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Perspective

Scale-spanning crosstalk between metabolism and information processing

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https://doi.org/10.1016/j.cmet.2025.10.012

SUMMARY

The research fields of brain intercellular signaling and brain energy metabolism evolved separately. One dealt with neurotransmission and the assembly of neural circuits and networks. The other focused on enzyme reactions and the compartmentation of biochemical processes between neurons and glial cells. High-order brain functions like cognition operate over long distances and can be fast. By contrast, metabolism is slow and, being limited by diffusion, operates over short distances. However, this comfortable division is now being challenged by the realization that lactate, beta-hydroxybutyrate, ATP/adenosine, and other key elements of the universal metabolic core also play the role of intercellular signals, acting via G protein-coupled receptors and other targets to modulate neural network activity, as showcased by exercise, fasting, and sleep. Here, we discuss the possible physiological meaning of such promiscuity. By arguing that it is no longer possible to understand signaling without understanding metabolism, and vice versa, the purpose of this feature is to raise awareness of the ongoing convergence and foster interdisciplinary collaboration.

INTRODUCTION

The study of energy metabolism and intercellular signaling flourished and matured through the identification of substrates and enzymes, neurotransmitters and receptors, and agonists and inhibitors, leading to the delineation of pathways, circuits, and networks. These two fields evolved separately because of conceptual, historical, and practical reasons. One could argue that metabolic and signaling systems are fundamentally different: whereas metabolism is about matter, signaling is about information. Energy metabolism was the turf of biochemists dealing with tissue extracts, purified proteins and organelles, radiotracer analysis, and respirometry. It gained wider recognition with the discovery that oxygen level is a good readout of local neural activity and the ensuing introduction of fMRI for cognitive studies and brain mapping. On the other hand, brain signaling convoked cell biologists, electrophysiologists, pharmacologists, and behavioralists, fond of living cells, studied in culture, in brain tissue sections, or ideally, in intact animals. Both groups of people wanted to know how the brain works, but they used different machines, attended different meetings, published in different journals, and organized themselves in closed societies. However, this cozy separation is now challenged by evidence that information processing and metabolic activity are fundamentally interconnected, to the point that it is no longer possible to understand one without taking the other into consideration. At the same time, the divide is being breached by the introduction of new techniques that make metabolic experiments easier for the non-initiated: genetic manipulation, high-resolution fluorescence imaging, omics, and others. This article aims to promote a more active dialogue between these two disciplines. We will focus on intercellular signaling in the brain. The wider topic of metabolites as cell signals has been reviewed elsewhere.[1]

RELATIONSHIP BETWEEN SIGNALING AND ENERGY METABOLISM

The notion that the brain operates like a digital computer is ingrained in popular culture. Brains are said to process and store information, carrying out "neural computation," with gray matter and thoughts being the respective equivalents of hardware and software. Another pervasive idea is that cognition relates to energy much like a computer needs electricity. More specifically, cognition is perceived as the prerogative of neurons, while astrocytes, oligodendrocytes, and other glial cells, together with the vasculature, take care of the less sophisticated task of procuring energy and building blocks, a paradigm under challenge by the discovery of gliotransmission.[2] No doubt a timely supply of energy is essential for the brain to do its thing and witness the rapid effects of ischemia and hypoglycemia, but is that all there is to it? A merely permissive factor that can either be "on" or "off"? The computational theory of the mind has been challenged on

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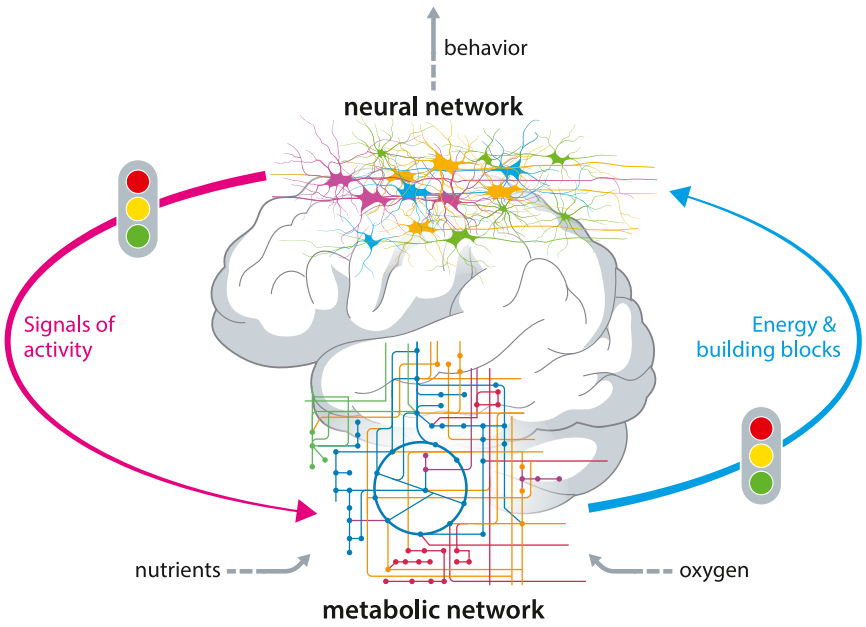

Figure 1. Reciprocal interplay between information processing and energy metabolism

The metabolic network, shaped by continuous oxidation and accretion of nutrients, responds to the demands of neural activity with changes in enzyme and transporter performance. Neurotransmission and neural plasticity are in turn conditioned by the timely availability of energy and building blocks generated by metabolism.

various grounds.[3] We endorse the view that this theory is also misleading when trying to understand metabolism. Computers are notoriously inefficient machines. With the advent of artificial intelligence based on computer networks and their mounting environmental cost, it seems that, for once, it is a technological development that may profit from a biological metaphor. Future computers will surely be asked to run more efficiently, perhaps by mimicking how the brain handles energy. In this context, the point of this article seems no longer academic.

Rather than a one-directional relationship in which neurons get the energy they need on demand, the interplay between neural activity and metabolism may be best understood as a closed-loop system in which control is exerted in a reciprocal manner (Figure 1). The neural network, acting via excitatory neurotransmission and action potentials, imposes substantial ATP expenditure on both neurons and glial cells, accounting for about 70% of total energy consumption of the brain.[4,5] In addition to turning on their own ATP production machinery,[6–8] active neurons release K^+, NO, NH_4^+, glutamate, adenosine, endocannabinoids, and many other substances. Acting at multiple spatiotemporal domains, the combined effect of these mediators is the marshaling of astrocytes and oligodendrocytes for the supply of energy substrates and oxygen to the active zone, tuned to the demands of the network.[9–11]

Control also occurs in the opposite direction, i.e., from cellular metabolism toward the neural network (Figure 1). A striking example is the preemptive shut-off response observed within seconds of brain ischemia, which helps to sustain ATP levels for several minutes despite pre-ischemic ATP turnover lasting only seconds.[12,13] In hibernating animals the shut-off phenomenon develops more slowly and may last for months.[14] Other examples of metabolic control of neural activity are the role of mitochondrial metabolism in social behaviors like interaction, aggression, and subordination[15–17] and the setting of species-specific neuronal development by mitochondrial oxidative metabolism.[18] The concept that neural energy dynamics can shape behavior, i.e., a bottom-up form of determinism, has been formalized as the Energy Homeostasis Principle. This stands in contrast to the traditional top-down view in which evolutionary selected mental states are mapped into neuronal networks and cells.[19]

CORE METABOLITES AS INTERCELLULAR SIGNALS

Most intercellular messengers are themselves metabolites. Of course, metabolites were the ingredients that our ancestors had in hand when neural networks evolved, besides a few inorganic species like protons, K^+, and NH_4^+. Metabolism predates neurons and brains, possibly even cells.[20,21] Here a distinction between two types of metabolites appears warranted. All living organisms, from mycoplasma to mammals and plants, share a metabolic core, an ancient set of about 30 enzyme and transport reactions comprising glycolysis and oxidative phosphorylation (OxPhos), acting sequentially to harness the reductive power of glucose into ATP. Minor fuels like amino acids, fatty acids, and ketone bodies are also oxidized via this universal core. Branching from the core, each cell type displays biochemical pathways that make them unique—for example, the distinctive capacity of specific neurons to make acetylcholine, noradrenaline, endocannabinoids, and other neurotransmitters. These specialized metabolites may be thought of as a "professional" signal, defined as a molecule situated at the end of a biochemical pathway, relatively isolated from the metabolic core by at least one far-from-equilibrium reaction that only occurs in certain cell types. However, there are major neurotransmitters and neuromodulators that are either very well connected to the core or are an integral part of it.

An early crack in the wall that separates the fields of signaling and metabolism was the realization that glutamate is a signal. Acetylcholine was identified in the 1920s and soon heralded as the first neurotransmitter, but it took another 50–70 years for glutamate to gain widespread acceptance. That a lowly non-essential amino acid could double as a mitochondrial energy substrate was bewildering enough, but the main neurotransmitter of the brain? "Hardly!"[22] The repurposing of glutamate may be seen as an early example of evolutionary exaptation. Glutamate is directly linked to the TCA cycle intermediate alpha-ketoglutarate by a near-equilibrium reaction. As a result, its concentration is sensitive to fluctuations of the metabolic core and vice versa. From an engineering perspective, one may ask why some brain functions would use highly selective

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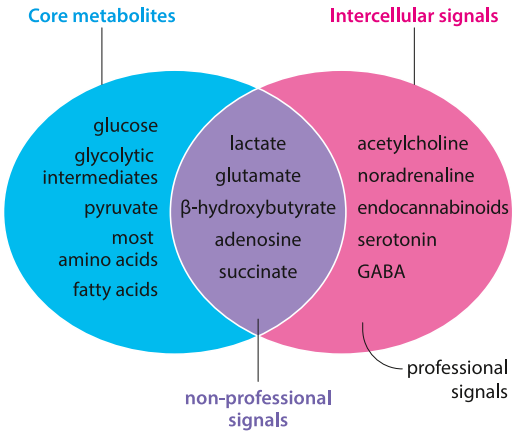

Figure 2. Professional and non-professional intercellular signals
Metabolites that play the role of intercellular signals can be classified as professional and non-professional. Professional signals are shielded from the metabolic core by far-from-equilibrium reactions that occur in specialized cell types like neurons. Non-professional signals are metabolites that belong to the metabolic core or are connected to the core via near-equilibrium reactions that occur in most cell types.

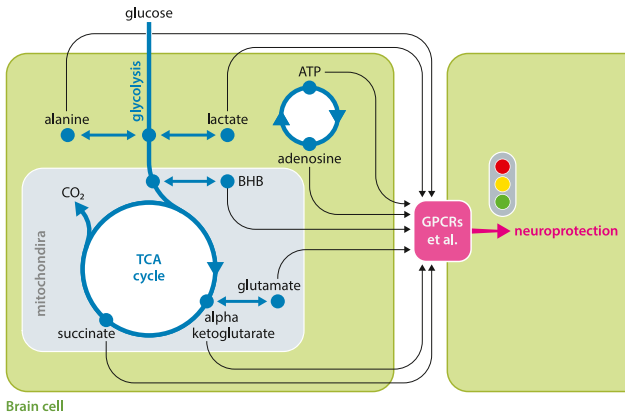

Figure 3. Core metabolites as neuroprotective signals
The metabolic core, the universal set of biochemical reactions where ATP is generated, comprises glycolysis and the TCA cycle. Some intermediates of the core (e.g., succinate) and others that are well connected to it via near-equilibrium reactions (e.g., lactate) are shown. These metabolites are released to the brain interstice during heightened activity, hypoxia/ischemia, and other pathological conditions, where they modulate neural activity via G protein-coupled receptors (GPCRs) and other signaling mechanisms.

molecules like acetylcholine, while others ended up relying on promiscuous glutamate? In analogous crossroads, *mutatis mutandis*, are lactate, beta-hydroxybutyrate (BHB), ATP, adenosine, and other members of a burgeoning club of core metabolites that moonlight as intercellular signals (Figure 2).

LACTATE: FROM HYPOXIC WASTE TO SIGNAL

Because of its strategic position halfway through the metabolic core and a direct connection to pyruvate via the near-equilibrium redox enzyme lactate dehydrogenase (LDH), lactate amplifies flux mismatches between glycolysis and OxPhos (Figure 3). Lactate was initially thought to be a muscle waste product, an epiphenomenon of the glycolytic response to hypoxia.[23] Local hypoxic pockets have recently been reported in brain tissue during physiological conditions, which could conceivably lead to local lactate increases,[24] though even under normoxic conditions there are strong lactate surges associated with afferent stimulation, explained by glycolysis surpassing OxPhos, a phenomenon termed aerobic glycolysis.[25–27] Long-standing lactate increases in some areas of the brain are associated with normal development and plasticity but also with increased susceptibility to beta-amyloid deposition.[28–30]

Exchanged between tissues and between neighboring cells,[31–34] lactate can modulate neuronal ion channels via redox potential.[35–37] But as for glutamate 30 years before, wider consideration of its signaling prowess had to await the identification of a G protein-coupled receptor.[38,39] Acting via HCAR1, lactate can inhibit or promote network activity in a synapse-specific manner.[40,41] Moreover, HCAR1 engagement promotes astrocyte serine production, thereby modulating synaptic NMDA receptor activity and cognitive performance.[42] Additional signaling mechanisms include engagement of the NDRG3-Raf-ERK pathway,[43] direct modulation of the mitochondrial electron transport chain activity,[44] control of the aggregation of mitochondrial antiviral-signaling (MAVS) protein,[45] and lactylation of histones[46,47] and mitochondrial components of the metabolic core like pyruvate dehydrogenase, citrate synthase, malate dehydrogenase, ATP synthase, and malic enzyme.[48–52] Each of these targets represents a different temporal domain, and their relative contribution to neural network activity and plasticity modulation is unclear. However, we do know that tampering with lactate dynamics by various means, like blocking glycogen mobilization or monocarboxylate transporters, perturbs brain function. Lactate is produced by glial cells upon neuronal cueing[53] but also enters the parenchyma from the circulation during exercise, when energy demand in brain tissue is highest. Conceivably, lactate acts as a traffic light for network activity, green or red depending on glucose/oxygen availability and other factors (Figure 1).

BHB: FROM FASTING FUEL TO SIGNAL

The ketone body BHB is linked to the metabolic core via acetyl-coenzyme A (CoA), the starting building block for fatty acid synthesis, and is also the product of their oxidation (Figure 3). In such a strategic location, BHB is a sensitive reporter of the balance between lipid turnover and OxPhos, reminiscent of the way lactate informs about glucose and OxPhos. Produced by the liver during starvation and exercise, circulating BHB is avidly taken up by the brain, sparing precious glucose for the reduction of glutathione via NADPH and the pentose phosphate pathway.[9,54,55] Relative to glucose consumption, the uptake of lipids by brain tissue is very slow, a fact that sets the brain apart from other energy-expensive organs like the heart, liver, and kidney. However, fatty acid turnover within brain tissue has gained recent attention. Hyperactive neurons were shown to produce toxic fatty acids, which are transferred to astrocytes in an ApoE-dependent manner.[56] Considering that astrocytes can produce BHB[57] and that BHB transfer from astrocytic lipid droplets to neurons has been demonstrated in *Drosophila*,[58] it seems

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plausible that neural activity leads to shuttling of BHB from astrocytes to neurons.[59] BHB inhibits ATP-sensitive potassium channels (K_{ATP}) in neurons, leading to hyperpolarization and reduced firing, a mechanism thought to contribute to the anti-epileptic effects of ketogenic states.[60] BHB also inhibits class I histone deacetylases (HDACs), promoting transcription of genes involved in stress resistance, neuronal plasticity, and mitochondrial biogenesis.[61] Another mechanism by which BHB impacts the neural network is the cognate G protein-coupled receptor HCAR2, which is strongly expressed in microglia and found to be neuroprotective against amyloid-induced neurodegeneration.[62]

ATP, ADENOSINE, AND SLEEP

ATP is released directly by neurons and astrocytes via vesicle fusion.[63] Packing a metabolite in a vesicle makes it more professional, as it introduces a thermodynamic step that shields it from the metabolic core, so a question arises as to the extent to which vesicular ATP content is sensitive to cytosolic ATP level, a possibility that would introduce an additional layer of regulation. In the interstice, micromolar ATP triggers the recruitment of microglial protrusions and can be converted to adenosine by microglial ectoenzymes.[64] A more powerful and less local source of adenosine is its cytosolic formation by ATP hydrolysis and release via facilitative nucleoside transporters.[65] Under low and moderate physiological activity neuronal ATP levels are very stable,[7,8] and therefore transporter-mediated adenosine release is likely more relevant during high activity, seizures, and hypoxia/ischemia. Remarkably, the Na^+/K^+ ATPase pump plays a permissive role on the release of adenosine in response to neural activity[66] and is also permissive for activity-dependent glycolysis in astrocytes and neurons.[8,33,67] The Na^+ pump, a key element of neurotransmission, is therefore a control link between intercellular signaling and metabolism. Adenosine reduces whole brain tissue energy consumption by mediating the sleep-inducing effect of prolonged wakefulness.[68] Sleep is a third fundamental brain state in which metabolism and signaling converge, with adenosine playing a neuroprotective role akin to those of lactate in exercise and BHB in fasting. Adenosine suppresses neuronal activity via A1 receptors, but at low concentrations it can also be excitatory via A2A receptors.[69,70] In addition, adenosine modulates astrocytic glucose consumption and lactate release via A2B receptors.[71]

Lactate, BHB, and ATP/adenosine are energy-rich molecules that sit close to the metabolic core, amplifying flux mismatches between major sections of the metabolic grid: glycolysis, fatty acid metabolism, and the TCA cycle, and are sensitive to the balance between fuel/oxygen supply and demand (Figure 3). Produced locally, but also arriving globally under physiological conditions like exercise, starvation, and sleep, they may be seen as parallel conveyors of the bottom-up message that local energy metabolism is not coping with the top-down demand imposed by the network. Accordingly, lactate, BHB, and adenosine are neuroprotective.[72–74] A caveat is that these three metabolites may also be excitatory under certain conditions and at certain concentrations, acting on alternative receptors. Glutamate is toxic at high concentrations but, acting at low concentrations via metabotropic receptors, can also be neuroprotective.[75] Quantifying metabolite dynamics at high spatiotemporal resolution by combining time-lapse microscopy with genetically encoded sensors, together with cell-specific manipulation of receptors and signaling pathways, seems a promising way to ascertain the relative contribution of these metabolites.[76]

OTHER METABOLIC CORE SIGNALS

The mitochondrial TCA cycle intermediates alpha-ketoglutarate and succinate can also appear in brain interstice and plasma (Figure 3). Alpha-ketoglutarate plays a protective role against oxygen-glucose deprivation[77] and demyelination.[78] It is released by exercising muscle and helps to enhance memory and reduce stress-induced social withdrawal by increasing brain tissue BDNF levels.[79] As observed with lactate, succinate accumulates during ischemia, and paradoxically, its tissue instillation in traumatic brain injury is neuroprotective.[80] However, its degradation upon reperfusion may release reactive oxygen species that lead to injury.[81] The G protein-coupled receptor for succinate, SUCNR1, is strongly expressed in macrophages and microglia and mediates developmental and hypoxic angiogenesis in the retina.[82] The amino acid alanine is linked to pyruvate via near-equilibrium alanine transaminase (ALAT; Figure 3), an enzyme that is abundant in glial cells and neurons. While pyruvate is in redox equilibrium with lactate, the other substrates of ALAT are glutamate and alpha-ketoglutarate, so alanine provides a complex reading of amino acid status, redox balance, glycolysis, and the TCA cycle. No specific surface receptors have been reported for alanine, but in liver cells, it directly activates AMPK, the master sensor of metabolic stress that integrates physiological signals to restore energy balance.[83] Experiments in *Drosophila* showed that glial cells secrete alanine and that genetic inhibition of ALAT in glial cells and neurons perturbs memory acquisition.[84,85]

There are other metabolites that play signaling roles and have pathophysiological relevance but seem more difficult to classify, as their sensitivity to fluctuations of the metabolic core is not yet clear. The most abundant metabolite of the central nervous system is N-acetylaspartate (NAA). Synthesized from aspartate and acetyl-CoA in neurons, NAA is released into the extracellular space and taken up primarily by oligodendrocytes.[86] NAA may serve both as a metabolic fuel and a modulatory signal, potentially aligning oligodendroglial function with axonal energy status and activity.[87] Altered NAA levels are observed in brain trauma and Canavan disease.[88] L-serine, a non-essential amino acid precursor of D-serine and glycine, co-agonists of synaptic NMDA receptors required for synaptic plasticity, is produced in astrocytes. Astrocytic L-serine synthesis is impaired in young Alzheimer's disease (AD) mice, and chronic oral administration of L-serine rescued the cognitive decline, revealing that astrocytic glycolytic flux is crucial to preserve cognitive functions.[89] In parallel, beta-amyloid and tau oligomers were found to inhibit astrocytic glycolysis and impair hippocampal function via stimulation of aryl hydrocarbon receptor by the tryptophan metabolite kynurenine.[90] In AD the loss of long-distance connections may help to lower metabolic cost,[91] at the expense of cognitive performance. In other words, as the availability of metabolic support decreases, the capacity for complex network interactions and computation becomes blunted. Because of space limitations, it

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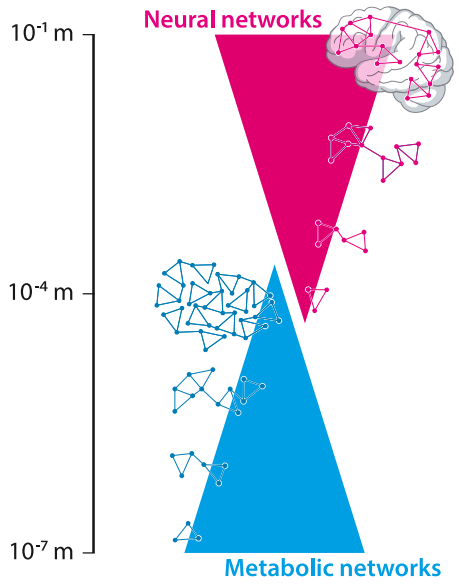

Figure 4. Energy metabolism and neural networks operate at different scales

High-order brain functions like cognition are based on vast assemblies of neurons, reaching up to tens of centimeters. By contrast, metabolic networks are small, limited by diffusion. They coexist in the range of 0.1 mm.

is not possible to describe in detail the dynamics of brain metabolites here. The interested reader may find this information, including sources, targets, mechanisms, and changes in disease, in other reviews.[9,10,92–94]

WHY PROMISCUOUS INTERCELLULAR SIGNALING IN THE BRAIN?

Unlike computers, brains evolved in a context of chronic energy shortage[95] and lie perilously on the verge of metabolic collapse.[96] This phylogenetic constraint to encephalization is thought to underlie various adaptations that augment network energy efficiency, including myelination,[97] parsimonious wiring,[91] sparse coding,[98] and coordinated axonal channel kinetics.[99] Adaptation also occurs within a lifetime. Mammalian brains undergo rewiring during learning and experience-dependent plasticity,[100] and in the neocortex of food-restricted mice, reduced AMPA receptor conductance saves synaptic ATP at the expense of coding precision.[101]

The use of core metabolites as non-professional neurotransmitters/modulators may be a fossil of a less specialized past, an example of evolutionary parsimony. We offer here an additional, non-exclusive explanation: scale-spanning coordination. Neural networks and metabolic networks are both organized hierarchically, with multiple echelons spanning orders of magnitude.[102] However, these two networks are not in register. While a neural network can reach centimeters,[91] the size of a metabolic network is capped by the limits of diffusion. Considering the turnover distance of ions, oxygen, and substrates, the largest echelon of energy metabolism is about 0.1 mm in radius,[103] 10–100 times smaller than the typical neural network, a mismatch that may be problematic. For example, if the demand imposed by the much larger network exceeds the supply capacity of the small neurogliovascular unit, as observed in seizures, excitotoxicity, sleep deprivation, and substance abuse, the consequence will be cell injury and death, pathogenic factors for neurodegenerative and major psychiatric diseases.[96] In view of the neuromodulatory effects of lactate, BHB, and adenosine, we propose that the use of non-professional signals constrains the activity of large-scale networks to the diffusional restrictions of local supply and metabolism (Figure 4). In this view, core metabolites transparently broadcast metabolic information, allowing circuits to self-regulate and adapt.

CONCLUSION

By pointing to evidence that energy production and information processing in brain tissue have a number of key metabolites in common and that global network activity is not impervious to local metabolism, the purpose of this perspective feature is to foster collaboration. It is our belief that we need new joint interdisciplinary efforts within the fields of metabolism and signaling to address the complexity of high-order brain functions.

ACKNOWLEDGMENTS

We thank Karen Everett for critical reading of the manuscript. This work was funded partly by ANID-Fondecyt projects 1230145 (L.F.B.) and 1230682 (I.R.); Inserm (G.M.); European Research Council project ERC-2017-AdG-786467 (G.M.); Fondation pour la Recherche Medicale project DRM20101220445 (G.M.); the Human Frontiers Science Program (G.M.); Region Aquitaine project CanBrain AAP2022A-2021-16763610 and -17219710 (G.M.); French State/Agence Nationale de la Recherche projects: ERA-Net Neuron ANR-21-NEU2-0001-04, ANR-23-CE16-0022-01, and ANR-23-CE14-0004-03 (G.M.); the French Government in the framework of the University of Bordeaux's IdEx "Investments for the Future" program/GPR BRAIN_2030 (G.M.); and La Caixa Research Health grant LCF/PR/HR23/52430016 (G.M.). The Swiss National Science Foundation (SNSF) supported A.S.S. (Eccellenza 187000) and B.W. (212508 and 219656).

DECLARATION OF INTERESTS

The authors declare no competing interests.

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