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Article

Oxygen and the Spark of Human Brain Evolution: a Complex Systems Account

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Abstract: Scientific theories on the functioning and dysfunction of the human brain require a good understanding of both its development — before and after birth, and through maturation to adulthood — and its evolution from the ancestral primate brain. Adopting a complex-systems approach, here we propose that the apparent uniqueness of humans' cognitive capacities might best be understood as emerging from multiple nested "virtuous cycles." In particular, we propose that the intimate link that exists between oxygen metabolic loops, cortical expansion, and ultimately cognitive and social demands is a key driver of genetic developmental programs for the human brain. Overall, our proposed evolutionary model makes explicit mechanistic links between metabolism, molecular and cellular brain heterogeneity, and behaviour that may in time provide a clearer understanding of brain developmental trajectories and their disorders.

Keywords: Human brain evolution; complex systems theory

Overview and Model Sketch

Since Darwin's proposal to embed *Homo sapiens* within an evolutionary continuum with the rest of the natural world, neuroscientists and evolutionary biologists have been tasked with providing a neural explanation for the cognitive gap between humans and other species, and for the emergence of such differences. Given that cognitive abilities depend on brain structure and function, such explanations have been attempted using several different observations across a range of scales — from the genetic to the metabolic, to the behavioural (endo)phenotype. Instead of attributing prevalence to a particular domain or scale, the aim of this work is to

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employ a complexity science perspective (Turkheimer et al., 2021) to argue that the peculiar evolution of the human brain may be the result of nested, mutually reinforcing cycles that operate and interact at different biological and temporal scales.

To guide the reader, here we provide a brief summary of our main argument — which will be expanded upon in the remainder of this work. The starting point of our argument is that growth of neocortices in humans has exceeded the capacity of oxygen delivery by the vascular system, so that brain tissues need to rely on non-oxidative (aerobic) glycolysis for the extra energy requirements. Because of the resulting lower oxygen tension, these tissues do not mature to the same extent as the primary cortices; hence, they retain a protracted capacity for plasticity and ongoing learning, which set the conditions for cognitive flexibility in response to environmental challenges — such as those imposed by complex social interactions. Life within a group also offers protection during protracted development, as well as the capacity for inter-generational learning, and greater hunting and foraging possibilities — the latter enabling an improved diet that can support the metabolic cost of cortical expansion. In this manner, a set of mutually reinforcing “virtuous cycles” ensue, with increasing expansion and increasing cognitive capacities enabling each other. The proposed model may be sketched as in Figure 1.

In the following sections, after a brief review of the rich literature on human brain evolution, we describe the various nested cycles of our proposed model — from metabolic and molecular to cognitive and social levels — and outline their complex rich interactions.

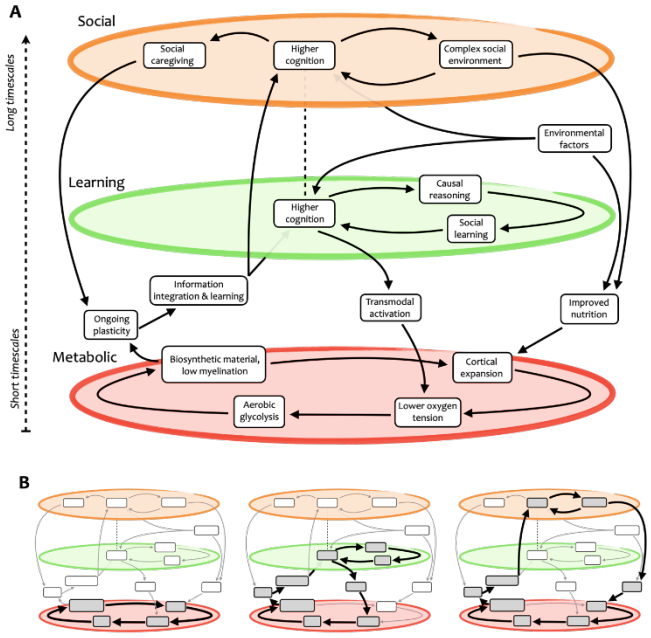

Figure 1. **Schematic overview of the complex-system account of human brain growth and evolution. (A):** Our approach presents brain evolution as resulting from multiple nested, mutually reinforcing cycles that span several

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domains and operate over a variety of different scales — some within the individual, others across generations. **(B):** Examples of cycles that exist within this complex process. The first part of our presentation focuses on the metabolic cycle (left), and the second part explains how it is embedded in a larger system involving learning and social aspects (center and right), which operate at longer timescales.

The Explanandum: Human Brain Evolution

What aspect(s) of brain organisation are responsible for humans' sophisticated cognitive capabilities? The human brain comprises a substantially greater number of neurons than the brains of other great apes: approximately 86 billion neurons for humans, 28 billion for chimpanzees, and 33 billion for gorillas (Herculano-Houzel and Kaas, 2011). Additionally, humans surpass other primates in terms of brain-to-body ratio (Silver and Erecinska, 1998). However, it has been suggested that these facts might not be in need of special explanations, as the human brain and its associated functional and metabolic characteristics may be understood as the mere allometric expansion of the primate brain (Herculano-Houzel, 2009, Seymour et al., 2016, West et al., 1997, White et al., 2019).[1] In effect, the human brain contains as many neuronal and non-neuronal cells as would be expected of a primate brain of its size (Herculano-Houzel, 2009) – although recent evidence does indicate the existence of neuronal differences between primates and non-primate mammals (Krienen et al 2020; Banovac et al., 2021).

Going beyond total brain size, however, human brains surpass those of other primates in terms of both total volume and total surface area of the neocortex (Donahue et al., 2018, Semendeferi et al., 2001, Herculano-Houzel et al., 2007). Accounting for 20.9% of total neuron count, the human neocortex outstrips any other mammalian neocortex by over 10% (Herculano-Houzel, 2012). Crucially, even across the cortex there are important evolutionary differences: both cytoarchitectonic and comparative neuroimaging studies have converged on the conclusion that so-called transmodal association cortices in the human brain, where multiple sensory streams from unimodal cortices converge for further processing (Mesulam, 1998), are greatly increased in volume relative to that of other primates (Glasser et al., 2014, Smaers et al., 2017). Moreover, this increase is an outlier compared to the allometric scaling of primate brains (Sherwood and Smaers, 2013, Smaers et al., 2017) [2]. Therefore, it seems clear that, even in purely physiological terms, human brains are indeed remarkable and in need of a dedicated explanation.

[1] Allometry is the study of the relationship of body size to shape, anatomy, physiology and finally behaviour. Allometric scaling relations, for example the 3/4 power law scaling for metabolic rates with body mass also known as Kleiber's law, are characteristic of all organisms (West, Brown, & Enquist, 1997). These relations are based on the general principle that cellular metabolism requires essential nutrients, and importantly oxygen, that are transported through space-filling fractal networks of branching tubes.

[2] The PFC is a region of particular interest due to its role in a range of specialised cognitive capacities such as language, imagination and complex decision making (Rushworth et al 2011; Gabrieli et al., 1998; Miller & Cohen, 2001). Granular prefrontal cortex may even be unique to primates (Preuss, 1995; Striedter, 2004). Since prefrontal cortex and related associative cortices do not scale well across anthropoid primates, their expansion is now purported as a non-allometrically derived feature of cortical organisation (Sherwood & Smaers, 2013; Smaers et al., 2017).

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This endeavour has proven fruitful, delivering a sizable number of comparative accounts of brain evolution that (implicitly or explicitly) aim to explain human cognitive evolution (Box 1). Although each of these explanatory strategies has clear merits, we note that they are not mutually exclusive, as they tend to address distinct parts of the brain's evolutionary process. We also note that most of the proposed factors exist on a continuum or are shared with other species, making it difficult to rely exclusively on any one of such factors to justify the apparent discontinuity that exists between humans and other species in terms of cognitive capacity. We are also yet to witness the introduction of uniquely human genes in other species being sufficient to produce the full range of human-level cognition. Together, these observations suggest that a suitable answer to the evolution of human brain and cognition might be best sought not in any single one of the currently proposed factors, but rather in the synergistic interactions between several of them. In other words, what is unique about humans might not be any of the proposed factors *per se*, but rather a specific combination of the interactions between them.

BOX 1: Approaches to explaining brain evolution

Four broad classes of explanations for brain evolution can be identified (Dunbar and Shultz, 2017): (1) relation to body size (2) opportunity-focused, (3) mechanism-focused, and (4) constraint-focused.

An influential early explanation related to body size was Cope's rule, which posits a gradual increase in body size over evolutionary time for most population lineages (Rensch, 1948) due to the higher selective value of larger individuals when they compete with smaller ones (Kingsolver and Pfennig, 2004). This trend is typically attributed to greater strength, resilience, speed, larger weapons, and sensory organs of larger animals (Rensch, 1959). Based on this well-established observation, an explanation of brain size increase over evolutionary periods could then be formulated under the assumption that a larger brain is required to govern a larger body (though note that this account does not focus on cognitive abilities specifically). However, recent evidence from fossil scans indicates that the brain-to-body ratio of placental mammals initially *decreased,* as body growth rate outstripped the rate of brain growth, and encephalisation only started to actively increase later (Bertrand et al., 2022).

Contrasting with this early account that simply posits a larger brain as a by-product of a larger body, *opportunity-focused* hypotheses propose associations between an increase in brain size and a consequent trait (typically, improvement in some aspect of cognition), which the environment can positively select upon. Depending on the focus, one can distinguish between *ecological* explanations (Harvey et al., 1980) whereby the growth of the primate brain allows a better interaction with demanding environmental conditions; and *social* explanations whereby larger brains are better suited to the complexity of primate sociality (Perez-Barberia et al., 2007, Shultz and Dunbar, 2007).

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Mechanism-focused hypotheses are based on the genetics of brain development and focus on identifying uniquely human genes that are implicated in cortical growth (Evans et al., 2005, Jayaraman et al., 2018, Mekel-Bobrov et al., 2005, Mirzaa et al., 2014, Montgomery et al., 2011, Uddin et al., 2008, Wang et al., 2008). In addition to expansion of non-protein-coding DNA in humans compared with non-human primates, evidence has been converging on human-specific genes involved in expansion of the foetal cortex and capable of stimulating neurogenesis, such as *ARHGAP11B* (Florio et al., 2015; Heide et al., 2020; Kalebic et al., 2018; Namba et al., 2020) and *NOTCH2NL* (Fiddes et al., 2018; Florio et al., 2018; Suzuki et al., 2018). Some of the most recent work in this area uses 3-dimensional organoids to mimic the processes that recapitulate the steps of tissue fate acquisition and morphogenesis during neurodevelopment (Benito-Kwiecinski et al., 2020, Chiaradia and Lancaster, 2020, Giandomenico and Lancaster, 2017, Li et al., 2017).[3] Additionally, several genes have been identified as being responsible for the development of the neocortex, because their mutation results in microcephaly (and associated linguistic and cognitive deficits), as revealed by convergent evidence in patients and animal models (Jayaraman et al., 2018).

Finally, constraint-focused hypotheses are concerned with the physiological limits to brain tissue expansion (Dunbar and Shultz, 2017), and how humans may have succeeded to circumvent them. A relevant constraint to brain expansion is the vulnerability that comes with humans' very protracted period of immaturity: for many years before reaching adulthood, humans are unable to fend for themselves. *Developmental* explanations propose that this constraint is overcome thanks to extended periods of parental investment (Barrickman et al., 2008) and protection by the social group, with the additional advantage of providing greater opportunity for explorative learning and a key opportunity for transgenerational teaching (Boyd et al., 2011).

Another key limiting factor for brain size is the energetic cost of its neuronal mass. In humans, although the brain only represents 2% of total body mass, it consumes an astonishing 20–25% of the total body energy budget; in comparison, other primates dedicate approximately 8–10% of their metabolism to brain function, and most other mammalian species only use 3–5% (Attwell et al., 2010, Leonard et al., 2003, Magistretti and Allaman, 2013). Such high energetic demands clearly place bounds on brain tissue growth (DeCasien et al., 2017, Fonseca-Azevedo and Herculano-Houzel, 2012, Herculano-Houzel, 2012, Isler and van Schaik, 2006, Kuzawa et al., 2014, Kverkova et al., 2018, Navarrete et al., 2011, Pontzer et al., 2016, Sukhum et al., 2016). According to the "expensive-tissue" hypothesis, the high energetic requirements of neurons and limited caloric yield of raw food impose a trade-off between body size and brain size (i.e., neuron count), which is still limiting the brain size of today's great apes; however, our ancestors overcame this limitation and unlocked the potential for greater neuronal count when *Homo erectus* started processing and cooking food, thereby

[3] Such organoid systems remain experimental models and are not a replacement for actual brain experimentation. With this caveat in mind, data from such systems are extremely useful since they permit ethical access to, and precise control of, human cells in a 3D environment that may be considered, very broadly, similar to early brain development.

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extracting more energy in considerably less time (Fonseca-Azevedo and Herculano-Houzel, 2012). In addition, cooking also offset the body's energetic requirements by a corresponding reduction of the requirements of other tissues, e.g., by reduction of the size of the gut thanks to increased digestibility of cooked food (Aiello and Wheeler, 1995, Huang et al., 2018). Cooking is also an excellent example of skill acquired from transgenerational learning, highlighting the possible interdependencies between different accounts.

Part I: Oxygen and the human brain

Here we put forward the core of our proposal, which capitalises on recent breakthroughs on the role of oxygen in the origin of life to provide an explanation for the role of lower oxygen tension and aerobic glycolysis on human brain development.

Background: Oxygen and the Evolution of Life

We start our exposition by focusing on the role that metabolism may have played in brain development, with a particular emphasis on a simple yet fundamental molecule: oxygen. For this purpose, we take a step back and first consider recent breakthroughs in our understanding of the role of energetic cycles in the origin and development of not just brains, but of life on Earth in general (Box 2).

BOX 2: Oxygen in the Earth geochemistry

Modern planetary science has shown how Earth's first biochemistry was shaped by the interaction of the energy of solar radiation and both the gases in the earth's atmosphere and the metals in its core. Oxygen is the most abundant element in the Earth's crust (Dole, 1965), and it was probably present in the Earth's crust from very early on.[4] Oxygen is an ideal electron acceptor (Allred and Rochow, 1958), being the second-most electronegative element. On the other hand, the Earth's core is comprised mostly of iron (inner core) and iron alloys (outer core), which are good electron donors. This creates a strong imbalance between powerful oxidative forces on the crust and reducing fluxes from the core that never fully equilibrate (since magmatic

[4] Due to its separation from aqueous vapour in the atmosphere by UV radiation from the sun (Lu et al., 2014, Nisbet and Sleep, 2001). This was even before its rapid increase due to the advent of oxygenic photosynthesis, during the Proterozoic aeon of the Precambrian period, ~2500–540 million years ago.

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fluxes in the oceans' depths keep replenishing the oxidised metals of the crust), which effectively creates conditions where the Earth is analogous to a giant battery (Figure 2) — with an oxygen-rich pole on the surface and an iron-rich pole in the core (Smith and Morowitz, 2016).

The interplay of iron and oxygen may be at the very core of the emergence of life on our planet (Wade et al, 2021). It has been postulated that life may have started during the Hadean period (~4 billion years ago) at the juncture between these two opposed poles – in alkaline vents in the bottom of the ocean that acted as electrochemical flow reactors (Miller and Bada, 1988). This model portrays the basic biochemistry of life as a consequence of the energy imbalances in the Earth's early geochemistry, with living creatures serving as relaxation channels to reduce the free energy gradients of our planet (Smith and Morowitz, 2016) – making organic life not an "unlikely" but perhaps almost a "necessary" product of biochemical potentials of the Earth's inorganic *milieu*.

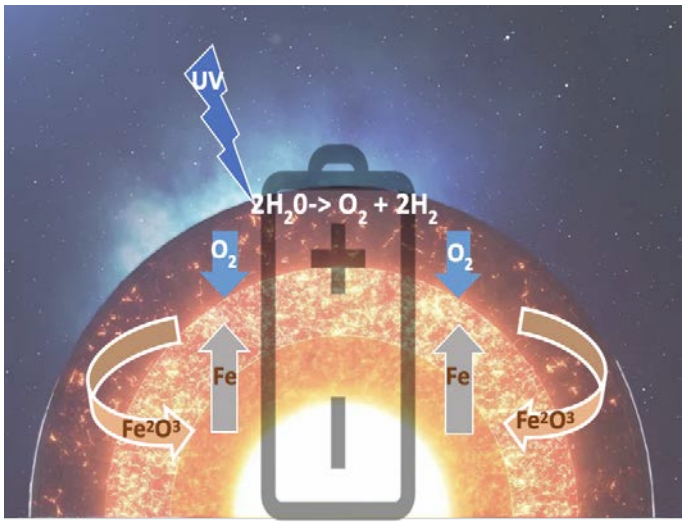

Figure 2. Oxygen-driven energetic fluxes of the Earth. Oxygen (O2), a strong electron acceptor, was likely present in the Earth's atmosphere from the beginning due to its separation from aqueous vapour in the atmosphere by ultraviolet radiation from the sun. Iron (Fe) and iron alloys in the Earth's inner and outer cores are good electron donors. This imbalance creates an electron flux towards the crust that does not reach equilibrium due to the magmatic fluxes at the bottom of the oceans that replenish the oxidized iron (Fe_2O_3) on the Earth's surface. This electron flux from solar emanations dominates earth biochemistry at various levels on the Earth's surface, from the depth of the oceans (anoxic environments) to the continents (oxidative environments), generating availability of bioenergy that can be used for growth by both organisms and organs.

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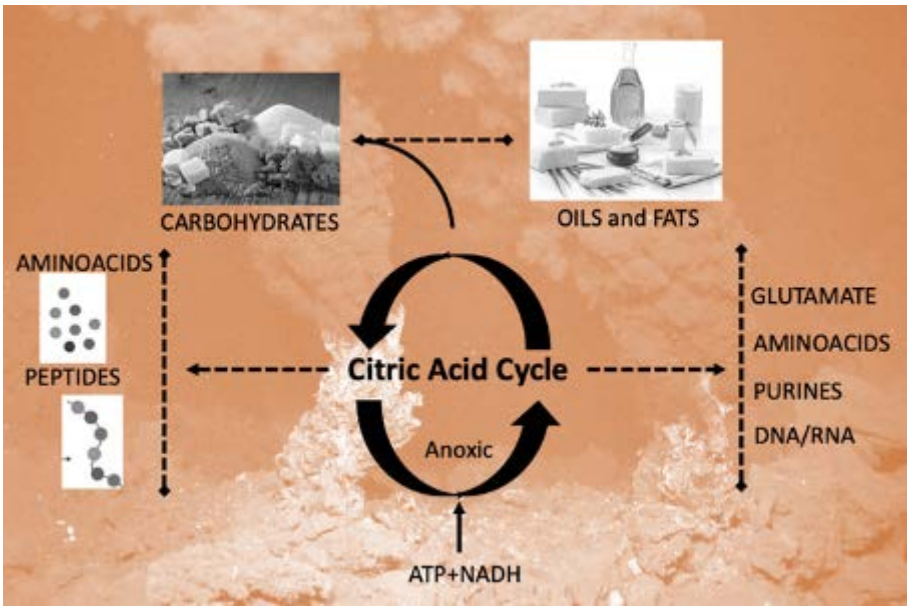
The resulting abundance of O_2 in the atmosphere likely promoted the survival of organisms capable of tolerating the toxicity associated with oxygen (damaging free-radical reactions) and favoured cellular mechanisms that could convert the gas safely and use it to extract energy. With time, oxidative phosphorylation developed into aerobic respiration, with the symbiotic merger of cells with the once free-living α-proteobacteria that then became the mitochondrion (Gray et al., 2001). In turn, thanks to its comparatively high ATP yield, aerobic respiration has been argued to have favoured the evolutionary transition from unicellular to multicellular organisms (Pfeiffer et al., 2001).

In bigger vertebrates, aerobic respiration then beckoned the evolution of organ systems that were dedicated to the absorption and transportation of O_2 — that is, the evolution of respiratory and cardiovascular systems (Bailey, 2019, Costa et al., 2014). Relationships between body mass and oxygen metabolism have been found in mammals (Dlugosz et al., 2013), gastropods (Marsden et al., 2011), and in insects, where experimental manipulation indicated that growth and size depend on the relative scarcity or abundance of oxygen (Harrison et al., 2010). It has also been argued that an increase in the abundance of atmospheric oxygen may have contributed to the evolution of larger mammals by facilitating placental mammal reproduction (Falkowski et al., 2005). Here, we argue that oxygen also played a pivotal role in the expansion of the human brain beyond body size - specifically, in the expansion of the human transmodal association cortex.



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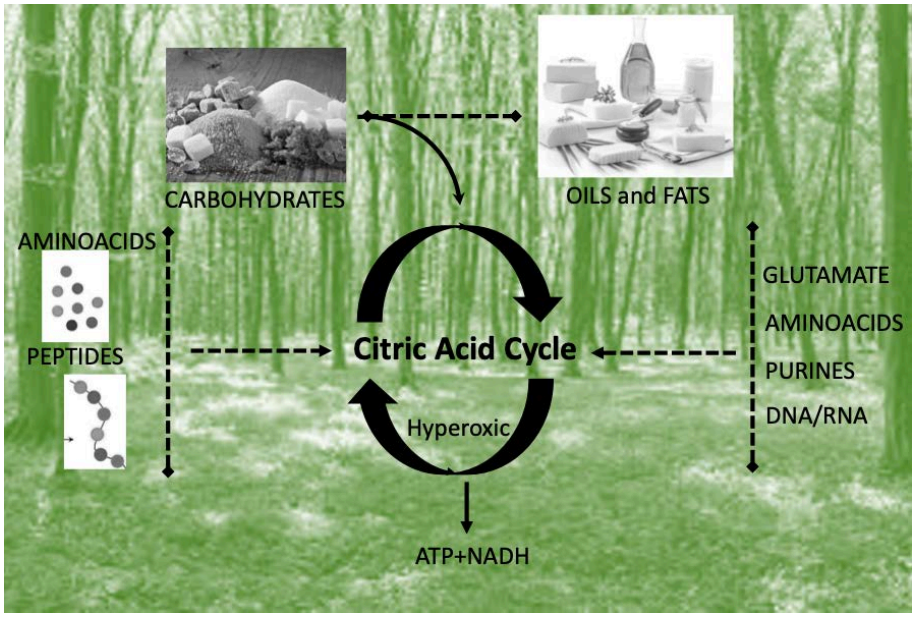

Figure 3: Opposite directions of the citric acid cycle depending on environmental conditions. Top: In anoxic environments with high temperatures (such as the ones found in deep sea alkaline vents) the citric acid cycle functions in anti-clockwise manner, fixating hydrogen on carbon chains and hence producing the basic constituents of life — including carbohydrates, aminoacids, and fats. **Bottom**. In the oxidative environments with low temperatures (such as on the continents) the citric acid cycle functions in clockwise fashion, oxidising carbohydrates, proteins, and fats. This fixates the excess O2 in the atmosphere into CO2 and releases of energy in the form of ATP. This can be seen as a primordial form of the citric cycle (also known as the 'Krebs cycle' or tricarboxylic acid cycle, TCA) that is the core motor of all metabolic reactions.

Non-allometric cortical expansion induces lower oxygen tension

The brain relies primarily on oxidative metabolism of glucose in order to extract ATP and fund its extravagant energetic expenditure - about half of which relates to synaptic transmission (Harris et al., 2012), with recent multimodal evidence revealing a positive association between regional glucose metabolism and synaptic density, as measured by synaptic vesicle glycoprotein 2A binding (van Aalst et al., 2021). However, as an entirely aerobic organ, the brain does not store glucose or oxygen, and hence it requires a constant supply of both (from the blood). Indeed, brain cells efficiently makes use of the full amount of oxygen delivered, as demonstrated by the fact that although some glucose is lost back into venous circulation in the form of lactate, all oxygen delivered to the parenchyma is disposed only in the form of CO_2 (Sonnewald, 2014). For this reason, brain growth and expansion require increased oxygen and glucose delivery through matching increases of cerebral blood flow (CBF) and vascular capacity (Seymour et al., 2016), which is accompanied by a higher efficiency in the development of brain circuitry (Herculano-Houzel, 2011, Levy and Baxter, 1996).

Although allometric relations are generally stable within each taxon, the upward divergence of the human brain with respect to other primates suggests that the oxygen tension (i.e., partial pressure of oxygen, reflecting the balance between local oxygen delivery and consumption) may be lower in the extra tissue of

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the evolutionarily expanded cortical regions. This is suggested by the following evidence: (i) allometric scaling relations are determined by the capacity of vascular systems to deliver nutrients (West, Brown & Enquist 1997); (ii) there is a strong relationship between oxidative metabolism and microvascular density (Keller et al., 2011, Weber et al., 2008), with non-primary cortical areas being similar in microvascular architecture, having lower density than primary visual, somatosensory or auditory areas (Schmid et al., 2019). Supporting this evidence from post-mortem and animal studies, a recent high-resolution atlas of the human brain's venous vasculature obtained from in-vivo 7T MRI indicates that the highest levels of vascular density are found in the insula and primary visual and auditory cortices (Huck et al., 2019). Hence, since it does not appear that vascular efficiency is increased in the human association cortex, circulation is then not able to provide the same amount of oxygen for unit volume for the tissue exceeding the allometric ratio[5].

Thus, evolutionarily expanded cortical regions - transmodal association cortices at the top of the cortical hierarchy - should be characterised by lower oxygen tension than the primary sensory and motor cortices; this is because all oxygen is already used efficiently and the extra tissue cannot rely on oxidative phosphorylation to extract energy from the remaining glucose provision, which exceeds oxygen availability. Consequently, evidence indicates that association cortices are especially rich in aerobic glycolysis, the metabolism of glucose outside of oxidative phosphorylation, by fermenting glucose into lactate[6] (Glasser et al., 2014, Goyal et al., 2014, Vaishnavi et al., 2010).

This regional difference in oxygen tension may explain how the human cortical hierarchy becomes established by regulating cytoarchitecture. Specifically, oxygen tension has been shown to regulate proliferation, differentiation, and maturity of glia and neurons from pluripotent stem cells (PSCs) in the developing brain (Simon and Keith, 2008). On one end, relatively higher oxygen tension seems to favour the growth of neurons and oligodendrocytes, with consequent increase in intracortical myelination, which is most pronounced at lower levels of the human cortical hierarchy (Burt et al., 2018). Relatively lower oxygen tension instead seems to rebalance the cell *milieu* away from myelinating oligodendrocytes and towards astrocytes (Xie et al., 2014, Yang et al., 2018) which support glucose transport and metabolism (Pellerin and Magistretti, 1994). Thus, by regulating the type of cells that develop in a given region, oxygen tension contributes to

[5] Note that there is considerable heterogeneity in oxygen levels within the body (21% O_2 in the atmosphere, 14% O_2 in the alveolar air, 12% O_2 in the arterial blood and 5.3% O_2 in venous blood), with a mean of 3% O_2 in tissues. In the mammalian brain, interstitial tissue oxygen levels are low and non-uniform, ranging from ~1 to 5% (Lahiri et al., 2006).

[6] In the human brain, aerobic glycolysis at the regional level is revealed by in-vivo PET scanning with radiolabelled glucose and oxygen to estimate a molar ratio between their respective metabolic consumption: if all glucose is metabolised through oxidative phosphorylation to produce CO_2 and H_2O, then a 6:1 ratio should be observed between oxygen consumption and glucose metabolism, whereas a lower ratio indicates that some of the glucose is not being oxidised (Vaishnavi et al., 2010).

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establish higher aerobic glycolysis at the top of the hierarchy, and higher myelination at the opposite (lower) end of the hierarchy.

Aerobic glycolysis promotes synapse growth and neoteny

Both aerobic glycolysis and myelination have important consequences for brain function, specifically in terms of how they regulate synaptic plasticity. Mechanistically, the capacity for ongoing learning throughout development and into adulthood — a key feature of human cognition — needs to be supported by persistent synaptic plasticity and synaptic turnover. This, in turn, requires constant availability of biosynthetic material in order to generate new synapses and maintain existing ones. Aerobic glycolysis is well suited to satisfy this need, because in addition to generating ATP, its glycolytic process also produces glycolytic intermediates (aminoacids, lipids) which can be used as building blocks to support biosynthesis (Vander Heiden et al. 2009; Bauernfeind et al., 2014). Indeed, aerobic glycolysis correlates with transcription of genes pertaining to synapse formation and growth (Goyal et al., 2014). In contrast, myelination has been shown to inhibit synaptic growth, both through signalling and by acting as a mechanical barrier (Fletcher et al., 2021). Prefrontal and associative cortices present distinct mRNA profiles that are enriched in the synaptic, dendrite, somatodendritic compartments and the perikaryon and neuron projection terminus components (Petanjek et al., 2011; Wei et al., 2019). Post-mortem tissue analyses (Jacobs et al. 2001) and in-vivo imaging (Finnema et al., 2016; Shafee et al., 2015) have demonstrated that the same cortices contain the lowest myelin density for the whole of the neocortex and the highest synaptic density. At this stage, we note that heavily myelinated areas function as redundant (parallel) processing modules; on the other hand, myelin-poor/synaptic-rich neural tissues are also richer in connections and highly plastic, and function as integrating cores (we will elaborate on these points in the following sections) (Luppi et al., 2020).

From a developmental perspective, the adult brain emerges as the result of two separate phases of neurodevelopment. In the first prenatal phase, modulation of brain growth arises largely from neurogenesis. Aerobic glycolysis occurs in rapidly dividing progenitor cells in the embryonic brain, such as the neural progenitors that are especially abundant in humans (Namba et al, 2021). The postnatal period instead involves a critical period of growth largely driven by experience-dependent formation of neuronal connections, which appears to involve neuronal arborization and synaptogenesis but also pruning, gliogenesis and myelination. However, these processes are not uniform across the cortex: in particular, association cortices of the human brain appear to be characterised by the persistence of these developmental features and processes into adulthood (“neoteny”) (Somel et al., 2009, Somel et al., 2011, Vaishnavi et al., 2010). [7] Indeed,

[7] Oxygen and metabolism play more than one role in neurodevelopment: evidence from rodents indicates that reactive oxygen species mediate adult hippocampal neurogenesis in response to physical activity (Adusumilli et al, 2021). Conversely, proliferation and neurogenesis of hippocampal neural stem/progenitor cells of the mouse is impaired by a genetic mutation that compromises lipid metabolism, leading to cognitive deficits; furthermore, embryonically derived cerebral organoids also showed reduced proliferation,

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aerobic glycolysis correlates with cortical neoteny (Goyal et al., 2014). Importantly, new evidence points to metabolism, via mitochondrial maturation, as controlling the timing of brain development: oxidative phosphorylation is less prevalent and mitochondrial development slower in human cortical neurons, compared with mouse neurons (Iwata et al., 2021).

Temporally, converging neuroimaging and meta-analytic evidence indicates that aerobic glycolysis is highest during the same periods of development when synaptic growth is fastest: it accounts for more than 90% of the glucose consumed in the preterm infant brain (Goyal et al., 2014, Vaishnavi et al., 2010), decreasing to 35% in newborns (Settergren et al., 1976) and then peaks again around 5 years of age when the rate of synaptic growth is highest, before reaching adult levels at around 10% of total expenditure (Boyle et al., 1994, Goyal et al., 2014, Raichle et al., 1970). Finally, aerobic glycolysis declines with ageing (Goyal et al., 2017).

Spatially, the metabolic switch from the initial prevalence of aerobic glycolysis to oxidative phosphorylation occurs earlier in primary cortices (at the bottom of the cortical hierarchy), than in transmodal association cortices (at the top of the hierarchy), which still retain high levels of aerobic glycolysis in adulthood - reflecting the asynchronous nature of cortical neurodevelopment (Bauernfeind et al., 2014, Jacobs et al., 2001). Nearly 25% of resting glucose consumption is nonoxidative in the medial prefrontal gyrus, whereas in non-association cortices glucose oxidation is virtually the sole metabolic support (Glasser et al, 2014; Goyal et al, 2014; Vaishnavi et al, 2010). Transmodal association cortices are also those with the longest maturation times, both relative to other regions of the human brain (Gogtay et al, 2004), and relative to other primates: the synaptic density of human PFC peaks around 4–5 years of age, whereas for macaques and chimpanzees, this region already achieves peak density within the first year of life (Liu et al., 2012). Thus, even during adulthood, aerobic glycolysis may support continued synapse formation and neoteny.

possibly implicating impaired prenatal neurogenesis in the humans with the mutation (Bowers et al 2020). See Namba et al (2021) for a recent review of metabolic regulation of cortical development and evolution.

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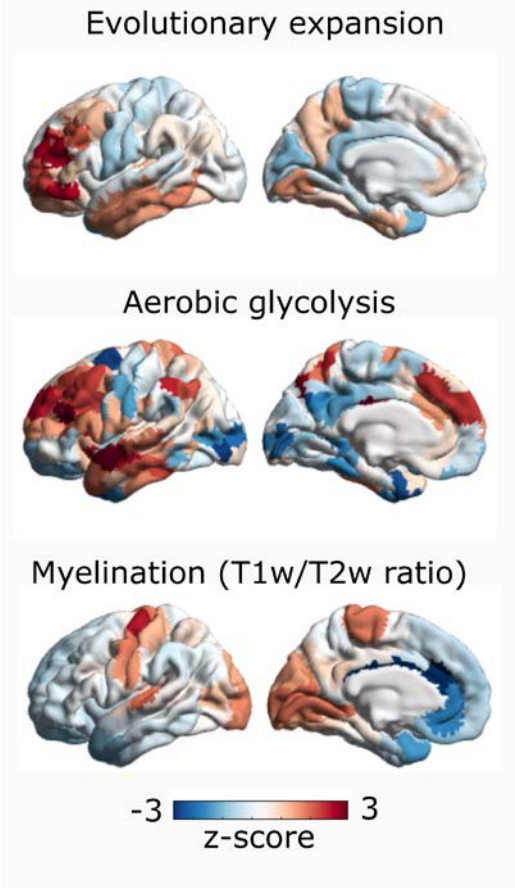

Figure 4. The most evolutionarily expanded cortical areas exhibit elevated aerobic glycolysis and low intracortical myelination. This correspondence is especially evident in lateral prefrontal and temporal cortices. The opposite pattern can be observed in primary visual and somatomotor regions, which reside at the opposite end of the cortical hierarchy and are high in myelination but low in both glycolysis and evolutionary expansion. Together, these observations support the idea that evolutionary expansion may be related to high aerobic glycolysis and low intracortical myelination, given their respective roles in facilitating and inhibiting plasticity, respectively.

In effect, the regions of transmodal association cortex exhibiting the highest rates of aerobic glycolysis are also among the most evolutionarily expanded, and they are characterised by the lowest levels of intracortical myelination – whereas the opposite is true for the sensory and motor regions at the opposite end of the brain's "archetypal axis" (Sydnor et al., 2021) (Figure 4). The adult human brain relies on aerobic glycolysis for a greater proportion of total resting glucose metabolism than other Old World primates, which also exhibit less pronounced regional differences in metabolism (Bauernfeind et al., 2014).

In summary, the evidence presented in the above sections provides the grounds for the two core tenets of our proposal (right-hand side of Figure 1):

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1. The excess growth of human association cortices exceeds the allometric capacity of oxygen delivery by the brain vascular system, causing lower oxygen tension (partial pressure of oxygen in the blood) and its compensation via increased aerobic glycolysis.

2. Oxygen tension is a key driver of cellular differentiation and maturation trajectories of different human cortices throughout development. A high oxidative metabolism in cerebellar, primary, and secondary cortices promotes myelination, which leads to efficient but rigid (e.g., less plastic) networks. In contrast, a lower oxygen tension in association cortices leads to lower intracortical myelination and favours higher rates of aerobic glycolysis, which in turn promotes a “neoteny” type of cellular milieu. As a result, association cortices at maturation are rich in synapses and still capable of supporting ongoing synapse formation and cortical growth (Figure 5 and Box 3).

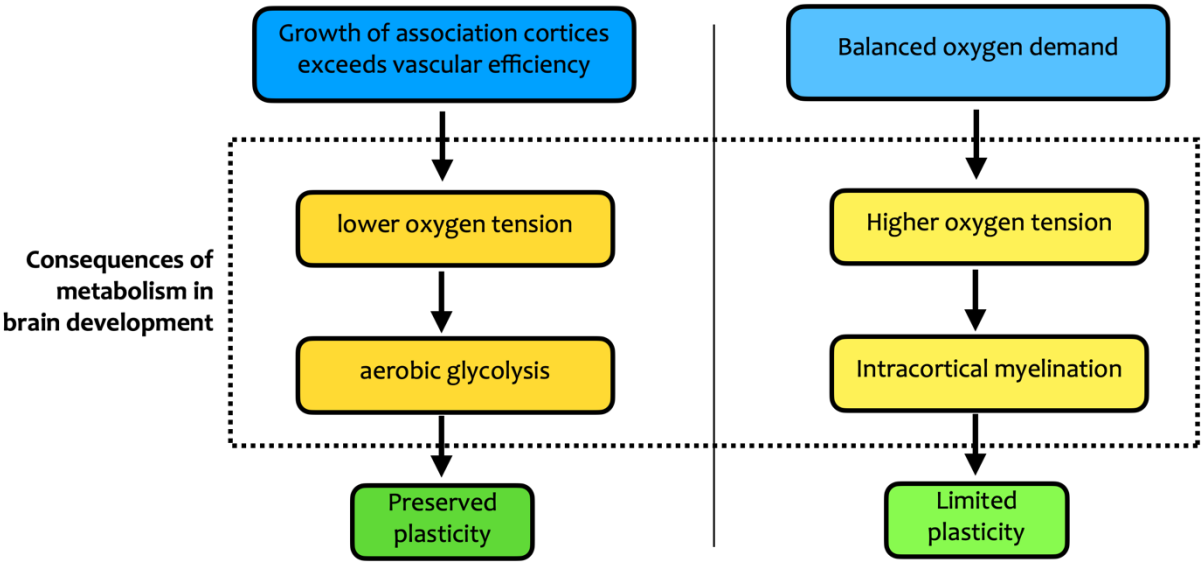

Figure 5: **The consequences of metabolism in brain development**. As outlined below, under suitable environmental circumstances this process can become a cycle, with plasticity and growth promoted by aerobic glycolysis resulting in further expansion across multiple timescales.

Box 3: Cell proliferation and the “dark side” of aerobic glycolysis

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Aerobic glycolysis is associated with cell growth and proliferation across a variety of contexts (Vander Heiden, et al, 2009; Lunt and Vander Heiden, 2011). Although fermentation of glucose into lactate is less energy-efficient than oxidation in the mitochondria, aerobic glycolysis allows for up to 100-fold faster rate of glucose metabolism than oxidative phosphorylation (Pfeiffer et al. 2001; Liberti and Locasale 2016). Since many unicellular organisms rely on fast proliferation to outcompete other cells, the faster metabolic rate of aerobic glycolysis makes it an appealing metabolic strategy even in the presence of abundant oxygen (Lunt and Vander Heiden, 2011). Such a strategy is unfortunately also adopted by malignant cells (Venneti and Thompson, 2017). Cancer cells are notoriously glucose-hungry, and rely predominantly on glycolysis to metabolise the additional glucose they consume (Lunt and Vander Heiden, 2011). In fact, the propensity of tumours for glycolytic fermentation of glucose into lactate even when oxygen is available (known as the "Warburg effect") was documented nearly a century ago (Warburg, 1924; 1956; DeBerardinis and Chandel, 2020; Liberti and Locasale, 2016).

In light of this evidence, it is not surprising that recent investigations indicate a link between aerobic glycolysis and glioma. High-grade gliomas exhibit the Warburg effect (Cairns et al., 2011; Koppenol et al., 2011), with elevated glycolysis mirroring the rate of tumour proliferation (Vlassenko et al 2015) and a recent report indicating that elevated expression of glycolytic genes corresponds to lower survival in high-grade glioma patients (Stanke et al 2021). Additionally, evidence from a large sample of patients indicates that gliomas tend to occur most commonly in temporal and especially frontal association cortices (Mandal et al., 2020). Thus, although here we focus on the effects of aerobic glycolysis in the context of healthy brain development and cortical expansion, the same metabolic process can also underpin pathologic runaway proliferation. Intriguingly, a recent study indicated that synapse-rich regions of high metabolic activity are also especially vulnerable to inflammation associated with depression, due to permeability of the barriers (Althubaity et al., 2022) – pointing to a broader vulnerability of these regions, and raising the additional question of how the human brain balances the costs and benefits of aerobic glycolysis.

Part II: From cortical expansion to cognitive evolution

The arguments presented so far suggest that the high level of cortical expansion observed in specific regions of the human brain may have been driven by regional differences in oxygen tension and aerobic glycolysis, resulting in non-uniform patterns of myelination versus plasticity across the cortex. However, this leaves two important open questions. (i) Are these disproportionately expanded regions, rich in aerobic glycolysis, a

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suitable candidate for explaining humans' sophisticated cognitive capabilities? If so, then (ii) what is a plausible account explaining how such expansion was selected for?

The second part of our exposition addresses each of these questions in turn. Our proposed explanation lies on "virtuous" feedback cycles entangling biological and social aspects. A core idea in our proposal is that the social environment has the potential for becoming continuously more complex, presenting an "arms race" for individuals in which improvements in affective-cognitive abilities can provide progressively more benefits. We then outline a potential path to "pay the energetic bill" for the metabolic expenditure of evolutionarily expanded regions, based on these regions' involvement in social cognition.

The benefits and costs of cortical expansion

One plausible candidate to explain how evolution resulted in cortical expansion is the additional cognitive capacities made possible by expanded association cortices and their elevated, persistent synaptic plasticity. We argue that by providing a substrate to support flexible learning, both from one's own experience and in terms of social learning (Boyd et al., 2011), brain plasticity makes it possible to survive and thrive in a wide range of complex environments – e.g., characterised by rapid climactic fluctuations, which may have been a driver of hominin evolution by requiring flexible foraging strategies (Potts et al., 2020).

Evolutionarily expanded transmodal association cortices are located at the anatomical confluence of multiple distinct information streams (Mesulam, 1988), being placed at the top of the cortical hierarchy — maximally distant from primary sensorimotor cortices — and associated with high-level cognition across a variety of neuroimaging tasks (Margulies et al., 2016, Fox et al., 2020, Sydnor et al., 2021). Recent evidence further indicates that the most evolutionarily expanded regions of the human cortex are especially well-suited to support integrative processes, because they are the best suited to exploit the synergy between multiple sources of information (Luppi et al., 2020; Mediano et al., 2019, Williams and Beer, 2010). Recent evidence also indicates that the human brain exhibits a higher proportion of synergistic interactions between its regions than the brains of macaques (Luppi et al., 2020).

Crucially, post-mortem transcriptomic evidence and in-vivo PET imaging converge to indicate that regional synergy also correlates with synaptic density and aerobic glycolysis (Luppi et al., 2020). Thus, evolutionarily expanded regions of the human brain that are high in aerobic glycolysis also coincide with synapse-dense regions that have the highest capacity to leverage synergistic information. Being endowed with ongoing plasticity and little myelination thanks to their elevated rate of aerobic glycolysis, these regions are ideally poised to provide the human brain with the flexibility required to master a variety of challenges, by leveraging the synergy between different information streams.

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However, plasticity is not without costs (DeWitt et al., 1998). In the brain, evolutionarily expanded regions are disproportionately expensive in terms of energy, owing to their reliance on aerobic glycolysis for their metabolism. This is because aerobic glycolysis is an inefficient way of extracting energy from glucose: it produces only 2 ATP molecules from each molecule of glucose, whereas oxidative glycolysis would produce 30 (Berg et al., 2002). This suggests that the process of cortical expansion leading to aerobic glycolysis should have happened in a context where less efficient methods to extract energy are still viable – whether because sources of energy were not overly scarce, or because cooking made it possible to extract more calories from food (Herculano-Houzel, 2016).

Building on this, it is reasonable to argue that such a process would critically rely on a scenario where the organism has access to plenty of energy, e.g., via a suitable diet. Over the course of human evolution, diverse sources of nutrients have featured in the diet of humans (Wrangham, 2013), which may have influenced brain expansion by providing the required energetic or biosynthetic supply (Namba et al., 2021). As an example of the potential relevance of diet, frugivory (nutrition based on fruit rather than leaves, which is therefore higher in energy-rich sugars) has been found to correlate with brain size across species (DeCasien et al., 2017), possibly by providing support for higher energetic turnover during development and beyond, while also reducing the amount of resources required for digestion (Isler and van Schaik, 2009, Pontzer et al., 2016).

Even if the environment provided the means for extracting sufficiently high amounts of energy, we still face the question of how the same environment also selected for expansion to occur. We address this question by building on the "social brain hypothesis" literature, which argues that evolutionarily expanded regions of the human brain appear to subserve key functions for successful social interaction, and we outline how this may have provided a path to "pay the energetic bill" for these regions' metabolic expenditure [8].

Cortical expansion and complex social dynamics: A virtuous cycle

Evolutionarily expanded regions exhibit remarkable overlap with the so-called "social brain", i.e., the set of regions pertaining to the understanding, predicting, and manipulating others' mental states ("mentalising", or "theory-of-mind"), a skill that is argued to be particularly sophisticated in humans compared to other

[8] We emphasise that the socially-focused account outlined here should be understood as a "minimal working example", rather than a definitive explanation encompassing all possible relevant factors. For instance, physical exercise influences both the extent and spatial distribution of brain oxygenation in rodents (Lu et al, 2020) and it is also known to induce neurogenesis in rodents (Overall et al., 2013). In humans, cross-sectional and interventional evidence associate aerobic exercise in older adults with greater cortical and whole-brain volume, as well as increased grey matter volume of lateral temporal and prefrontal cortices (Raichlen & Alexander 2014). It has been argued that the shift to hunter-gatherer diet imposed increasing demands for endurance running on *Homo erectus* (Raichlen & Alexander 2014). Therefore, this increase in physical activity and its effect on regional oxygenation may also have played a role in the oxygen-dependent expansion of human association cortices - a hypothesis that warrants further investigation, especially given the well-established positive effects of physical exercise on mental health and cognitive aging (Raichlen & Alexander 2014).

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primates (Saxe, 2006). The regions supporting mentalising include temporo-parietal junction and medial prefrontal cortices, which are also part of the brain's high-synergy "default mode" network (DMN) (Raichle et al., 2001; Dohmatob et al., 2020; Sallet et al., 2012) (Figure 6). Changes in functional connectivity within the DMN and structural changes in white matter tracts connecting DMN nodes have also been shown to correlate with the size of an individual's social network (Noonan et al 2018). Regions belonging to the DMN have been shown to exhibit correlated activity across different individuals observing the same movie (Yeshurun et al., 2021). Crucially, however, this similarity of DMN activity is dependent on the social distance between the individuals in question, being strongest between friends, weaker in friends-of-friends, and virtually absent beyond that (Yeshurun et al., 2021). Neurons have even been identified in dorsomedial portions of the DMN that not only monitor another's action to guide your own (Yoshida et al 2011, 2012) but also predict an opponent's behaviour (Haroush & Williams, 2015). These observations suggest that DMN regions (which are evolutionarily expanded in humans) may support humans' ability to predict the mental states of their closed associates in response to a given event, which is a key requirement for successful social coordination. Indeed, even when matched in terms of general cognitive skills, human children display far greater skill at social cognition than chimpanzees or orangutans (Herrmann et al., 2007).

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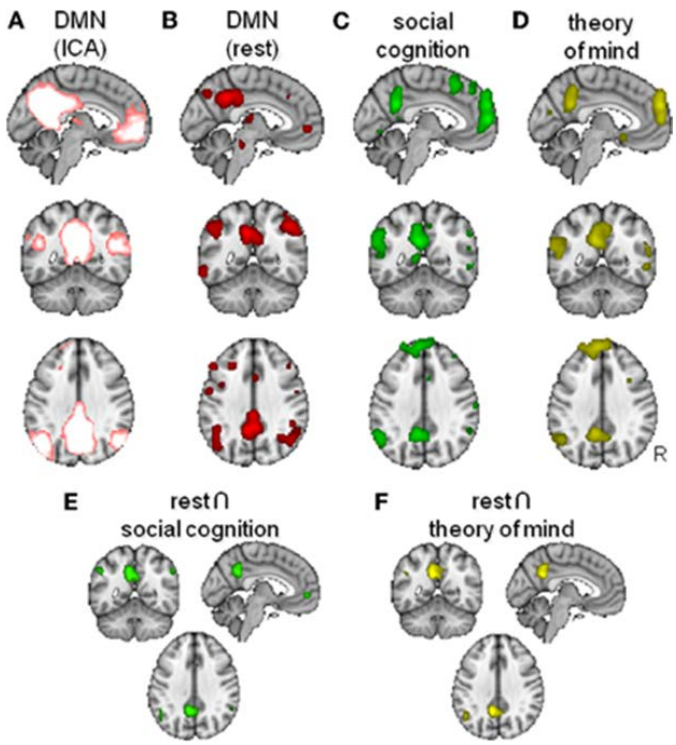

Figure 6. Overlap between the DMN and the "social brain". (Figure from Mars et al., 2012).

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Building on this intriguing overlap, the "social brain hypothesis"[9] posits that the necessity to navigate complex social dynamics within the group and with out-group conspecifics (Ashton et al., 2020) would have exerted evolutionary pressures that favoured the ability to interpret, predict, leverage and manipulate other individuals' behaviour – and the consequent growth of associated cortical structures (Humphrey, 1976; Byrne and Whiten, 1989; Whiten and Byrne, 1997). Dealing with such interactions extends the range and diversity of cognitive abilities that are required from a given individual, thereby contributing to the development of progressively more domain-general and flexible cognitive capacities (Humphrey 1976). In turn, as proponents of the social brain hypothesis have long argued, there is a deep analogy between inferring others' mental states as causes of their actions and inferring unobserved causes of observed effects; similarly, predicting others' behaviour based on their inferred mental states involves the same kinds of processes required for more general causal reasoning (Molapour et al. 2015). Additionally, cooperation allows social animals like primates to engage into more elaborate strategies for gathering food. Interestingly, this fits well with the so-called "clever foraging hypothesis" (Striedter, 2004), which posits that highly encephalised species tend to forage or hunt strategically (i.e., leveraging the target's properties or habits), while less encephalised species tend to gather food opportunistically.

Another key opportunity of living in groups is the possibility to learn from conspecifics over developmental rather than evolutionary timescales (Molapour et al., 2015). Living with a group of conspecifics offers the opportunity for cumulative intergenerational learning — at which humans are especially successful thanks to language — and to learn from others' mistakes, rather than one's own, while benefiting from their successes (Whiten, 2005). As Boyd et al (2011) argued, the capacity to learn from each other "enables humans to gradually accumulate information across generations and develop well-adapted tools, beliefs, and practices that no individual could invent on their own", representing an essential element of humans' ecological success. This kind of learning is ongoing rather than one-off, both across generations and during one's lifetime – thereby benefiting from the ongoing plasticity of transmodal association cortices.

In summary, cooperating as part of a group provides greater capacity to obtain resources, while being able to form alliances and out-manoeuvre rivals in the group ensures a greater share of such resources for oneself and one's offspring. Through this arms-race dynamic, the social environment has the potential for becoming continuously more complex as each generation's skills at group politics and navigating social interactions grow, presenting a scenario wherein increased ability to negotiate with and benefit from others can keep getting advantageous. For this reason, we conjecture the existence of a feedback cycle between brain plasticity within the social brain areas and more complex social dynamics (see Figure 7).

[9] Also known as the "Machiavellian intelligence hypothesis". This line of reasoning has been extended by the more recent "Napoleonic intelligence hypothesis" (Ashton et al., 2020).

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Indeed, there is within-species evidence in both humans and rhesus macaques indicating that expansion of the cortical regions related to social cognition (which in humans are also among the most evolutionarily expanded) covaries with social group size, and may be brought about by increased social complexity. For example, early work from Bickart and colleagues (Bickart et al., 2011) reported that the size of a person's social group (as indicated by the number of their contacts on the social network Facebook) correlated with thickness in prefrontal cortex (PFC) and anterior cingulate cortex (ACC). The size (grey matter volume) of human DMN regions is also predicted by an individual's skill at theory-of-mind tasks (Powell et al., 2014, Powell et al., 2010), which itself also correlates with number of friends (Powell et al., 2012, Stiller and Dunbar, 2007), thereby offering connections between group size, social cognition, and size of the corresponding brain regions. Analogous results also extend to other primates (Devaine et al., 2017), which in addition provide causal evidence supporting that social network size influences regional grey matter. For example, Sallet and colleagues housed macaques in groups of different size, and found that animals housed in larger social groups exhibited increased grey matter in PFC and superior temporal sulcus (STS) — regions of the macaque's "social brain" (Sallet et al., 2011). Additionally, the thickness of these regions was also found to positively correlate with the animal's social status within the group (Noonan et al, 2014). More recently, an association was also observed across primates between the number of cortical neurons and social complexity (indexed by size of the social group) (Yokoyama et al 2021), providing converging evidence not only within, but also across species.[10] Taken together, these results provide evidence for a link between the opportunity and need for greater skill at social cognition and cortical size of regions involved in it.[11]

A second virtuous cycle: metabolism, expansion and cognition

In turn, our metabolic/biosynthetic lens also provides another key insight about the relationship between cortical expansion and cognitive demand. In addition to the cortical midline structures of the DMN, transmodal association cortices also include lateral frontal and parietal cortices, broadly part of the so-called fronto-parietal control network (FPN). Whereas the DMN is recruited by social cognition (as well as other situations

[10] Additionally, the social environment is known to be particularly salient during adolescence, when higher-order regions of the "social brain" are still maturing, which may account for further interdependencies between the two (Sydnor et al., 2021).

[11] To be clear, this evidence pertains to changes within the lifespan rather than across evolution, and it does not tell us whether such association was in fact also selected over evolutionary timescales — although this account is compatible with the evolutionary expansion of the same regions. Nevertheless, it does tell us that a more complex social environment may directly promote the expansion of these regions in the primate brain.

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that require transcending the here-and-now), the FPN is engaged by cognitively demanding tasks, such as focused attention or working memory (Duncan, 2010; Zanto and Gazzaley, 2013) [12].

Since DMN and FPN activation is typically inferred from functional MRI, this means that the most expanded regions are also those that most increase their consumption of oxygen and glucose in response to social engagement or cognitive demand. Importantly, these regions are also those where glucose most exceeds the availability of oxygen for oxidative metabolism. Thus, although activation (e.g., due to engaging in social cognition or a difficult task) leads to more oxygen being brought to these regions, their metabolic demand exceeds this delivery of oxygen, meaning that they need to rely on aerobic glycolysis to an even greater extent than usual in order to extract the required energy from glucose. Indeed, evidence indicates that in instances of acute metabolic demand such as functional activations, the expansion of oxygen consumption is quite limited and is outstripped by greater glucose delivery, sometimes in excess of the metabolic demand (Paulson, 2010).

As we have argued in the first part of this article, oxygen is more than just fuel for neuronal activity: aerobic glycolysis generates biosynthetic materials as a by-product. As a result, by increasing aerobic glycolysis in evolutionarily expanded association cortices, engagement in social interactions and cognitively demanding activities will increase in these regions the availability of biosynthetic materials that are required for synapse formation and turnover. Taken together, this means that engaging with a socially rich and challenging environment provides both (i) an occasion to learn (from complex and challenging experiences and other beings); and (ii) increased availability of biosynthetic material to support this learning at the neural level. Crucially, this availability occurs in the regions that are most plastic, that are involved with integrating multimodal information, and that play a prominent role in supporting social cognition and cognitive control.

Therefore, to benefit from the opportunities it offers, the individual will need ongoing capacity for learning: that is, ongoing plasticity. As we have argued, this is precisely what is available in evolutionarily expanded association cortices, which exhibit:

(i) a high capacity to integrate multimodal information;
(ii) transcription of genes pertaining to synapse formation, and low levels of plasticity-inhibiting intracortical myelination;
(iii) the biosynthetic material required to enact synapse formation and turnover, made available as a by-product of aerobic glycolysis.

In turn, a virtuous cycle also exists between learning and evolution: although what is learned by the phenotype cannot be transmitted to the genotype, the capacity for flexible learning can provide a path for evolution in

[12] Note that the distinction is not clear-cut: see Vatansever et al (2015a,b) for evidence of DMN involvement in cognitive tasks, and Jackson et al. (2022) for evidence suggesting FPN rather than DMN involvement in social cognition.

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environments where no viable evolutionary path is available for non-learning organisms (Hinton and Nowlan, 1987). Indeed, computational work has shown that for complex evolutionary searches, this fact can provide a considerable boost to evolutionary time-scales, because a learning trial is enormously less time- and energy-consuming than the production and evaluation of an entire de-novo organism (Hinton and Nowlan, 1987). The invention of cooking, and its proposed role in overcoming the energetic barrier to neuron count and brain expansion (Fonseca-Azevedo and Herculano-Houzel, 2012) may be seen as a prominent example of learning shaping evolution. Intergenerational learning thanks to group life and language provides humans with a further multiplier of this powerful adaptation (Boyd et al., 2011).

The broader virtuous cycle: expansion and evolution

Overall, we now have converging reasons to explain why networks of transmodal association cortices would have been the focus of selective pressure. First, they support ongoing learning – both from one's own experience and from others. Second, they enable the individual to navigate a complex social environment. In turn, our oxygen-focused perspective provides a neurobiological account of how a socially and cognitively enriched environment contributes to a differential development of the two ends of the cortical processing hierarchy: activity in response to social and cognitive demand increases aerobic glycolysis at the higher (associative) end of the cortical hierarchy — making available additional biosynthetic material and contributing to plasticity and ongoing learning.

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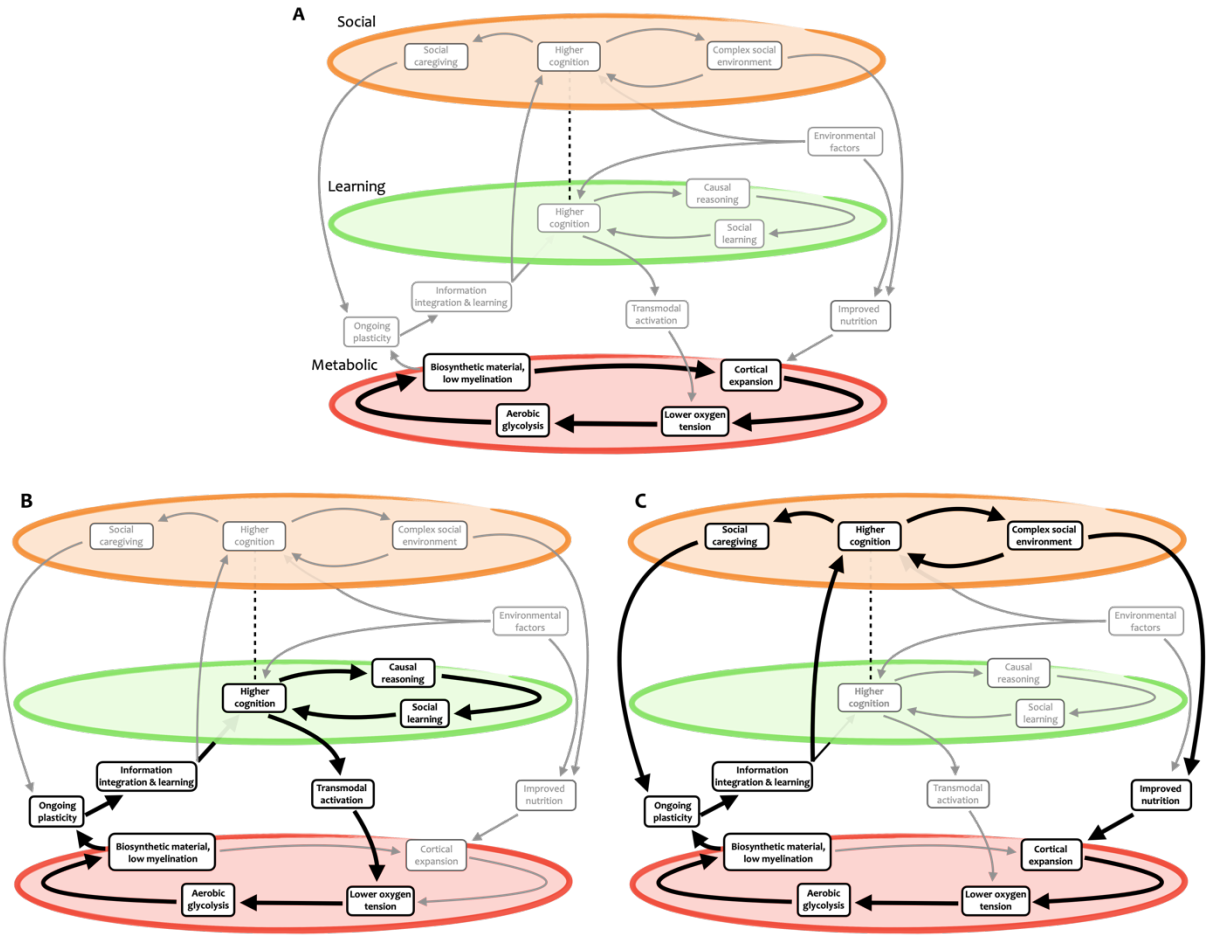

Figure 7. Nested virtuous cycles supporting human brain expansion. Different cycles and sub-cycles are highlighted, including ones involving metabolic (A), learning and cognitive (B), and social (C) aspects. Note how some elements participate in multiple cycles at different scales. While these paths are highlighted for illustration purposes, we emphasise that more paths through this complex system could be devised, possibly representing hypotheses yet to be formulated and tested.

Importantly, the prolonged period of immaturity that accompanies the development of a highly plastic brain is made affordable by being part of a group, which can provide essential protection for juveniles from predators. Additionally, being part of a group that hunts and gathers food together provides access to a more diverse and higher-quality nutrition, which is required to fuel high cortical metabolism and enable cortical expansion. Finally, being part of a group provides ample opportunity for intergenerational learning and for acquiring and practising social cognition skills. The conjunction of all these elements sets a broader “virtuous cycle” that brings together brain expansion, cognition, and evolution, constituting the core of our account (see Figure 1)[13].

[13] Needless to say, our account is inevitably an oversimplification of the immensely rich and complex web of interactions between metabolism, expansion, social cognition, and evolution. As just one example, under conditions of maternal immune activation resources and energy are switched in the fetal brain to protection from inflammatory insult, and recent

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Conclusion

Aerobic glycolysis was recently dubbed “a mystery in neuroscience” (Theriault et al., 2021). In this manuscript we proposed to turn this statement on its head, and use aerobic glycolysis to make sense of another mystery: the evolution of the human brain. The account sketched here proposes that the apparent uniqueness of humans’ cognitive capacities may be best understood as emerging from nested “virtuous cycles” involving several mutually supporting factors — metabolic, molecular, and behavioural, in the context of a favourable environment. Correspondingly, this view posits that what is unique to humans might be not any of these individual factors, but rather be the unique interaction between the three.

Under this perspective metabolic fixation of O_2 on carbon generates energy and a tendency towards growth. In the case of the human cortex, the expansion of neocortical regions went beyond what is expected from allometric growth, making them reliant, in part, on aerobic glycolysis as a metabolic pathway, which generated conditions for neoteny and protracted plasticity. This, in turn, enables the integration of complex information and continuous learning, supporting greater flexibility in response to the environment and its cognitive challenges, leading to a rich social environment. A socially complex and cognitively stimulating environment provides the opportunity for ongoing learning and cognitive flexibility to become advantageous, while also requiring greater activation of the association cortices subserving high-order cognition, resulting in greater aerobic glycolysis in these regions and, as a by-product, increased availability of biosynthetic materials for synaptic growth and turnover. Additionally, a more complex social organisation affords several benefits, including protection during a protracted development period, inter-generational learning, and improved nutrition to fuel the metabolic demands of plastic expanded cortices.

By embracing complexity, we also acknowledge that the account presented here is inevitably incomplete: not only could there be additional paths connecting the various elements of Figure 1 (as outlined in Figure 7); but additional elements will almost certainly also need to be considered, in order to provide the full picture. We also acknowledge that the account provided here has been decidedly cortico-centric, and that extending this account to subcortical structures will be an important next step. Of particular interest for future developments is the role of the cerebellum: the cerebellum displays one of the lowest rates of aerobic glycolysis, yet ultra-high-resolution neuroanatomical investigation of human and monkey specimens suggests that the human cerebellum has expanded its surface area even more than the cerebral cortex (Sereno et al., 2020). Abnormal

evidence indicates that mice exposed in utero to MIA have low social preference index and this may be the strongest (although not the only) predictor of susceptibility (Mueller et al. (2021)). In the frontal cortex of these susceptible animals there is also down-regulation of mitochondrial and metabolic pathways. Thus, the rich interplays between these aspects are not confined to the evolutionary scale, but rather they occur across diverse timescales.

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cerebellar function is also associated with a multitude of psychiatric and neurodegenerative disorders (Moberget and Ivry, 2019; Gellersen et al., 2017, 2021; Argyropoulos et al., 2019), and prefrontal-projecting cerebellar lobules are especially expanded in humans relative to other primates, suggesting potential interplay between cerebellar and cortical expansion (Balsters et al., 2010).

The account presented here may be relevant for the novel framing of further studies of neurodevelopmental disorders and mental health. For example, metabolism and vascular health are already well-known factors underpinning psychiatric disorders (Baruah and Vasudevan, 2019, Meier et al., 2013, Sukumar et al., 2020, Turkheimer et al., 2020). By emphasising the role of metabolism in controlling growth and cellular composition during brain maturation (Iwata et al., 2021), this model points to a clear need for imaging technologies able to assay blood flow as well as oxygen and glucose metabolic rates in very young cohorts. Hence, experimental metabolic modulation should be added to current advanced organoid research (Notaras et al., 2021) both to illustrate how metabolic deficits may precipitate genetic risks for mental or degenerative disorders, or how enhanced metabolism may recover genetic phenotypes. There is also evidence that respiratory complications and hypoxia are associated with increased rates of psychosis (Kalucy et al., 2013; Partti et al., 2015), which can also be induced acutely by extreme altitude (Hüfner et al., 2018) — pointing to further promising lines of investigation about natural or induced variations in oxygen supply to the brain. Metabolic therapies as well as hyperbaric treatments have shown very mixed results in the treatment of mental illness in the young (Rossignol et al., 2009, Rossignol et al., 2007, Cheng et al., 2017), but imaging assays could be used to phenotype those young patients that may best respond to these treatments as well as inform on the optimal timing of interventions along the developmental trajectory. Imaging could also provide potential insights into healthy versus pathological ageing at the other end of the lifespan.

As a second example, the mechanistic links between metabolism and cellular differentiation in development suggest that in those psychiatric disorders where there is evidence of disturbed oligodendrocyte function and myelin, not only in the developing brain - as in psychosis (Mighdoll et al., 2015) - but also in the adult brain in major depression (Takahashi et al., 2011, Williams et al., 2019), the underlying pathophysiology may be driven by disordered tissue oxygenation. More broadly, consideration of an individual's regional balance of oxygen/glucose metabolism may also shed light on the opposite end of the neurodevelopmental trajectory, e.g., neurodegenerative disorders.

Taken together, our proposal emphasises the relevance of oxygen and metabolism on brain evolution, and highlights the benefits of a complex-systems approach for integrating different perspectives about brain evolution, highlighting their complementarity and interdependence. It is our hope that this work may foster future investigations shedding further light to these promising avenues for deepening our understanding of what makes human brains unique.

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