences in adulthood

Aerobic glycolysis occurs within a broader context of the metabolic and biomolecular demand of the brain. Studies of gene evolution and regulation indicate that the molecular machinery related to glucose metabolism via oxidative phosphorylation has been a target of natural selection during primate evolution. In particular, a switch in an isozyme of lactate dehydrogenase during catarrhine evolution (the part of the primate lineage that includes Old World monkeys and apes) favors oxidative metabolism to anaerobic metabolism in the brain (Goodman et al. 1969). In the anthropoid lineage (that which includes New and Old World monkeys and apes), there are several genetic changes resulting in nonsynonymous amino acid substitutions supporting structural and regulatory changes for the subunits of cytochrome *c* oxidase, the final and regulatory component of the electron transport chain (Goldberg et al. 2003; Grossman et al. 2001, 2004; Hüttemann et al. 2011; Schmidt et al. 2005; Uddin et al. 2008); these include human-specific changes (Uddin et al. 2008). It has also been suggested that changes to cytochrome *c* during anthropoid evolution, including to a phosphorylation site linked to respiratory chain activity, have largely occurred at positions important for respiration (Pierron et al. 2011). Regions of the adult human neocortex are marked by an upregulation of genes related to both oxidative metabolism and synaptic transmission, suggesting that per unit mass the human brain is more metabolically expensive (Fu et al. 2011; Preuss 2011; Preuss et al. 2004; Uddin et al. 2004). Taken together, the results of these studies are indicative 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 metabolism pathway, but research has not yet fully explored whether these changes have made oxidative phosphorylation more efficient. It is reasonable to speculate that genetic changes affecting oxidative phosphorylation may benefit ATP availability for synaptic activity and also regulation of the efficiency with which energy is used.

Even still, in humans, aerobic glycolysis persists into adulthood, accounting for 10–15 % of the brain's glucose usage (Boyle et al. 1994; Raichle et al. 1970). This ratio marks a departure from the higher levels of aerobic glycolysis during earlier stages of development when the biomolecular requirements of the brain are higher to meet the needs of maturing neurons (Fig. 3). Little is known about the energetic provisioning of the brain at rest and how the contributions of aerobic glycolysis and oxidative phosphorylation might differ with respect to biomolecular turnover and neuronal upkeep.

Whereas PET studies have attempted to track the differences in energy allocation of the brain by using either radiolabeled oxygen or glucose, the results of such studies should be interpreted with caution because glucose metabolism may be balanced between metabolic pathways differently among species and time of lifespan. Furthermore, it is not known if aerobic glycolysis is the more prevalent pathway in the brain of some species during adulthood compared to others. An early study utilizing radiolabeled oxygen species in a broad sample of adult vertebrates found that the human brain uses less oxygen per gram of tissue while at rest than other species (Mink et al. 1981; but see Karbowski 2011). Indeed, based on Kleiber's law, the amount of energy required per gram of tissue decreases with increased mass of an organ (Kleiber 1932). Because of its large mass, the human brain would, therefore, be expected to be more energy efficient than the smaller brains of other primates, a feat potentially achieved by decreased neuronal density and larger neuronal size

(Tower 1954; Hofman 1983). However, glucose demands per unit tissue of the adult human cerebral cortex (Clarke and Sokoloff 1999) fall within the margins of error for that of the macaque monkey (Kennedy et al. 1978). Taken together, these data imply that the adult human brain may process more glucose via aerobic glycolysis during resting state than other catarrhine primates. Under our proposed model of metabolic appropriation (Fig. 2), this result may indicate that, although the human brain uses energy more efficiently to power synaptic activity (oxidative phosphorylation), there is a higher cost for biomolecular turnover and synaptic plasticity in the human brain (aerobic glycolysis) compared to other primates. Such a perspective is aligned with molecular evidence that has found aerobic metabolism (via oxidative phosphorylation) to be adaptive in the human lineage (Uddin et al. 2004) to support efficiency of synaptic transmission (Cáceres et al. 2003), while still accounting for the large glucose budget of the human brain (Preuss 2011).

The default mode network

Although aerobic glycolysis increases within the vicinity of task-induced changes in brain activity (Fox et al. 1988; Kasischke et al. 2004), it has also been shown to be present in specific regions of the brain at rest (Buckner 2011; Raichle and Snyder 2007). In particular, the medial and lateral prefrontal cortex, lateral parietal cortex, posterior cingulate cortex, precuneus, lateral temporal gyrus, gyrus rectus, and caudate nucleus were found to have significantly elevated levels of aerobic glycolysis at rest (Buckner et al. 2008; Vaishnavi et al. 2010). Although the reason for regional specificity of aerobic glycolysis at rest is unknown, the spatial overlap between these regions and those that comprise the default mode network (DMN) is noteworthy (Vaishnavi et al. 2010).

The DMN is a network of brain areas that consistently exhibit a high degree of metabolic activity at rest but become less active during focused cognitive tasks (Gusnard et al. 2001; Gusnard and Raichle 2001; Raichle et al. 2001). Several functions have been ascribed to the brain areas within the network. In the anterior portion of the DMN, the ventromedial prefrontal cortex (VMPFC) is associated with integrating cognitive and emotional information and online monitoring of sensory inputs, and the dorsomedial prefrontal cortex (DMPFC) is associated with processes related to theory of mind (Buckner and Carroll 2007; Spreng et al. 2009). In the posterior DMN, the posterior cingulate cortex (PCC) and precuneus are thought to process emotion and to contribute to episodic memory retrieval (Buckner et al. 2008; Buckner and Carroll 2007; Cavanna and Trimble 2006; Spreng et al. 2009). Also in the posterior DMN, the lateral parietal and lateral posterior temporal cortices attend to salient and novel or unexpected external stimuli (Constantinidis and Steinmetz 2001; Gusnard and Raichle 2001; Jenkins et al. 1994), particularly biological motion (Grèzes et al. 2001; Grossman and Blake 2001; Gusnard and Raichle 2001). Recent publications have included medial temporal cortex and the hippocampus in the DMN (Buckner et al. 2008; Greicius et al. 2004; Vincent et al. 2006), suggesting a strong memory component to its activity and function.

Two recent PET studies have demonstrated human-like DMN in chimpanzees. Rilling et al. (2007) described patterns of regional metabolic brain activity in chimpanzees at rest using a whole-brain analysis. The areas of the chimpanzee brain shown to be most active at rest overlapped significantly with those identified as part of the DMN in humans, particularly those along the cortical midline, including the DMPFC, VMPFC, PCC, and precuneus. Barks et al. (2013) further described deactivation of these DMN areas (most saliently, the PCC and the precuneus) in chimpanzees during working memory tasks, demonstrating functional as well as anatomical similarity in the DMN between that species and humans. Similar resting activity in DMN areas has also been described in macaques (Hayden et al. 2009; Kojima et al. 2009; Vincent et al. 2007). Kojima et al. (2009) further demonstrated that the DMN of macaques is not only highly active at rest, but also less active during tasks—that it deactivates in a functionally similar way to that of humans and chimpanzees. Lu et al. (2012) recently investigated DMN for the first time outside the primates, using functional magnetic resonance imaging to examine resting brain activity in rats. They found clear evidence of a DMN in this species. Although differences between rat and primate (including human) DMN exist, there are also similar patterns of cortical midline—both posterior and anterior—and hippocampal activity at rest. Taken together, these data suggest that patterns of DMN activity are roughly similar in humans, chimpanzees, macaques, and rats, suggesting that glucose uptake in the regions identified as the DMN is homologous in all mammals.

Because many of the regions of the DMN also have high levels of aerobic glycolysis at rest in humans (Vaishnavi et al. 2010), here we offer a working model of the utility of aerobic glycolysis in these areas. While the purpose of aerobic glycolysis in the adult brain may support plasticity and biomolecular turnover, the elevated rate of aerobic glycolysis in specific regions of the cerebral cortex at rest suggests that these regions require a uniquely high degree of preparedness for synaptic change into adulthood. The DMN has been suggested to integrate multimodal sensory information (Buckner et al. 2008; Lu et al. 2012), a process that would require development of local cortical circuits

and synaptogenesis to respond quickly to changes in the continuously changing world (Raichle 2006). If aerobic glycolysis is found to be elevated in the DMN in other species besides humans, including rats, the DMN may prove to be a relatively widespread adaptation within placental mammals that allows the brain to respond efficiently with synaptic modifications in response to social cues and threats from conspecifics and predators.

Implications for human aging and neurological disease

There are reasons to suspect that aerobic glycolysis may serve as a neuroprotective mechanism, helping to attenuate the effects of aging in the brain. One theory of aging posits that the progressive accumulation of reactive oxygen species (ROS), a byproduct of aerobic mitochondrial metabolism, and more so from defective mitochondria function, damages both mitochondrial and nuclear DNAs and thereby contributes to the process of senescence (Beckman and Ames 1998; Fraser et al. 2005; Kirkwood and Austad 2000). The production of energy by aerobic glycolysis reduces the amount of ROS that would otherwise need to be produced by oxidative phosphorylation (Brand and Hermfisse 1997). Indeed, there is evidence that regulation of lifespan is brain-dependent (Mattson et al. 2002; Wolkow et al. 2000) and is mediated by factors that modulate metabolism and, accordingly, oxidative stress (Myers and Olson 2012; Ramadori and Coppari 2011). Even the amount of ROS produced can in principle alter the activity and metabolic profiles of neurons (Diano et al. 2011). Additionally, glucose metabolism through the PPP has also been shown to regulate cellular redox state, which in turn inhibits apoptosis in neurons and prolongs their longevity (Vaughn and Deshmukh 2008). Such protective mechanisms may have profound implications for human neurodegenerative diseases and neuronal aging (Hof and Morrison 2004), particularly in light of the extended lifespan of humans compared to other primates. From a comparative perspective, the human brain is unique in that cerebral gray matter and white matter exhibit overt decreases in volume with advanced age, whereas chimpanzees and other primates do not (Sherwood et al. 2011). To what extent spatial overlap exists between continued aerobic glycolysis in adulthood and ROS-related damage or neuronal apoptosis resulting in volume loss is unclear and also warrants further investigation.

Cognitive decline, including memory deficits and deficiencies in executive functions, is a typical manifestation of aging in humans (for review see Salthouse 2009). In human neocortex, pyramidal neurons within some regions and layers are affected by the aging process, and some measures of neuronal complexity, including dendrite length and spine density, are known to decline with age (Anderson and Rutledge 1996; Jacobs et al. 1997; Uylings and de Brabander 2002). Indeed, such age-related changes in humans are evident on a larger scale as less coordination is seen between regions whose communication subserves higher-order associative functions (Andrews-Hanna et al. 2007). Although the human lifespan is protracted relative to other primates, data from aged macaque monkeys show that similar changes in neuronal morphology, including reduction of synapses and degradation of myelinated axons with age, are not limited to humans (Bowley et al. 2010; Duan et al. 2003; Kabaso et al. 2009; Dumitriu et al. 2010; Peters et al. 2008).

Although synaptic decline occurs through senescence in all primates, the neuronal death and dementia that is emblematic of AD affects humans and not other primates, even in very advanced age (Hof et al. 2002; Walker and Cork 1999). In AD, specific subclasses of neurons in the hippocampus and pyramidal neurons within the neocortex display greater susceptibility to cell death than others (Hof and Morrison 2004; Hof et al. 2003; Yang et al. 2003). Within the neocortex, pyramidal neurons form long corticocortical association pathways (Bussière et al. 2003a, b; Hof et al. 1990), suggesting a selective, but global, loss of connectivity. The most vulnerable neurons are those that develop neurofibrillary tangles (NFT) comprised of the hyperphosphorylated protein tau, and strong correlations exist between intracellular NFT formation in postmortem human samples and the extent of cognitive impairment (Bussière et al. 2003a, b; Giannakopoulos et al. 2003; Haroutunian et al. 2007). A prominent theory of AD pathogenesis predicts that amyloid-β plaque accumulation occurs prior to tau-pathology and is necessary for the development of NFTs (Selkoe 2000). Although the exact progression of events in AD etiology is contested (for review see Mudher and Lovestone 2002), diffuse amyloid-β plaques have been found in several species of aged New and Old World monkeys (Gearing et al. 1996; Geula et al. 1998; Kimura et al. 2003; Lemere et al. 2004, 2008; Mufson et al. 1994; Poduri et al. 1994; Walker et al. 1987) and in great apes, including chimpanzees (Gearing et al. 1994; Gearing et al. 1996; Rosen et al. 2008), gorillas (Kimura et al. 2001; Perez et al. 2013), and orangutans (Gearing et al. 1997). Investigations of tau pathology in great apes have been limited, but evidence has been found in a single chimpanzee (Rosen et al. 2008) and several western lowland gorillas (Perez et al. 2013).

Regions susceptible to AD pathology are also characterized by overall glucose hypometabolism (Reiman et al. 1996, 2005; Small et al. 2000; Valla et al. 2001, 2010) and the downregulation of genes that relate to aerobic metabolism and synaptic transmission (Wang et al. 2010). On the other hand, the activity of key regulatory glycolytic

enzymes (i.e., LDH, phosphofructokinase, and pyruvate kinase) are increased in the brains of AD patients, and the specific activities of these enzymes are correlated with disease severity (Bigl et al. 1996, 1999), which suggests elevated activity of aerobic glycolysis may in fact be indicative of AD etiology. "Pittsburgh compound B" (PiB) is a radiotracer used in PET studies, which is taken up in regions of the brain prone to accumulation of AD neuropathology (Klunk et al. 2004; Mintun et al. 2006). Recently, a high degree of spatial overlap was found between the regions of the brain that uptake PiB in neurologically normal individuals and those that engage higher than average levels of aerobic glycolysis at rest (Vlassenko et al. 2010). This evidence suggests that regions of the neocortex that are susceptible to AD pathology are characterized by increased aerobic glycolysis and decreased oxidative phosphorylation, and indeed, these characteristics are evident prior to other neuropathologic changes in AD (Chandrasekaran et al. 1994; Fukuyama et al. 1996; Rapoport et al. 1986; Trushina et al. 2012).

Consequently, a primary defect of AD may be a neuron's diminished ability to produce energy by oxidative phosphorylation and, thus, increased reliance on aerobic glycolysis to meet the neuron's energetic demands. Regions where aerobic glycolysis is normally elevated (Vaishnavi et al. 2010) may be less able to carry the metabolic load in the face of a faltering system of oxidative phosphorylation. Furthermore, as the cell struggles to meet the essential metabolic requirements of the cell, the use of glucose for anabolic processes, such as maintaining synapses (Akram et al. 2008; Schnaider Beeri et al. 2012) and long-range corticocortical connections (Bussière et al. 2003a, b; Hof et al. 1990) will falter. On the other hand, regions where aerobic glycolysis contributes a minor fraction of the metabolic burden can suffer greater damage to the system of oxidative phosphorylation before manifesting a phenotype. However, the fact that aerobic glycolysis prevents apoptosis through regulation of the cell's redox state (Vaughn and Deshmukh 2008) may be beneficial for cellular longevity under the conditions of AD (Newington et al. 2011). Extensive research is warranted to understand the relationships between metabolic appropriation and the onset and progression of AD.

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 both within humans and compared to other species remains to be explored, particularly as they relate to brain function and disease vulnerability. Additionally, while there is a large extent of overlap in the regions that comprise the DMN in mammals, it is unclear if the same distribution of aerobic glycolysis during the resting state exists in other species than humans. Finally, the extent to which metabolic dysfunction contributes to human-specific aging and age-related dementing illnesses remains unanswered. However, as to the latter, the frequency of depression and depressive traits in individuals with mitochondrial disease (Anglin et al. 2012; DiMauro and Schon 2008; Kaufmann et al. 2002, 2004), the association of mitochondrial DNA variants with susceptibility to AD (Coskun et al. 2004, 2010, 2012; Lakatos et al. 2010; Silva et al. 2011), and the fact that many genes associated with bipolar disorder and schizophrenia also relate to mitochondrial function (Atkin et al. 2011; Eykelenboom et al. 2012; Maeda et al. 2006) suggest that the connection between metabolic dysfunction and cognitive diseases will continue to develop and is an area where more inquiry would be fruitful. Furthermore, interspecific comparisons of metabolic function pertaining to senescence may allow us to learn about this uniquely human condition. We may elucidate these areas of inquiry, and others, with a more comprehensive understanding of metabolic and biomolecular supply to the brain that will be obtained with more attention paid to aerobic glycolysis.

Important considerations have been excluded from our consideration of metabolic pathways and energetic appropriation. First, we do not consider the energetic costs of non-neuronal cells in the central nervous system, including glia and those that comprise the epithelium of blood vessels, whose metabolic demands are not well explored. Additionally, we have not explored regulation of anabolic processes. While recent research has examined the effect of energy levels on protein synthesis (Horman et al. 2002) and axonal elongation (Amato et al. 2011) through the action of the energy-sensitive protein adenosine-5′-monophosphate (AMP)-activated protein kinase, the exploration of the regulatory processes that control anabolic pathways remains nascent. Future investigations into the regulation of these processes should investigate how the coupling between metabolic activity and neuronal maturational processes may be differentially regulated across species.

We have proposed a model whereby the metabolic and biomolecular needs of neural tissue are dynamic over the course of a lifetime, and non-oxidative glucose metabolism is effective in helping developing neural tissue meet the demand of biomolecule procurement. Because the human neurodevelopmental sequence is protracted compared to other primates, the model predicts that the corresponding

shift from aerobic glycolysis to oxidative phosphorylation will occur later in humans than other primates, which provides additional time for the synthesis of proteins and lipids necessary for integrative neural connections to be established. Furthermore, because regional neurodevelopment is asynchronous in humans, as well as other great apes, the shift from aerobic glycolysis to oxidative phosphorylation will also occur asynchronously with the change in metabolic pathway following maturation of cytoarchitecture. We hypothesize that the time course by which aerobic glycolysis is elevated during development can be adaptive in humans and other primates to support neurodevelopment and activity-related synaptic changes that underlie plasticity and learning. In this context, aerobic glycolysis is another mechanism that may play a major role in determining cognitive differences among primate species.

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