Paying the brain's energy bill

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Perspective

Paying the brain's energy bill

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Abstract

How have animals managed to maintain metabolically expensive brains given the volatile and fleeting availability of calories in the natural world? Here we review studies in support of three strategies that involve: 1) a reallocation of energy from peripheral tissues and functions to cover the costs of the brain, 2) an implementation of energy-efficient neural coding, enabling the brain to operate at reduced energy costs, and 3) efficient use of costly neural resources during food scarcity. Collectively, these studies reveal a heterogeneous set of energy-saving mechanisms that make energy-costly brains fit for survival.

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Introduction

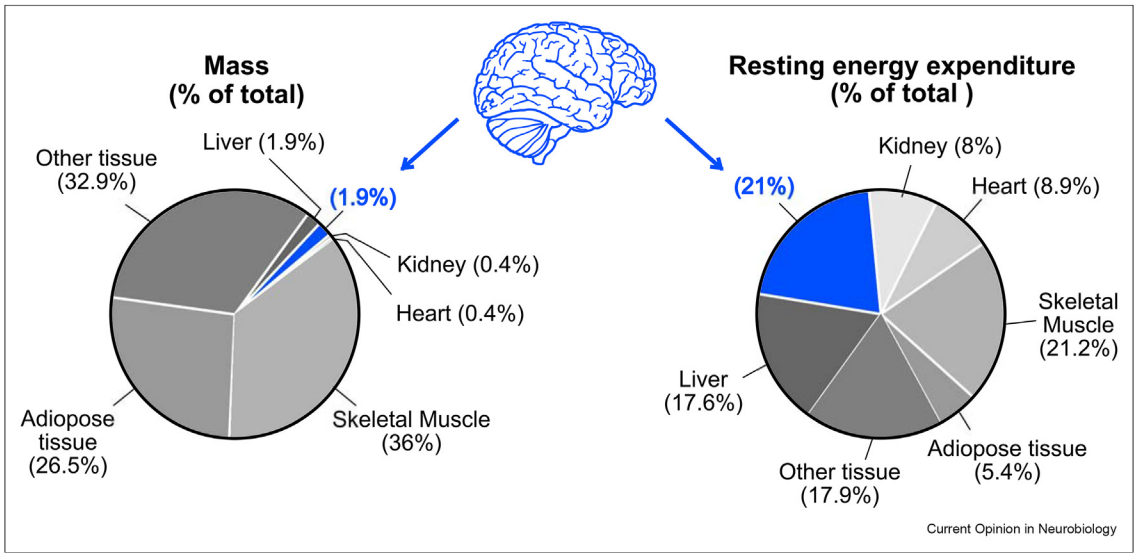
The brain is metabolically expensive. In humans, the brain consumes approximately 20% of our metabolic energy, despite comprising only 2% of our body mass, making it amongst the most energetically costly organs in the body (Figure 1a) [1,2]. How have animals evolved to maintain their expensive brains? One possibility is that the evolution and expansion of the brain coincided with, or even facilitated, an increase in calorie intake that would cover the costs of the brain (reviewed in Ref. [3]). Whilst there is evidence to suggest this is true to some extent — for example, larger-brained animals generally consume more calories than smaller-brained ones [3,4] - the availability of calories in the natural world can be volatile and fleeting [5–8], and the operational costs of the brain can also fluctuate depending on cognitive demand [9–12]. Additional strategies have therefore likely evolved to maintain expensive brains across unpredictable times and conditions. Here we present evidence in support of three such strategies: 1) a reallocation of energy from peripheral tissues and functions to fuel brain activity, 2) implementation of energy-efficient neural coding, enabling the brain to operate at reduced energy costs, and 3) efficient use of costly neural resources during food scarcity.

Reallocation of energy from peripheral tissues and functions to fuel brain activity

According to the Expensive Brain Hypothesis [13], and related hypotheses, the evolution and expansion of the brain was likely paid for, at least in part, by reducing the size of other metabolically expensive tissue, such as skeletal muscle, or other expensive processes, such as growth and reproduction (reviewed in detail in Ref. [3]). Several lines of evidence support this. For example, 1) brain size is inversely correlated with pectoral mass in birds [14], and is also inversely correlated with muscle use, and therefore smaller in migratory species compared to sedentary ones [15,16]. 2) Gestational age is increased in larger-brained animals and growth rate is reduced [3,17,18], particularly during the development of the brain. Indeed, in humans, growth rate falls to a minimum during early childhood (around the age of five), when synaptic density peaks and the brain's energy demand comprises approximately 45% of caloric intake, which reflects a twofold greater rate of glucose consumption than the adult brain [19]. 3) Finally, reproduction is more delayed and less frequent in larger-brained species compared to smaller-brained ones [3,13,20].

Energy trade-offs are also required to support the operational costs of the brain, which are not constant across the lifespan [9,10,12]. Learning and memory formation, for example, incurs significant energy costs, which have been well elucidated in insects. Indeed in honey bees, appetitive odour conditioning is accompanied by a 20% reduction in trehalose, which is the main energy substrate in insects [9]. Similarly in *Drosophila*, aversive conditioning is accompanied by an over two fold increase in caloric intake [10], as well as an increased energy consumption in the mushroom

Figure 1



The brain is energetically expensive given its mass. Depicted are pie charts showing the relative mass (left; % of total body mass) and relative levels of resting energy consumption (right; % of total energy consumption at rest) of various organs in the human body. The brain's relative mass and resting energy expenditure are depicted in blue. (Data from Ref. [1], brain image from doi.org/10.5281/zenodo.3925989).

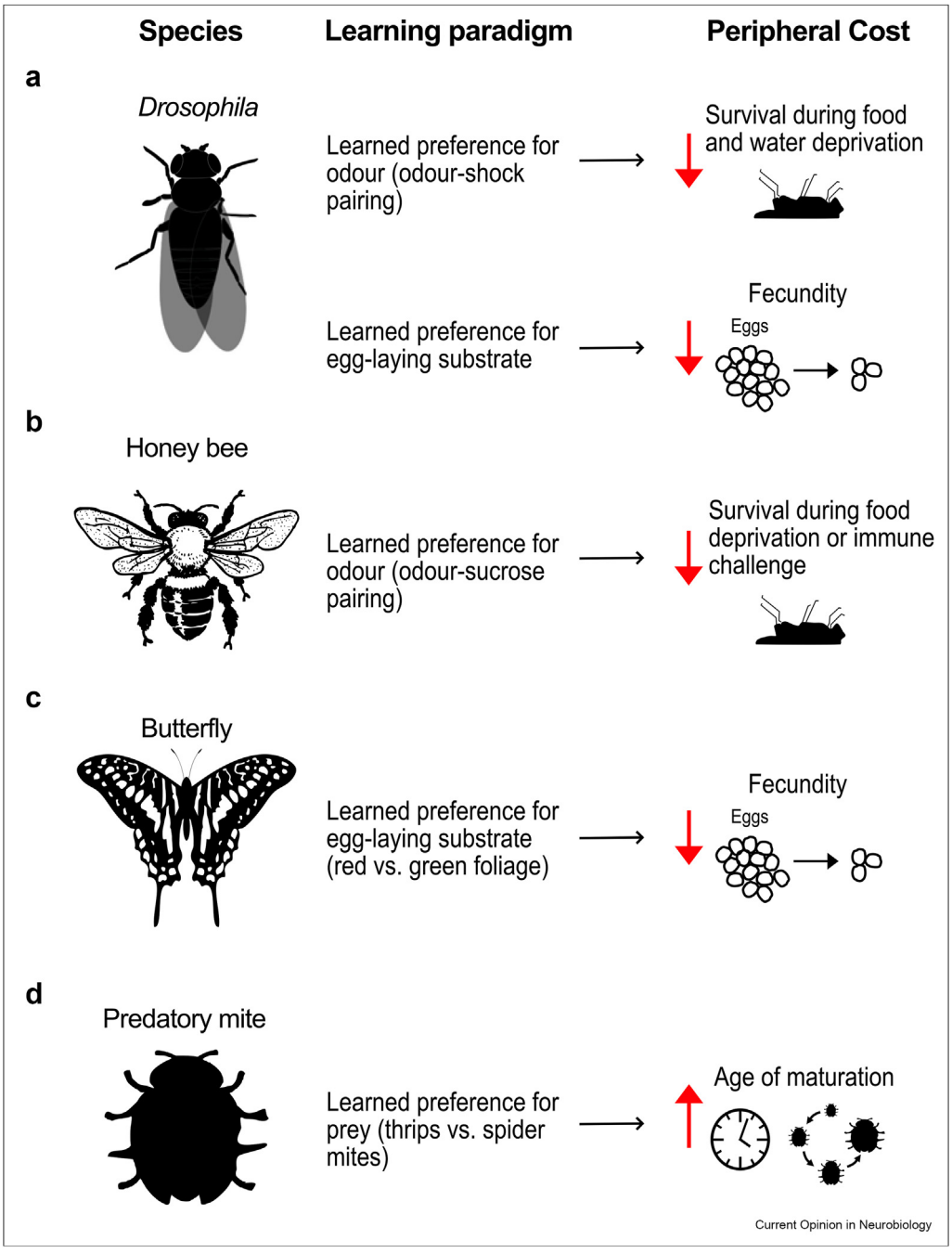
bodies, which is both necessary and sufficient for long-term memory formation [10]. Conditioning is also accompanied by an increase in glial transport of glucose to mushroom body neurons, where it is used in the pentose phosphate pathway to produce NADPH, potentially to reduce the oxidative stress associated with increased mitochondrial respiration [21,22]. In mammals, learning and memory also incurs significant energetic costs. For example, in rats performing a spontaneous alternation task, which requires spatial working memory, glucose levels are selectively decreased within the hippocampus. The level of decrease scales with task difficulty: glucose is reduced by 11% during a three-arm maze and by 32% during a more challenging four-arm maze [11]. Task performance is also limited by glucose levels, and is therefore improved with prior glucose supplementation [11]. Recently, hippocampal sharp wave ripples, which are important for memory and working memory functions [23,24], have been shown to trigger decreases in systemic glucose levels via a pathway involving the lateral septum, a critical node of communication between the hippocampus and the hypothalamus [25]. These findings suggest that peripheral metabolic state and cognitive functions are intimately coupled.

The metabolic cost of learning and memory is paid for, in part, by trade-offs in peripheral functions. This is well established in invertebrates. For example, long-term memory formation: 1) impairs survival during extreme food and/or water deprivation in *Drosophila* and honeybees [9,26], 2) impairs survival during immune challenge in honey bees [9], 3) reduces life-time fecundity in *Drosophila* and butterflies [27,28], and 4) delays the age of maturation in predatory mites [29] (Figure 2). Moreover, *Drosophila* and butterflies that have been bred to excel at learning – specifically, learning a target substrate for egg-laying - have reduced lifespan [30], impaired reproductive ability [27,30], and bear larvae with reduced ability to compete for food [31]. Conversely, learning is impaired in flies that are either innately long-lived [30] or resistant to nutritional stress [32], and in butterflies with faster reproductive development [27].

In contrast to invertebrates, less is known about the trade-offs incurred by learning and memory in vertebrates. One study, however, has shown that guppies, artificially selected to have larger brains and an improved performance on a numerical learning test, produce fewer offspring [20]. This suggests that similar trade-offs in peripheral functions may operate across species to fuel brain function. Of importance would be to establish to what extent learning and memory impacts peripheral functions in mammals. This could be done, for example, by assessing the life span and fecundity of mice exposed to daily or weekly learning tasks (for example, a behavioural task with changing rules), ideally across the life span, and comparing it to respective controls (for example, the same task without changing rules).

Collectively, these studies suggest that brain function comes at a cost of peripheral tissue and functions.

Figure 2



The cost of learning across species. (**a**) In *Drosophila*, learning an odour-shock pairings reduce survival when challenged with food and water restriction [26]. Learning which of two egg-laying substrates contains quinine reduces fecundity (i.e. number of eggs laid) [28]. (**b**) In honey bees, learning an odour-sucrose pairing reduces survival during food deprivation or in response to an immune challenge [9]. (**c**) In butterflies, learning a preference for an egg-laying substrate (red vs. green foliage) reduces fecundity [27]. (**d**) In predatory mites, leaning a preference for prey (thrips vs. spider mites) early in development delays the age of maturation [29]. (Drosophila image from doi.org/10.5281/zenodo.3926137).

Energy-efficient neural coding enables the brain to operate at a lower energy cost

Accumulating evidence indicates that the brain operates energetically efficiently, enabling it to operate with reduced energy use [33]. Thus, whilst the brain is metabolically expensive, its cost reflects a lower bound required for function. A sizeable fraction of the brain's energy expenses are used to support electrical signalling, specifically to reverse the Na^+ influxes associated with electrical activity via the action of the Na^+/K^+ ATPase pump [34,35] at the cost of 1 ATP per 3 Na^+ extruded. In mammalian brains, the principal drivers of ion fluxes across the membrane in grey matter are excitatory synaptic signalling and action potentials, which respectively comprise approximately 57% and 23% of the brain's energy budget for electrical signalling [35–37]. According to the efficient coding framework, electrical signalling in the brain, has evolved to maximize the amount of information transmitted per molecule of ATP (i.e. bits/ATP) [33,38–41]. This framework accounts for a number of experimentally observed features of the brain, including the low mean firing rates of neurons [33]. Indeed, given that 1) information transmission (bits/s) increases sub-linearly as firing rate increases, and 2) ATP expenditure (ATP/s) increases proportionally with firing rates, energy efficiency (bits/ATP) is optimized at low firing rates, which are observed experimentally ($\leq$10 Hz) [33,34,40]. These low firing rates are a fraction of the half-maximal firing rates (approximately 200 Hz) that would otherwise maximize information transmission (bits/s), but at a disproportionally higher ATP cost ($\geq$20 fold). Energy-efficient coding also accounts for experimentally observed sparse coding strategies, whereby a given sensory stimulus or action is encoded by elevated spiking activity in a small proportion of neurons (<10%) [34,42].

In addition to spiking activity, excitatory synaptic transmission is also constrained at the synapse to maximize energy-efficient coding. One striking example of this is the low release probability with which glutamate, the principal excitatory transmitter in mammalian brains, is released at central synapses following an action potential. For example, the release probability at cortical synapses is approximately 25–50%, which theoretically maximizes energy-efficiency (bits/ATP) [35,43]. Moreover, at retino-thalamic visual synapses, excitatory postsynaptic current amplitudes maximize retinal information transmission per ATP [44]; artificially amplifying currents improves information transmission rates, but at a disproportionate increase in ATP cost. Similar findings have been recently reported at thalamo-cortical synapses [45].

Collectively, these studies suggest that the brain has evolved energy-efficient coding strategies, enabling it to operate effectively at lower energy costs.

Efficient use of costly neural functions during food scarcity

Reducing non-essential, costly neural functions to save energy in times of food scarcity

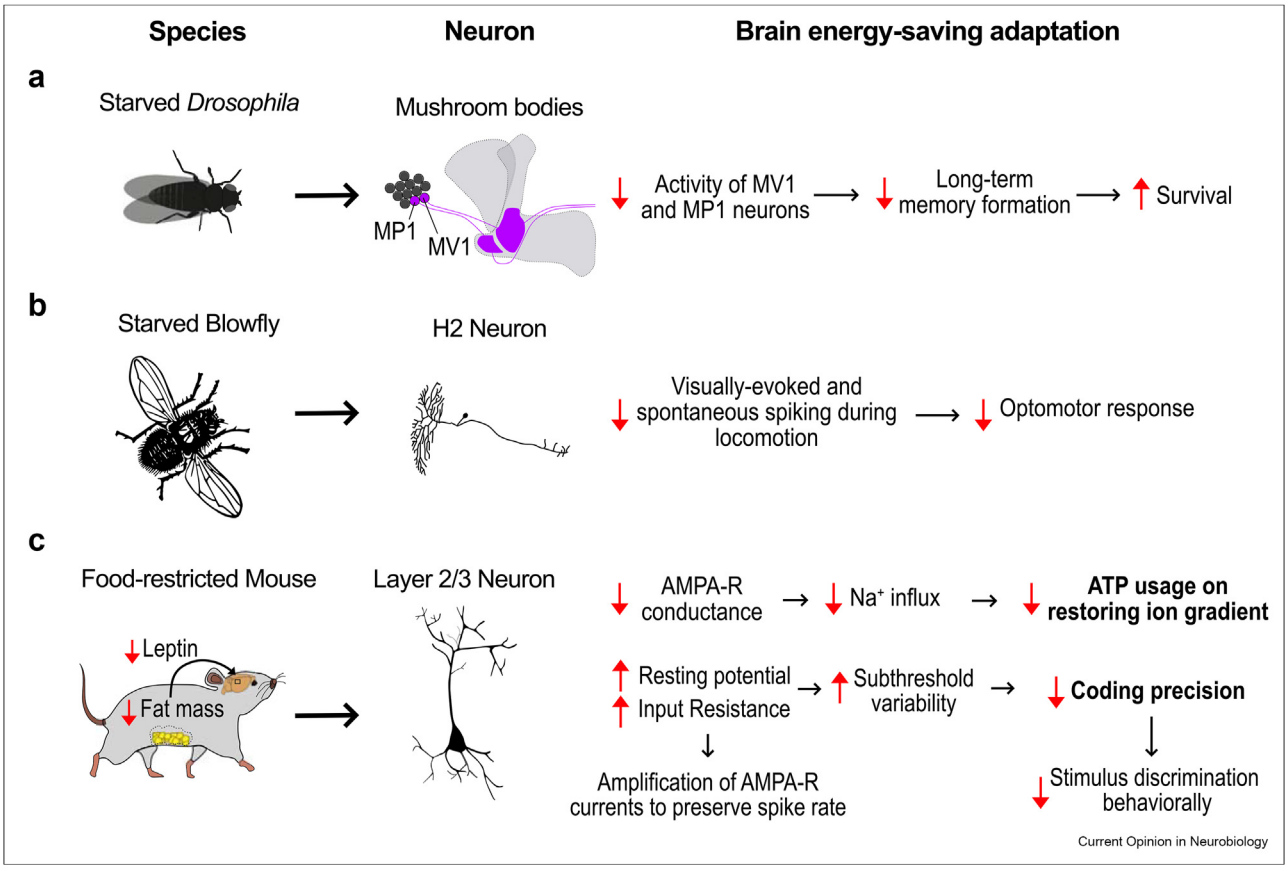
In 1920, Marie Krieger documented that malnourishment in humans profoundly impacted the weight of a number of organs, including the heart, liver, kidneys and spleen, all of which lost approximately 40% of their mass; the brain, however was negligibly impacted [46]. Similar results were reported for food-deprived rodents by Villeneuve et al. (1977) and Schärer (1977) [47,48]. These findings would later be replicated by a number of additional studies over the years, which collectively would provide support for the Selfish Brain Hypothesis [49,50]. The hypothesis posits that the brain prioritizes its own needs over that of peripheral tissue, and does not (or cannot) reduce its own energy expenditure in times of need. However, recent, and more detailed recordings of neuronal activity suggest that the brain is not as selfish as once thought and can reduce costly, neural functions when food is scarce.

Energy-saving changes in the brain were first documented by Plaçais and Preat (2013) [51]. They discovered that in *Drosophila* the formation of a metabolically costly form of memory – specifically, long-term, protein-synthesis dependent memory of odour-shock associations - was inhibited by starvation (Figure 3a). Mechanistically, starvation silenced the activity of MV1 and MP1 dopaminergic neurons, which gate long-term memory formation in the fly's mushroom bodies (Figure 2a). Reactivation of these neurons via exogenous expression of thermosensitive cation channels (dTrpA1) restored memory formation, but significantly impaired survival. Food deprivation has also been shown to impair long-term memory formation in honey bees [9] and in *C. elegans* [52].

In addition to memory formation, starvation reduces other aspects of neural function, consistent with energy-saving adaptations. For example, Longden et al. (2014) demonstrated that in blowfly, starvation reduced both visually-evoked and spontaneous spiking in the H2 visual interneuron [53] (Figure 3b). This occurred specifically during locomotion and resulted in the impairment of the yaw optomotor response. The effects of starvation increased with time (1–3 days) but did not reflect pathophysiology since they were not correlated with changes in total haemolymph carbohydrate, and were reversed with one day of refeeding. These findings suggest that enhanced gain control of sensory responses during locomotion is suppressed during food restriction, consistent with reduced energy expenditure.

Recently, we demonstrated that the mammalian neocortex, which is responsible for over half of brain's energy consumption [2], also adapts its energy use and

Figure 3



Energy-saving adaptations in the brain during food scarcity. (**a**) Starvation in *Drosophila* leads to an impairment of costly long-term memory formation via the silencing of MP1 and MV1 dopaminergic neurons to improve survival [51]. (**b**) Starvation in blowfly compromises the optomotor response by reducing visually-evoked and spontaneous spiking of the H2 neuron during locomotion; reduced neuronal spiking is consistent with energy savings [53]. (**c**) Food-restriction in mice reduces AMPA receptor (AMPAR) conductance in layer 2/3 cortical neurons, resulting in reduced Na^+ influx and therefore less ATP required to restore the ion gradient. Decreased AMPAR conductance is compensated by increases in resting potential and input resistance which preserve spiking rates but increase subthreshold variability leading to reduced coding precision; this is associated with reduced stimulus discriminability in behaving animals. Reduction of circulating levels of the fat-mass regulated hormone leptin is necessary for the observed energy-saving changes [54]. (Drosophila image from doi.org/10.5281/zenodo.3926137, Layer 2/3 cortical neuron image from doi.org/10.5281/zenodo.3925905).

function in response to food scarcity [54] (Figure 3c). We food restricted male mice to 85% of their body-weight over the course of 2–3 weeks. We found that this resulted in 29% reduction in synaptic ATP use in the visual cortex during visual processing, mediated by a reduction of postsynaptic AMPA receptor (AMPAR) currents. This reduced synaptic current was compensated by an increase in resting membrane potential and input resistance. Whilst these compensatory changes normalized spike rate to *ad libitum* fed controls, they also amplified the trial-to-trial variability of visually-evoked subthreshold depolarizations, which increased the likelihood that smaller depolarizations, elicited by non-preferred visual stimuli, would cross spike threshold, resulting in a loss of stimulus selectivity of spike output. The loss of stimulus selectivity degraded fine coding precision and was associated with an impaired ability for food-restricted animals to make fine visual discriminations between visual stimuli. Critically, we found that energy-saving adaptations in the cortex were mediated by leptin signalling. Leptin is a hormone that is secreted by adipocytes in proportion to fat mass [55], and is therefore reduced with food restriction. Exogenous supplementation of leptin in food-restricted animals restored stimulus selectivity and coding precision to control values.

Food restriction may also reduce brain energy expenditure by modulating sleep. In humans, one study found that calorie restriction increased the proportion of sleep spent in deep sleep (Stage 4), during which cerebral oxygen and glucose consumption is reduced compared to REM sleep or wakefulness [56,57]. Moreover, food restriction can increase sleep time in rodents, though this depends on when in the light/dark cycle food becomes available [58]. Food restriction also increases the

likelihood of entering torpor, a state in which neuronal and synaptic activity is substantially reduced, along with whole-body metabolism [59—62].

Overall, these studies establish that costly neuronal functions are reduced in times of food scarcity, to reduce energy use and improve survival.

Selective enhancement of useful, costly neural functions in times of need

Whilst reducing costly neuronal functions in times of need can save energy, some neural functions are important for securing food in resource-poor environments; several studies find that such functions are indeed selectively enhanced. For example, it is well established that neural responses to food cues are enhanced selectively during hunger, but not satiety, in humans [63]. Similar observations have recently been made in mice, where hunger enhances the neural responses in brains regions associated with food cue processing, including the postrhinal cortex, the lateral amygdala, and the insular cortex [63—65]. These enhancements improve the discriminability of food vs. non-food visual cues, and are rapidly dissipated following satiety [64]. Mechanistically, hunger-related signals from hypothalamic agouti-related peptide (AgRP)-expressing neurons gate hunger-induced enhancements of food cue responses. Indeed, optogenetic activation of these neurons is sufficient to enhance neural coding of food cues in sated animals [65]. These signals are conveyed from the hypothalamus, via the paraventricular thalamus and the basolateral amygdala, to the insular cortex, and potentially to other brain areas [65,66]. Such specific enhancement of neural coding of food cues, and selectively in times of hunger, reflects an efficient use of costly neural resources in times of food scarcity.

As with food scarcity, water scarcity is also a metabolic challenge in which animals can enter a negative energy balance. Indeed, water deprived animals consume less food, and therefore, like food-deprived animals, lose weight and fat mass [67—69]. Notably, as with hunger, recent studies have noticed a selective, thirst-dependent enhancement of neural responses to water cues [66]. Indeed, water cues can trigger increased neuronal activity in thirsty animals, both within the insular cortex, and across the cortex, in the context of a go/no-go task [66,70]. These changes are quenched by satiety, though can be re-instated via optogenetic activation of thirst-sensing neurons within the medial preoptic nucleus (MnPO) or subfornical organ (SFO) of the hypothalamus [66,70].

Collectively, these studies demonstrate that the use of costly neural resources is efficiently and selectively gated by physiological need to maximize the chances of securing food or water in times of need.

Future studies and outlook

Despite recent advances, there are several outstanding questions regarding brain energy use. For instance, what mechanisms enable the dynamic reallocation of energy from peripheral functions to the brain, especially when the brain's energy needs increase, such as during development or learning? Then, in times of food scarcity, when the brain's energy demands cannot be met, how are energy-saving adaptations triggered in the brain? Are they common across species, or even across regions of the brain? Are the different energy saving adaptations described in this review complementary and used concurrently, or are they mutually exclusive? Moreover, given that peripheral responses to food restriction differ between males and females, and between young and old animals [71], it will be important to examine the sex- and age-dependencies of energy-saving adaptations in the brain. Finally, whilst most studies have focussed on neurons, less is known about how other cell types such as glia, pericytes, and inhibitory interneurons, contribute to energy-saving adaptations in the brain. Addressing these outstanding questions will shed fundamental insights into the dynamic regulation of brain energy use.

Conclusion

The brain is one of the most metabolically-expensive organs in the body. Here were review evidence in support of several adaptions that enable animals to maintain expensive brains. First, peripheral tissue and functions have been sacrificed to support the metabolic need of the brain. Secondly, the brain has evolved energy-efficient coding strategies to operate at reduced cost. Finally, the brain efficiently uses costly neural resources during food scarcity; this requires both a decrease in energy expenditure of non-essential neural functions, and a selective enhancement of useful neural functions to maximize the chances of finding food and water in times of need.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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