Trends in
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Review

The metabolic costs of cognition

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Cognition and behavior are emergent properties of brain systems that seek to maximize complex and adaptive behaviors while minimizing energy utilization. Different species reconcile this trade-off in different ways, but in humans the outcome is biased towards complex behaviors and hence relatively high energy use. However, even in energy-intensive brains, numerous parsimonious processes operate to optimize energy use. We review how this balance manifests in both homeostatic processes and task-associated cognition. We also consider the perturbations and disruptions of metabolism in neurocognitive diseases.

Highlights

The brain is organized to minimize energy consumption while maximizing computation. This means that, while the brain consumes the largest proportion of energy in the body, it is remarkably energy-efficient considering its computational power.

The metabolic costs of goal-directed cognition are only 5% greater than the ongoing costs of resting neural activity and homeostasis.

Brain energy supply and use are kept in a delicate and dynamic balance. Disruption of neural energy homeostasis is associated with cognitive decline and neurodegeneration.

These considerations motivate further research into the variability of homeostatic and task-directed metabolic costs across individuals, their daily cycle, and in disease states.

Frontier molecular neuroimaging technologies provide opportunities to study brain energy metabolism with greater spatial and temporal resolution than traditional approaches.

Glucose is the primary fuel for cognition

Cognition arises from neural dynamics in large-scale brain systems and their context-dependent neuromodulation. Glucose is the primary source of energy for these processes, and provides the majority of the energy 'currency' – **adenosine triphosphate** (**ATP**;see Glossary) – to fuel neurotransmission, neurotransmitter biosynthesis, and recycling, manage oxidative stress, and maintain resting potentials (Box 1)[1,2]. To maintain brain health, the supply of glucose needs to be both reliable and scalable (i.e., efficiently up- or downregulated). Even brief disruptions of neural glucose can lead to cognitive dysfunction, seizures, neuronal death, loss of consciousness, coma, and death [1]. A significant proportion of the energy budget of the brain is spent on maintaining neural integrity and related homeostatic processes [2,3]. Neural processes that support cognition interface with these baseline homeostatic processes to shift energy utilization from restorative to proactive and responsive.

Here, we review the **metabolic costs** of cognition – that is, how glucose metabolism sustains brain functions, including core homeostasis, memory consolidation, repair, and the execution of specific cognitive tasks. We review the metabolic cost of neural homeostasis, the additional costs of task-associated cognitive processes, and the numerous strategies to optimize energy utilization. We highlight the consequences of metabolic failure in neurodegenerative disorders, and finish by surveying frontier developments in measuring and modeling neural–metabolic coupling in health and disease.

Core metabolic costs of neural activity

The capacity of the human brain to adaptively predict, process, and act on complex information comes with a considerable energy burden. Although it accounts for only 2% of body weight, the human brain accounts for 20% of its resting metabolism, more than tenfold the amount expected based on its weight [4]. This requirement is even greater at the peak of early childhood neurodevelopment when it uses up to half of the basal nutritional requirements of the body [5]to support the synaptic and glial remodeling that enables growth and learning.

All brain regions are metabolically active, but there is substantial temporal and regional variability at the tissue and systems level. The regional variability in resting cerebral glucose metabolism is partly attributable to neuroanatomy and cytoarchitecture. Neurophysiological studies demonstrate significant heterogeneity of resting metabolism between gray and white matter. Gray

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Box 1. Supply of glucose to support the energy demands of the brain

'Metabolism' refers to all the chemical reactions that provide the body with energy. Catabolic metabolism breaks down molecules into simpler ones, releasing the energy stored in the molecule. Anabolic metabolism combines simple molecules to generate more complex ones. Almost all the energy required by the brain is provided by glucose. Glucose is primarily metabolized in an oxidative catabolic reaction known as cellular respiration to produce 30–32 molecules of ATP, the energy 'currency' of the body. Cellular respiration comprises four reactions: glycolysis, the formation of acetyl-CoA, the tricarboxylic acid (TCA or Krebs) cycle, and the electron transport chain (ETC) reactions. Glycolysis, the TCA cycle, and the ETC provide almost all the ATP required for cellular activities [1,81]. Neurons rely upon oxidative catabolism of glucose for ATP generation, particularly in the cell soma [119]. Disruption of the supply of either glucose or oxygen can be catastrophic, leading to decline in function, cognition, and consciousness [1].

If glucose is not immediately required for ATP production, it can be stored in astrocytes as glycogen, ready to be resynthesized to glucose via glycogenolysis when required. However, the energy stores in the brain are extremely small in comparison to its high metabolic requirements; thus, a continuous and reliable supply of glucose is necessary to maintain neural function and cognition. Glucose enters the brain via the endothelial cells of the blood–brain barrier, primarily via the facilitative transporter GLUT1 [76] (Figure I). Once in the brain, extracellular glucose is rapidly taken up by astrocytes, neurons, and glia. Glucose can travel from the capillary to the neuron either via direct diffusion from the extracellular space or by being transported (via GLUT1) through the astrocytic end-feet that surround the capillary walls to the adjacent neuron [81]. GLUT3 is the major transporter in neurons, and has a higher affinity and transport capacity for glucose than GLUT1, thereby providing neurons with preferential access to available glucose in the brain [76].

Seventy percent of the energy demands of gray matter are associated with neuronal signaling (comprising synaptic transmission 49%, action potentials 9%, glutamate/GABA recycling 4%, presynaptic calcium activity 8%), and the remainder is dedicated to non-signaling activities (maintenance of resting potentials 20% and housekeeping needs 11%) [2]. In white matter, 18% of total ATP consumption is dedicated to signaling (comprising neuronal signaling 13%, glial calcium activity 3%, action potentials in nerves 1%), and 82% to non-signaling (resting potentials 58%, housekeeping 24%) needs [2].

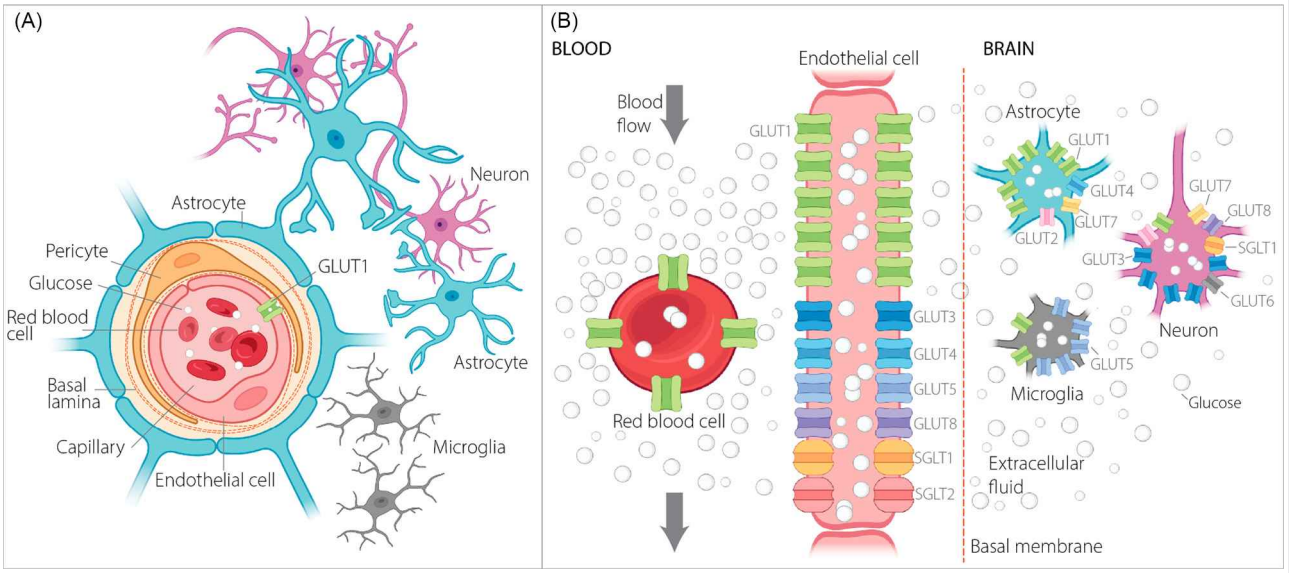

Figure I. Supply of glucose to the brain across the blood–brain barrier. (A) Cellular components of the blood–brain barrier. The blood–brain barrier is formed by the capillary endothelial cells, basal lamina membrane, and astrocytic end-feet. Figure adapted, with permission, from [120]. (B) Movement of glucose across the blood–brain barrier. Under normal physiological conditions, the concentration of glucose molecules (white spheres) is higher in the blood (4–6 mM) than in the brain extracellular fluid (1–2 mM). The high energy demands of the brain increase the transfer of glucose into the brain across the facilitative glucose transporters (GLUTs) and sodium-dependent glucose transporters (SDGTs). GLUT1 (green) is the most abundant glucose transporter, and is present on red blood cells, endothelial cells, astrocytes, neurons, and microglia. GLUT3 (dark blue) is the most abundant glucose transporter on neurons, and GLUT5 (light purple) is the most abundant glucose transporter on microglia. Figure adapted, with permission, from [76].

matter comprises the cell bodies, local axons, dendrites, and synapses that form the functional circuits of the brain, whereas white matter mainly comprises myelinated axons that support the long-range anatomical connections that scaffold these circuits into functional networks [6]. Approximately 70% of the metabolic costs of t he gray matter are concerned with neuronal

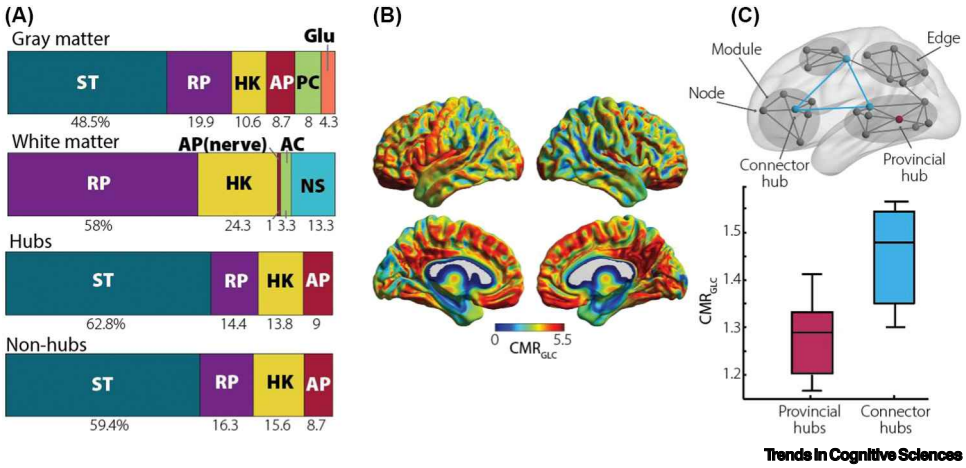

Figure 1. Regional variability in the metabolic costs of signaling. (A) Energy budgets for gray and white matter (top) plus hub and non-hub regions (bottom) derived from physiological recordings and models [2,3]. Signaling types include synaptic transmission (ST), maintenance of the resting potential (RP), housekeeping (HK), action potential (AP) and AP in the nerve (APnerve), postsynaptic calcium (PC) and astrocytic calcium (AC), glutamate recycling (Glu), and neuronal signaling (NS). Gray matter spends the largest proportion of the energy budget on synaptic transmission, whereas white matter spends the largest amount of energy on maintaining the resting potential. Within gray matter, hubs spend a larger proportion of their budget on synaptic transmission than do non-hub regions. (B). Regional variability in cerebral metabolic rate of glucose utilization (CMR_{GLC}, in units of mg/100 ml/minute) derived from 75 healthy individuals [67,68]. (C) (Top) Schematic representation of brain networks. Each region is represented as a **node** (sphere) and connections between them are edges. Subnetworks or modules are represented by shaded areas. The gray, blue, and red dots within each of the networks are nodes, the lines inside the networks are within-network edges, and the lines crossing networks are between-network edges. The red node depicts a provincial hub (that strongly connects nodes within the same network), and the blue nodes depict connector hubs (that connect nodes between different networks). Connector hubs have important and often long-range connections running through them, and connect nodes between different networks to form a rich club network. (Bottom) Consistent with evidence from physiology, hub regions have higher metabolic rates of glucose (measured as standardized uptake value ratio, SUVr) than non-hub regions. Furthermore, connector hubs have higher levels of glucose metabolism than provincial hubs. Data derived from [23].

signaling, contrasting with 18% in white matter (Box 1 and Figure 1A) [2,7]. In rodent gray matter, the postsynaptic effects of glutamate and the ensuing action potentials consume much of the energy (34% and 47%, respectively), whereas the resting potential consumes 13% and glutamate recycling uses only 3% [8].

Because the brain does not store substantial energy, regional variation in glucose concentration is limited [9]. Instead, glucose is supplied adaptively by the vasculature as needed, and its use in individual brain cells is controlled by intricate feedback and feedforward mechanisms [10]. More metabolically active regions have more capillaries and a higher cell density than less metabolically active regions [11–13], a characteristic that contributes to regional variability in the BOLD (blood oxygen level-dependent) signal captured in functional neuroimaging data (Box 2)[1,14,15]. The metabolic needs of brain networks also change across the daily cycle, and regional cerebral blood flow (rCBF) increases from morning to evening and decreases after a night of sleep, particularly in the hippocampus, amygdala, thalamus, and occipital and sensorimotor cortices [16].

The regional variability in baseline glucose metabolism reflects the presence of multiple **functional systems or subsystems** that show ongoing coherent activity regardless of immediate cognitive demands [17]. These functional networks possess coherent BOLD signal fluctuations [4] whose amplitudes are associated with concurrent glucose metabolism [18,19]. Notably, functional networks that are more active during cognitively demanding tasks such as attention, working memory, and decision-making also have higher energy costs at rest than sensorimotor networks. The interactions among these networks are highly

Glossary

Adenosine triphosphate (ATP): the nucleotide that is the source of energy at the cellular level. Energy can be both stored and used in the form of ATP molecules. The brain consumes the highest proportion of ATP in the body.
[^{18F}]fluorodeoxyglucose (FDG)-positron emission tomography (PET): [^{18F}]-fluorodeoxyglucose (FDG) is a radioactively labeled glucose analog that enters the metabolic pathway in the same way as glucose. It becomes trapped at the synapse at the phosphorylation stage of the glucose metabolic pathway, and emits a positron which is detected by the PET camera. Positron emission is used to infer where in the brain the FDG is trapped.
Functional connectivity: correlation or coherence between neurophysiological time-series from different regions of the brain. It is often seen as an indirect proxy for information transfer between these regions. A functional network approach considers the correlations between these regions as forming an integrated system rather than considering each region in isolation.
Functional system or subsystem: a set of regions that show coherent functional activity both during task and at rest. May also be referred to as a functional network or module. Canonical functional systems include the dorsal attention network, the frontoparietal network, the salience network, and the default mode network, among others.
Glucodynamics: time-varying glucose metabolism, or how glucose moves throughout the body and/or brain.
Hodgkin–Huxley model: a mathematical model of how action potentials are generated and propagated across membranes. The model attributes the change in conductance during the action potential to opening of sodium (Na^+) and potassium (K^+) channels on the neuronal membrane.
Hubs: derived from topological models of brain network organization, hubs are brain regions that show high structural interconnectedness ('degree') with other brain regions. A 'provincial' hub shows high interconnectedness with regions within its functional module; a 'connector' hub shows high interconnectedness with many different modules. Hubs are classically defined using structural connectivity, but strongly overlap with hubs in functional networks and show baseline high metabolic activity.

coordinated [20]by **hub** regions that are strongly anatomically and functionally connected, particularly to other hub regions [20,21](Box 3). The 'hubness' – the degree of interconnectivity with other regions – is associated with higher glucose cost [22], and central 'connector' hubs show higher rates of metabolism than pro vincial hubs which connect primarily within regions of the same subnetwork [23](Figure 1C). Hub regions tend to have higher neuronal and synaptic densities and firing rates [24], and spend more energy on synaptic transmission and action potentials than non-hub regions (72% versus 68%; Figure 1B) [3]. This ongoing metabolic activity forms the baseline energy expenditure of the brain, and provides a foundation for understanding how cognitive tasks reshape energy use and how the higher metabolic cost of hubs contributes to vulnerability to neurodegenerative processes, leading to cognitive impairment.

Metabolic costs of goal-directed cognition

Engaging in active cognitive and sensory processes increases cerebral blood flow (CBF), glucose metabolism, and ATP production in task-relevant regions [25,26]. Early **[^{18F}]fluorodeoxyglucose (FDG)-positron emission tomography (PET)** studies in humans demonstrated robust increases in the cerebral metabolic rate of glucose (CMR_{GLC}) in visual regions during the presentation of visual checkerboard stimuli [27]. These observations extended to somatosensory activity [28], memory [29], language [30], and tasks engaging complex cognitive processes [31]. Gamma oscillations, which are associated with information transfer within local cortical circuits, are also associated with higher glucose metabolism [32]. Notably, the increase in metabolic activity in task-relevant regions is associated with a relative decrease in the default mode regions – a regional exchange of metabolic demand that is reversed following task completion [4].

Box 2. *In vivo* measurement of the metabolic costs of cognition

Glucose use increases linearly with spike frequency [121], and the total energy cost for synaptic transmission by excitatory neurons is estimated to be 1.58×10^9 ATP/s at a firing rate of 1 Hz [2]. Microanalysis measurements in animals show metabolic flux and spike frequencies that are detectable at a sub-second scale[122]. In humans, changes in glucose signals are detectable at the scale of seconds using *in vivo* imaging. Human macroscale functional neuroimaging methods capitalize on the tight spatial and temporal coupling of neuronal signaling and oxidative metabolism of glucose to measure neuronal activity during cognition.

Deoxyglucose (2-deoxy-D-glucose, DG) is a glucose analog that is transported from the blood to the neural tissue by the same carrier system as glucose, and is metabolized exactly as glucose until the stage of phosphorylation during glycolysis (Figure I) [123]. While glucose continues along the glycolytic pathway, metabolism of DG ceases at this point in the pathway and it is effectively trapped in the tissue. By labeling DG with a radioligand, DG imaging relies upon the fact that DG remains trapped within the cell for the duration of measurement [123]. [^{14}C]-DG autoradiography [123] and the more common [^{18F}]-fluorodeoxyglucose (FDG) positron emission tomography (PET) [124] therefore provide a measure of the cerebral metabolic rate of glucose utilization (CMR_{GLC}) in the initial stages of glycolysis, but cannot provide insight into subsequent processes in the glucose metabolic pathway, including the later stages of glycolysis and oxidative metabolism [1,123,124].

Metabolic processes can also be inferred using magnetic resonance spectroscopy (MRS). Later processes in the glucose metabolic pathway can be measured using [^{13C}]-glucose (or [^{13C}]-lactate or [^{13C}]-acetate) MRS [1,125]. Metabolic processes beyond glucose, such as fatty acid and amino acid metabolism, can be studied with deuterium metabolic MRS [126].

The exact mechanisms underlying the blood oxygenation-level dependent (BOLD) fMRI response are not fully understood (e.g., [14]). Increased neural activity results in an increase in cerebral blood flow (CBF), the cerebral metabolic rate of oxygen metabolism (CMR_{O2}), and ATP production from glucose oxidation [25,27,28]. The increase in CBF (and CMR_{GLC})exceeds the increase in CMR_{O2}, and the uncoupling of CBF and CMR_{O2} forms the basis of the BOLD response [127]. Our understanding of how the BOLD response is linked to glucose metabolism is constrained by our limited understanding of the link between CMR_{O2} and CBF [14], and the link between neuronal activity and glucose metabolism (astrocyte–neuron lactate shuttle [128] versus the neuron–astrocyte lactate shuttle [15]). Thus, although the exact mechanism linking CMR_{O2} and CMR_{GLC} to the BOLD response is not fully understood, it is clear that neural activity requires glucose [1], glucose requires oxygen in order to be metabolized, and CMR_{O2} is the relevant metabolic rate that initiates the change in CBF to alter blood and tissue oxygenation [14], indirectly leading to the BOLD-fMRI response.

Insulin: the anabolic hormone that is primarily produced by the pancreas and controls blood glucose homeostasis and prevents hypoglycemia. Insulin sensitivity refers to how sensitive the body is to the effects of insulin. Low insulin sensitivity, known as insulin resistance, occurs when the body fails to respond normally to insulin and requires higher levels of insulin to maintain blood glucose homeostasis. Insulin resistance results in increased blood glucose levels.

Metabolic connectivity: coherence in the time course of glucose metabolism between brain regions, sometimes measured using functional PET (fPET). This contrasts with metabolic covariance, which measures covariation in metabolic rates of glucose across subjects. Metabolic connectivity is analogous to functional connectivity as measured using fMRI or electroencephalography (EEG),

Metabolic connectivity mapping (MCM): an analytical technique that is applied to simultaneously acquired BOLD-fMRI and [^{18F}]FDG-PET images. Under the assumption that FDG uptake primarily reflects postsynaptic activity, colocalization of BOLD and FDG signals is used to estimate the directionality of fMRI-derived measures of connectivity.

Metabolic cost: the amount of energy used to perform a specific task or maintain physiological functions. For example, the amount of glucose metabolism needed to sustain a brain function or perform a specific cognitive task. This cost is often measured as metabolic rates of glucose or in calories or joules expended relative to the function or task.

Node: in graph theory, the brain regions that form a network. Nodes may be categorized as hubs or non-hub regions depending on their level of interconnectedness.

Predictive coding: atheoryofbrain function that proposes that the brain actively generates an internal model of the world that it uses to predict incoming sensory input rather than passively responding to it. This internal model is represented across multiple timescales and levels of the cortical hierarchy and is updated based on the differences, or prediction errors, between expected and actual sensory data. Much of cognitive function is concerned with minimizing these prediction errors, thus yielding a parsimonious model of the world.

Rich club: a network organization where the hub regions tend to be more densely interconnected with each other than with non-hub regions.

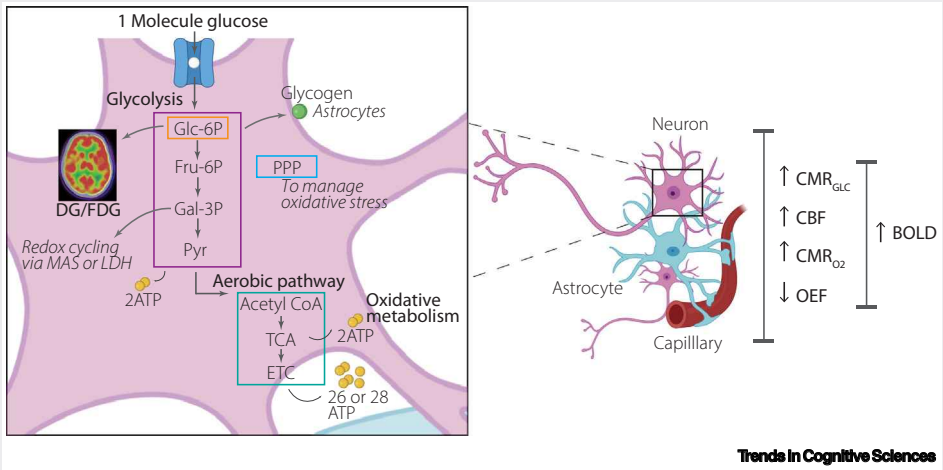

Figure I. Simplified glucose metabolic pathway and its relationship to neurovascular elements. One molecule of glucose (Glc) enters the cell via the GLUT transporter and undergoes cellular respiration to generate adenosine triphosphate (ATP), the source of energy at the cellular level. This results in an increase in the metabolic rates of glucose (CMR_{GLC})and oxygen (CMR_{O2}), increased cerebral blood flow (CBF), a decrease in the oxygen extraction fraction (OEF)), and an increase in the blood oxygenation level dependent (BOLD response. The full process of cellular respiration of glucose to generate ATP involves four sets of reactions: glycolysis, the formation of acetyl-CoA the tricarboxylic acid (TCA or Krebs) cycle, and the electron transport chain (ETC). Fluorodeoxyglucose (FDG) and deoxyglucose (DG) enter the glucose metabolic pathway in the same way as glucose and become trapped at the glucose phosphorylation stage. As such, DG/FDG imaging provides insight into the earliest processes of neural glucose metabolism, and not later stages ([1,14,15,129] for details). Abbreviations: Fru-6P, fructose-6-phosphate; Gal-3P, galactose-3-phosphate; Glc-6P, glucose-6-phosphate; LDG, lactate dehydrogenase reaction; MAS, malate–aspartate shuttle; PPP, pentose phosphate shunt pathway; Pyr, pyruvate,

Simultaneous PET and magnetic resonance (PET/MR): arelatively recent technological advance that allows simultaneous measurement of multiple dimensions of neuronal activity such as glucose uptake and hemodynamic response, cerebral perfusion, and neurotransmitter release.
Sparse coding: sparse codes represent and transmit information through the bursty activity of a small proportion of neurons in a population. Sparse coding is a metabolically efficient computational principle.

Recent studies using **simultaneous PET and magnetic resonance (PET/MR)** imaging confirmed that the increase in glucose metabolism within task-relevant regions is associated with an increase in CBF and the BOLD signal, as well as with an increase in **functional connectivity** (e.g., [33–36]). For example, CMR_{GLC} increases in the visual cortex upon eye-opening. This local increase in CMR_{GLC} determines the level of functional connectivity between the visual cortex, other regions within the visual hierarchy, and transmodal regions such as the salience network, hence enabling crosstalk between unimodal networks [33]. Although the observed metabolic and functional association was relatively widespread, it was predominantly confined to task-relevant regions and did not extend globally. A recent simultaneous PET/MR study using BOLD-fMRI and high temporal resolution [^{18F}]FDG-fPET (Box 3) found that, during checkerboard stimulation, BOLD changes in the visual cortex were associated with [^{18F}]FDG signal in the visual cortex tissue as well as in the central cerebral draining vein [35]. In other words, the task-related BOLD signal in the visual cortex was associated with glucose signals from both vascular and neural tissues, a finding compatible with the vascular and indirect nature of the BOLD signal. Finally, performing a cognitively demanding task results in further increases in CBF and the BOLD response across convergent cortical regions. Once initiated by task engagement at the easy level, the coupling between neurovascular and metabolic responses is further modulated by higher cognitive demands, but the changes imposed by more difficult task challenges comprise subtle modulations of relationships within the same cortical regions [37].

The metabolic costs of cognition increase with increasing difficulty not only within a domain but also differ across domains (Figure 2). However, this difference largely reflects the depth and extent of the functional networks that are recruited for their execution: relatively simple unimodal

tasks (such as visual perception and visuospatial processing) are less costly than complex multidomain tasks (such as social cognition and emotion). Moreover, complex cognitive processes do not simply have a higher metabolic cost in specific cortical regions. They also draw upon neuromodulatory processes that enable context-dependent and flexible adaption [38]. There is a three-way spatial convergence between the energy costs of signaling in specific cortical regions, the complexity of the cognitive tasks those regions support, and the upregulation of slow-acting neuromodulator signaling. In particular, energy-consuming signaling is enriched in frontoparietal network regions (Figure 2A). These regions, in turn, exhibit an upregulation of signaling at G protein-coupled receptors and support more complex cognitive functions such as reading, memory, and emotional processes (Figure 2B) [20]. Consequently, signaling pathways in these evolutionarily expanded regions have up to 67% higher energy costs than phylogenetically preserved sensorimotor regions [13].

Although these observations regarding energy utilization are convergent, an important caveat is that engagement in explicit goal-directed behavior and cognition is associated with only a relatively small increase (~5%) in glucose consumption [4]. This is consistent with evidence from neurophysiology that the majority of the energy budget of the brain is spent in maintaining core homeostatic processes plus neural activities that are not tied to immediate task demands such as memory consolidation [2,3,23]. Theoretical arguments suggest that background fluctuations in the postsynaptic potential are 'tuned' to maximize synaptic signaling per quantum of ATP utilized [39]. Intriguingly, analysis of physiological data using information theoretic techniques suggests the two processes (homeostatic and task-related) are not independent, but instead set in a dynamic balance such that rapid and adaptive increases in local computation can be achieved with a relatively modest increase in energy consumption [39]. Put differently, very sparse neural activity with fewer metabolic demands than are observed *in vivo* would be associated with a sluggish and inefficient task-initiated start-up. The dynamic balance underlying this 'metabolic spiking homeostasis' [40,41] reconciles the apparent contradiction between the substantial metabolic load of global brain function versus the relatively modest additional burden of specific goal-directed activity.

Neural activity unfolds on a complex structural backbone, namely the human connectome [42]. The connectome is organized around a **rich club** of highly interconnected hub regions whose dense inputs are accommodated by a unique local cytoarchitecture and capacity for greater local metabolism [24]. The high metabolic cost and dense external connectivity of hub regions support their ability to 'catalyze' the engagement of different functional networks [43]and hence switch flexibly between sedentary and goal-directed behaviors [3,23].

Functional and metabolic networks also show a complex association that changes with goal-directed cognition. A recent simultaneous PET/MR study used **metabolic connectivity mapping (MCM)** [44] to examine the dynamics of this functional-metabolic coupling when initiating goal-directed cognition [37]. MCM allows inference of the direction of BOLD-derived functional connectivity between any two brain regions (Box 3). In this study, engaging in a complex cognitive task led to increased glucose metabolism, which was associated with stronger functional connectivity. At rest, the association between glucose metabolism and functional connectivity was confined to a functional system (the dorsal attention network). By contrast, during a task, the FDG/BOLD association increased between functional systems (dorsal attention and visual networks). A strong association between glucose metabolism and BOLD-derived functional networks was activated by the initial switch from resting to the easy levels of the task. There was only a minor additional change in this coupling when ramping up to more difficult task, indicating that the largest reorganization of metabolic and functional networks occurred with

the initial engagement. This is consistent with evidence that interactions between functional networks, particularly at hub regions [3], might be the most energy-costly when switching from segregated network activity at rest to integrative activity during goal-directed behavior [23,45].

Mechanisms to minimize metabolic costs

Thus far we have emphasized the considerable metabolic needs of brain function relative to other organs. However, the brain nonetheless runs continuously on only ~17 watts of power [45,46]. By comparison, a large high-performance computing cluster uses up to six orders of magnitude more power, operating at ~2 megawatts. From this perspective, our brains are remarkably energy-efficient relative to their computational depth and agility. As with all organ systems, this parsimony is achieved through numerous adaptive mechanisms.

The need to minimize energy use impacts on all facets of brain function, starting with communication by 'sparse spikes' to offset the energy-intensive process of long-range communication, which is up to 35-fold more energy-intensive than computation in local circuits [46]. Neural interactions occur through the human connectome, which itself possesses a parsimonious organization. Most connections are local, while long, energy-intensive connections between connector hubs are sparse [47](Box 3). Hubs are classically defined using structural (anatomical) connectivity, but structural hubs strongly overlap with hubs in functional networks and show baseline high metabolic activity [48]. The common topological overlay of structural and functional networks with metabolic hotspots helps to confine energy-intensive communication processes to a relatively sparse spatial rich club [48].

Coding principles also play a role. In the visual system, the decluttering of natural scenes into a minimally redundant **sparse code** is a canonical example of neural parsimony [49]. Across perceptual systems, the principle of **predictive coding** circumvents the energy costs that would be necessary to continually process and respond to the full depth of ongoing stimuli, thus allowing important neural resources to be deployed only for the far sparser prediction mismatches [50]. An additional policy of minimizing prediction errors extends this principle to adaptive behavior [51] and to constraining and hence normalizing social interactions [52]. Because physically interacting with the environment consumes metabolic resources in skeletal muscles, we spend more time (and hence expend more cerebral resources) when planning for effortful behaviors [53]. This is another demonstration of the trade-off between cortical energy use versus cognitive complexity and behavioral investment.

More broadly, evolution occurs in an optimization landscape that seeks to minimize energy consumption while maximizing computation and survival, leading to vastly different solutions across species [54]. The energy-costly human brain pre-empts and controls its environment, using sophisticated, hierarchical inference [55]. Other species, such as reptiles, are biased towards smaller and less energy-intensive brains that execute more stereotypical behavioral repertoires [56]. In both birds and primates, behavioral innovation is correlated positively with the relative size of association areas in the brain [57]. Notably, there is a remarkable allometric scaling (positive linear relationship) between the energy costs of signaling and brain expansion from mice through rats, cats, sheep, goats, and baboons to humans [13].

These considerations suggest that shared evolutionary constraints operate across diverse species on the balance between energy utilization and functional optimization [54]. However, to date much of this work rests largely upon modeling studies. These, in turn, motivate new experimental investigations to test and refine our understanding of this intriguing area.

Hormonal regulation of the metabolic needs of cognition

While the brain operates with remarkable energy efficiency, this balance depends on precise metabolic regulation, particularly the availability of glucose. The brain plays an important bidirectional role in regulating neural and systemic glucose metabolism, which, if impaired, contributes to the development of cognitive impairment and neurological disease. Whole-body (systemic) levels of glucose in the bloodstream are controlled by the hormone **insulin** [1]. Insulin signaling in the hypothalamus controls hepatic glucose production [58]. In turn, the reliable systemic supply of glucose to the brain is necessary for the integrity and adaptive function of brain systems [59]. Beyond this well-characterized homeostatic circuit, insulin receptors are present throughout the brain (primarily in neurons and astrocytes [60,61]), the vagus nerve, sympathetic nerves, and peripheral organs (liver, muscles, pancreas). These distributed systems work together to regulate body insulin signaling and, therefore, systemic and cerebral glucose metabolism[61].

Glucose transport across the blood–brain barrier into interstitial fluids and brain tissue is largely insulin-independent. Neurons absorb glucose mainly through insulin-independent (GLUT1 and GLUT3) receptors rather than the insulin-dependent (GLUT4) receptors that are prevalent in peripheral tissue [62]. However, insulin itself crosses the brain to influence intracellular glucose metabolism [60,63] and other molecular pathways important to neural function [64]. Insulin also regulates circulating levels of glucose in the bloodstream by modulating hepatic glucose production. That is, insulin indirectly affects brain metabolism by regulating the amount of glucose available in the blood, which can influence cognitive performance, particularly hippocampus-mediated processes [65], under conditions of extreme (hypo- or hyper-) glycemia [60]. Furthermore, via second messenger signaling, insulin modulates the expression of genes involved in cerebral glucose metabolism, neurotransmission, and the biosynthesis of neural cholesterol [63]. Neural cholesterol biosynthesis is necessary for the synthesis and maintenance of myelin and the plasma membrane of neurons and glial cells [66]. Increasing peripheral insulin levels tips the balance of neural gene expression away from glucose uptake and metabolism towards the cholesterol biosynthesis pathway, enhancing the synthesis of plasma membranes and synaptic remodeling [63]. In sum, peripheral insulin plays an important regulatory role in the metabolic costs of cognition by mediating the systemic supply of glucose in the bloodstream [60]andin fluencing the expression of genes that regulate glucose metabolism, myelin formation, and the synthesis of neuronal and glial cell plasma membranes [63]. While peripheral insulin levels are likely to affect most cognitive processes [67], evidence to date suggests that hippocampus-dependent processes are particularly susceptible [65,68].

Disturbances in the adequate supply or metabolism of cerebral glucose can lead to cognitive dysfunction. Disruption of glucose homeostasis occurs in insulin resistance, where insulin has a reduced influence on target tissues. Insulin resistance in the central nervous system is associated with cortical atrophy, cognitive decline, and a pattern of neural pathology similar to Alzheimer's disease [69]. The prefrontal cortex, fusiform gyrus, hippocampus, striatum, insula, and hypothalamus are particularly susceptible to the deleterious effects of insulin resistance [70]. Normative variability in insulin resistance is associated with poorer working memory and altered coupling between cerebral glucose metabolism and CBF, even in younger people [67,68].

Increased blood glucose (hyperglycemia) is associated with poor memory and executive function, greater amyloid burden, brain atrophy, and reduced cortical thickness, even in the absence of clinically significant metabolic syndrome [71]. Similarly, hypoglycemia is associated with decreased attention, working memory, and cognitive flexibility [72], reduced gray matter volume [73], as well as cortical atrophy [74] and neuronal death [75]. Thus, maintaining the balance of blood glucose homeostasis is critical for cognitive and neural health. The expression of the

Box 3. Network neuroscience and metabolic connectivity

Brain connectivity can be measured across structural and functional dimensions. Structural connectivity refers to the physical connections between brain regions. Across macro- and microscopic scales, the full composite of structural connectivity of the brain is known as the connectome [20,42]. The connectome comprises short connections that form regional clusters and sparse, long-range connections that form a 'high-cost, high-capacity backbone' for global communication [48]. As such, even though most nodes of a network are predominantly connected to neighboring regions, there are only a few intermediate steps between one node and all the other nodes of the entire network. Much of the metabolic load is concentrated in structural hubs (e.g., precuneus, anterior and posterior cingulate cortices, and medial temporal lobe) which have enriched connectivity with other regions [21]. This is an energetically efficient topology which balances the wiring costs (building and maintaining neuronal circuitry) and metabolic costs while maximizing information transfer [3,6,47].

Functional connectivity is defined as the coherence of neurophysiological signals between distant brain regions, which may or may not be associated with underlying physical connections between the regions. At a macroscale level, the functional connectivity of the brain is most commonly measured with BOLD-fMRI (see Box 2 in the main text) and electroencephalography (EEG). Increasing recognition of the importance of glucose metabolism in healthy cognitive function and psycho-/neuropathology has renewed interest in examining **metabolic connectivity** using [^{18F}]FDG-PET. Some of the first network analyses of human neuroimaging data were conducted with [^{18F}]FDG-PET [130]. Until recently the [^{18F}]FDG-PET approach was limited to acquiring a single image per subject, and indexed the cumulative FDG uptake between FDG administration and the scan (hereafter referred to as 'traditional PET'; refer to [100] for discussion of the terms 'static' and 'dynamic' which vary between disciplines). Studies using traditional PET approaches have found that metabolic networks show moderate overlap with networks obtained using BOLD-fMRI (e.g., [131]) and predict unique aspects of cognition compared with fMRI [101,102]. However, unlike BOLD-fMRI and EEG, which provide time courses of hemodynamics and electrophysiology, respectively, traditional [^{18F}]FDG-PET does not provide a time course of glucose uptake that can be correlated to estimate a functional connectivity matrix. The recently developed 'functional' [^{18F}]FDG-PET ([^{18F}]FDG-fPET) approach [132] provides a time course of glucose uptake with sub-minute resolution [37,100,133]. Simultaneously acquired BOLD-fMRI and [^{18F}]FDG-fPET data suggest that metabolic networks show similarities with functional (BOLD-fMRI) networks, particularly in networks that encompass frontoparietal and default mode regions [100,101]. However, there are clear differences between metabolic and functional BOLD-fMRI networks – largely in temporo-occipital regions [100] – indicating that metabolic networks show both unique and complementary information to functional BOLD-fMRI networks.

primary glucose transporter that facilitates transport of glucose across the blood–brain barrier (GLUT 1, Box 1) is downregulated in hyperglycemia and upregulated in hypoglycemia [76]. Autoregulation of GLUT1 at the blood–brain barrier helps to maintain the supply of glucose needed to support neural function and prevent neuropil damage [76]. However, in chronic hyper- and hypo-glycemic conditions, these regulatory functions may decline, leading to neurodegenerative disease.

Role of glucose metabolism in neurodegenerative diseases of aging

The parsimonious metabolic work of the brain is also perturbed during healthy aging, which is associated with incremental declines in cerebral glucose metabolism, particularly in frontal and temporal regions [77]. These subtle metabolic changes are associated with changing executive function and episodic memory [78–80]. Most age-related neurodegenerative diseases are characterized by hypometabolism of glucose at rest and during cognition, including in Alzheimer's, Huntington's, and Parkinson's diseases, frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies [81]. A putative pathogenic mechanism of impaired cerebral glucose metabolism has been proposed for several other conditions that affect cognition, including schizophrenia [82], mood disorders [83], and epilepsy [84]. Importantly, cognitive abnormalities in age-related neurodegenerative diseases are not simply attributable to a reduction in the energy required to support neuronal function. Instead, disrupted cerebral glucose metabolism may be both a trigger and a catalyst for the progression of diseases in a destructive neurodegenerative cycle [81].

Declining neural energy use frequently precedes clinical diagnosis in many age-related neurodegenerative diseases, including familial Alzheimer's disease [85], Huntington's disease [86], carriers of *FTLD* gene mutations [87], and the earliest stages of prodromal sporadic Alzheimer's disease [88], Parkinson's disease [89], and dementia with Lewy bodies [90]. These conditions are

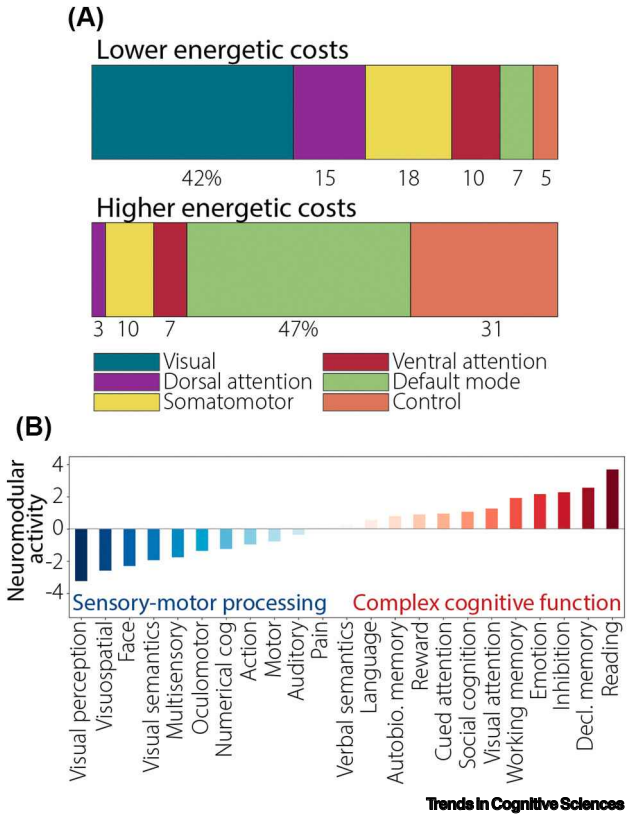

Figure 2. The link between cognitive networks and neuromodular activity. The cortical distribution of neuromodulators is enriched in regions with higher energetic costs of signaling that support complex cognition. (A) The distribution of regions with lower (top) and higher (bottom) energy costs of signaling across the six canonical functional brain networks. Regions with reduced energy costs occur predominantly in sensorimotor networks (75% in visual, somatomotor, and dorsal attention networks). By contrast, regions with higher energy costs are primarily situated within frontoparietal networks (78% in salience/ventral attention and control networks [13]. (B) A high density of slow-acting neuromodulator activity shows spatial overlap with high regional energy costs, which in turn map across different cognitive domains. Energy costs and neuromodulatory activity colinearly increase from simple sensory processing to higher cognitive functions. Figure adapted, with permission, from [13]. Abbreviations: Autobio., autobiographical; cog, cognition; Decl., declarative.

associated with insulin resistance and glucose intolerance [81], as well as with disrupted GLUT activity at the blood–brain barrier [76]. With further age-related neurodegenerative disease progression, glucose metabolic dysfunction is associated with numerous downstream pathologies that reinforce the destructive neurodegenerative cascade and associated loss of cognitive fidelity. Impaired glucose metabolism leads to a deterioration of gamma oscillations, and likely impacts on information transfer in local cortical networks and, hence, cognitive function [32]. Coupling between glucose metabolism and functional connectivity patterns, such as increased network segregation, is attenuated in mild cognitive impairment (MCI) and Alzheimer's disease [91,92]. This suggests that glucose hypometabolism is associated with loss of information transfer between networks. Such nuanced changes in metabolic–functional coupling could serve as a biomarker in neurodegeneration.

Chronic disruption of cerebral glucose metabolism can trigger neuroinflammation and the accumulation of toxic proteins in age-related neurodegenerative diseases [32,93,94]. Metabolic and immune responses are tightly linked across the body, and there are causal links between inflammatory responses and metabolic disorders [94]. The hallmark of intracranial inflammation is the activation of microglia, the macrophage-like cells that mount an immune response to toxic proteins such as amyloid and tau [95]. Inactive microglia rely upon oxidative phosphorylation for ATP production (Box 1), but when activated they switch towards aerobic glycolysis for ATP generation [95,96]. This metabolic switch to microglial activation is impaired in Alzheimer's disease, leading to inefficient clearance of protein and the accumulation of protein aggregates [96]. Moreover, early amyloid accumulation interferes with the suppression of responses to irrelevant stimuli, leading to sustained, task-irrelevant neural activity that triggers the accumulation of tau [97].

In sum, cerebral energy disruption is multifactorial in cause and consequence, and triggers numerous pathological cascades that converge onto destructive positive feedback loops. Chronic disturbance of glucose supply/metabolism and insulin resistance threaten the integrity of the neurons that support cognition and also trigger neurotoxic protein accumulation and pathological inflammatory responses. The most vulnerable cognitive processes may be the complex executive functions that have greater metabolic costs and recruit energy-costly hub regions [98]. The central role that glucose metabolism plays in these events, either as a primary cause or significant contributor, has led to acknowledgment that effective diagnosis and treatment lie with the glucose metabolic pathway [32,61,69,81,93].

New frontiers in understanding neural–metabolic coupling

Multimodal neuroimaging recognizes that a comprehensive understanding of metabolism, cognition, and brain function can only be achieved by measuring the multiple dimensions of neuronal activity (Box 4). Neural-metabolic coupling can now be studied at multiple spatial and temporal scales. Metabolic networks can be derived from common metabolism across participants or time-resolved PET time-series and their topology compared with BOLD-derived functional connectivity networks [99–102](Box 3). This in turn can facilitate insights into how disturbances of glucose metabolism impact on the efficiency of information transfer across scales from microcircuits to large-scale networks [103].

Recent research in multiorgan analysis has highlighted the key role that metabolism plays in mediating health in a 'whole-body network' [104]. In a large-scale multiorgan analysis of brain age and mortality using blood and other biomarkers, a recent study [105]showed that metabolic age strongly influenced brain age, and a 1 year increase in whole-body metabolic age is associated with a ~23 day increase in brain age and a 24 day increase in gray matter age. Whole-body metabolic and pulmonary aging showed the largest effect on gray matter aging. Further, neuropsychiatric disorders shared a substantial and largely overlapping imprint of poor body health [106]. Together, these studies illustrate the central role that whole-body metabolism plays in mediating gray matter aging in health and neuropsychiatric disorders.

Box 4. New multimodal imaging platforms to study the metabolic costs of cognition

Recent developments in macroscale imaging of glucose metabolism using variants of [^{18F}]FDG-PET have enabled new research into the relationship between glucose metabolism, brain function, and systemic health. The functional architecture that supports cognition is multidimensional, and includes electrophysiological (action potentials, field potentials), molecular (glucose, neurotransmitter), and hemodynamic components. Technologies such as simultaneous PET/MR enable concurrent imaging of multiple dimensions of brain function to achieve a more complete picture than is possible using a single modality. Simultaneous PET/MR technology has already been widely used to study the relationship between cerebral glucose metabolism and functional activity and connectivity measured using BOLD-fMRI [23,37,44], as well as **glucodynamics** – which measures the timeseries of glucose uptake during rest or in response to a task [34,35,100,101,132]. Trimodal systems which add electroencephalography (EEG/PET/MR) [134]andultrahigh field MR-PET at 7T [135] are under development.

Next-generation PET scanners enable more direct assays of interorgan molecular and metabolic connectivity than population studies that use proxy biomarkers. By using continuous bed motion (CBM) acquisitions, it is possible to examine correlations between FDG uptake across organs in a standard-length PET/CT camera. In healthy adults [104], within-subject metabolic connectivity methods [100,136] were applied with CBM to examine whole-body metabolic connectivity. Metabolic effects were strongest between the liver and brain, and the strongest associations were between the liver and temporal, occipital, and parietal regions. These results underscore the influence of hepatic health on brain function. The field will continue to welcome advances in interorgan metabolic mapping in the coming years with the increasing availability of whole-body PET cameras which provide FOV encompassing most of the torso [Siemens Quadra, 106 cm field of view (FOV)] and whole-body PET cameras which encompass the full body (EXPLORER camera with a 194 cm FOV). These cameras can acquire the timeseries of glucose metabolism across the major body organs, thus providing a within-subject interorgan metabolic connectome.

Models of multiscale neural dynamics range from spiking neurons to circuits, and can provide unique insights into the computational principles of neural activity [107], but they almost invariably focus on neural dynamics without considering their energy consumption. The existence of mutual links between cognition and metabolism motivates the development of hybrid models that couple neurons to their metabolic resources [108]. These models allow activity-dependent consumption of oxygen, ATP, and potassium, which in turn alter the membrane dynamics that underlie neuronal firing [109].

Such an objective can be accomplished at the level of single neurons by taking the classic **Hodgkin–Huxley model** [110] of membrane conductance and making the activity of potassium and sodium pumps dependent on the concentration of oxygen and ATP in the immediate neighborhood of the neuron [111]. By modeling metabolic energy consumption during seizures, this approach has shown how hypoxia [112] or extracellular potassium [113]can induce and spread seizures by compromising the homeostatic restoration of membrane potentials.

Larger *in silico* cortical circuits with metabolic constraints can be constructed from these single-neuron models by simulating populations of interacting excitatory and inhibitory cells, each with their own metabolic coupling. Such a hybrid population model has been used to study burst suppression, an electrocortical pattern seen in hypoxia and deep anesthesia in which high-voltage activity alternates with isoelectric quiescence [114]. The interplay of fast neuronal dynamics and slow metabolism leads to pathological bursting followed by epochs of suppression – the defining features of burst suppression [115]. Crucially, a slight disruption in the homeostatic exchange of potassium and oxygen perturbs the balance of excitation and inhibition in these populations, triggering bursts of excitation in a pathological feedforward cycle of runaway neural activity followed by oxygen depletion and consequently neuronal quiescence [115].

The success of these models in epilepsy and burst suppression can be seen as low-hanging fruit for early models of neuronal-metabolic coupling targeting conditions with clear pathological neuronal or metabolic activity. However, the core role of the excitatory–inhibitory balance that these models capture is also a central feature of healthy, adaptive brain function [116,117]. Bringing such models into the frame of cognition and constraining them with multimodal imaging data promises to be a fruitful line of future research to elucidate the diverse strategies for energy optimization and regulation that underlie brain health. Testing these models at the whole-brain level will require that we move from contrast-based fMRI towards quantitative methods such as calibrated fMRI, quantitative BOLD imaging, and MR-based estimates of oxygen extraction [118] (see Outstanding questions).

Concluding remarks

Task-directed cognitive processes arise from and reshape the background 'resting state' mosaic of reflection, consolidation, and future prospecting. Likewise, the additional metabolic load of task-directed cognitive processes largely reshapes the ongoing homeostatic work of repair, consolidation, and regeneration that comprise the metabolic burden of the brain. For simple processes such as sensory processing and motor execution, the additional metabolic imposts are minor. Executive tasks, particularly processes such as reading and working memory, bring an additional burden according to how much multimodal integration, long-range communication, synaptic plasticity, and neuromodulation they require. From this perspective, the cognitive costs of specific cognitive processes largely reflect the specific combination of these resources over and above domain-specific needs.

Outstanding questions

How will whole-body PET, the next frontier in molecular imaging, transform molecular and metabolic connectivity studies? Improvements in sensitivity and signal detection have the potential to dramatically reduce radiation dose exposure and scan time. This offers new opportunities including the use of dual tracer studies (e.g., FDG with amyloid tracer) and repeated measures of the same individual.

What are the novel clinical perspectives that derive from understanding neuronal-metabolic coupling? For example, is there a role for new metabolic agents in preventing or treating dementia?

How does the upregulation of neuromodulator activity in evolutionarily expanded regions facilitate complex cognition? Could this foster new pharmacological therapies for the management of cognitive disorders?

How will the introduction of neuronal-metabolic coupling into biophysical models of neuronal activity improve our understanding and treatment of pathological states such as epilepsy and burst suppression?

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Declaration of interests

The authors declare no competing interests.

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