ESSAY

The brain and immune system prompt energy shortage in chronic inflammation and ageing

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Abstract | Sequelae frequently seen in patients with chronic inflammatory diseases, such as fatigue, depressed mood, sleep alterations, loss of appetite, muscle wasting, cachectic obesity, bone loss and hypertension, can be the result of energy shortages caused by an overactive immune system. These sequelae can also be found in patients with chronic inflammatory diseases that are in remission and in ageing individuals, despite the immune system being less active in these situations. This Perspectives article proposes a new way of understanding situations of chronic inflammation (such as rheumatic diseases) and ageing based on the principles of evolutionary medicine, energy regulation and neuroendocrine–immune crosstalk. A conceptual framework is provided to enable physicians and scientists to better understand the signs and symptoms of chronic inflammatory diseases and long-term disease consequences resulting from physical and mental inactivity.

Chronic inflammatory diseases, such as rheumatoid arthritis (RA), and the process of ageing are often accompanied by shared signs and symptoms, including fatigue, depressed mood, sleep alterations, loss of appetite and context-associated anorexia, anaemia, malnutrition, muscle wasting, bone loss, insulin resistance, decreased fertility, loss of sexual interest, increased sympathetic and low parasympathetic activity, high blood pressure and hypercoagulability[1]. Given the pervasive influence of these sequelae on an individual's well-being, quality of life, functional capacity and physical and mental activity, they might be considered to constitute a long-term risk of illness and early death. The aforementioned sequelae seem to be separate manifestations; however, when viewed from a perspective of energy shortage, especially in the presence of inflammation-related and age-associated anorexia[2–5], these sequelae can be considered to be interrelated.

Inflammation is widely suspected to be central to those sequelae common to chronic inflammatory diseases and ageing. Indeed, ageing is often accompanied by an increased pro-inflammatory load[6], and chronic inflammatory diseases are known to accelerate the ageing process[7,8]. However, the low-grade inflammation seen in ageing individuals or in patients with chronic inflammatory diseases that are in remission cannot be compared to the degree of inflammation seen in patients with newly diagnosed chronic inflammatory diseases (or during disease flares)[9–14]. This comparison is true not only for direct measures of immune system activity (for instance, serum levels of IL-6), but also in terms of inflammation-induced energy expenditure[13]. Although inflammation in such newly diagnosed and active chronic inflammatory diseases can induce extra energy costs of 10–15% of an individual's total energy expenditure[1,9–12], the low-grade inflammation seen in ageing individuals or in patients with chronic inflammatory diseases that are in remission should, according to data derived from experimentally induced mild inflammation in healthy individuals[13,14], lead to maximal extra energy costs of 2–3%. If such sequelae are triggered by an energy shortage induced by energy expenditure, it follows that extra energy costs (that is, energy costs not related to inflammation) must exist during ageing or in a chronic inflammatory disease that is in remission. So what is the cause of these extra energy costs when the immune system is not solely responsible for the energy shortage? Based on the special roles of the immune system and brain in energy regulation, it is postulated that extra energy costs could be caused by increased psychomotor activity (for example, as a result of pain, stress and sleeping problems). In an update to previous models[1,15], the model proposed in this Perspectives article states that energy shortage is based on the sum of all extra energy costs (psychomotor activity plus inflammation). In ageing individuals or patients with chronic inflammatory diseases that are in remission, these extra energy costs lead to unwanted mental and physical inactivity and their associated consequences.

This Perspectives article does not aim to discuss energy regulation at the cellular level (reviewed elsewhere[16–19]) or to discuss the molecular interface between metabolism and the immune system, such as how nutrients act through pathogen-sensing and other inflammatory pathways[20]. Instead, the reader encounters an integrative approach at the level of the entire body — the bird's-eye view of an internist — to address complex symptomatology in a manner summarized by Walter B. Cannon[21]: in a healthy individual, "the internal environment is kept constant [homeostasis] so that we are freed from limitations imposed by internal and external conditions that could be disturbing." The article begins by describing the hierarchical position of the brain and immune system in energy regulation, introducing the idea of 'selfishness' and conceptualizing the interrelation between energy regulation and memory in these two systems (FIG. 1). Next, a detailed description of the concepts of energy expenditure stimulated by the immune system and energy expenditure instigated by the brain is provided, and the notions of volitional (or intentional) energy

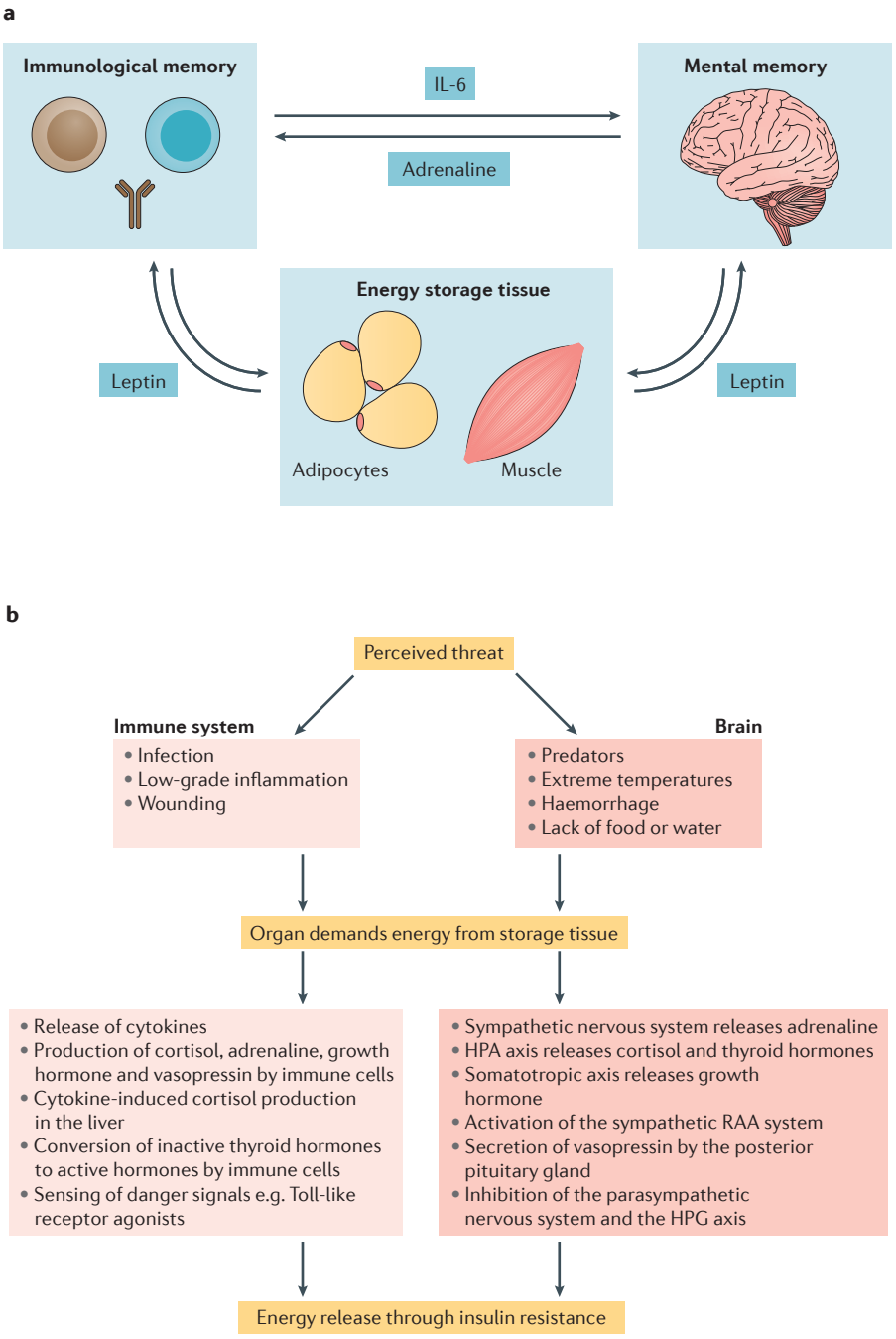

Figure 1 | **Regulation of energy storage and energy release.** Three organ systems, each of which has a form of memory, are instrumental in energy regulation, particularly in storing and releasing energy from reserves. Energy reserves provide a 'memory' of food availability, food intake, general health status and times of previous energy shortage. **a** | Energy reserves are protected by the immune system and by the brain. Signals from energy storage tissues to the immune system and the brain via leptin indicate the amount of energy stored in the body's reserves. The brain and the immune system also signal to each other by mechanisms including IL-6, adrenaline and many others. **b** | In situations in which an individual encounters short-lived energy-demanding threats, such as predators, food shortages, extreme temperatures, infectious agents, wounding and haemorrhage, either the immune system or the brain can demand energy-rich fuels by stimulating insulin resistance, lipolysis and other energy-liberating pathways. Examples of mechanisms used by the brain or the immune system to induce insulin resistance include cortisol release[92] by the hypothalamic–pituitary–adrenal (HPA) axis and also by immune cells, which can convert cortisone to cortisol locally, and vasopressin, which can stimulate lipolysis[93]. HPG axis, hypothalamic–pituitary–gonadal axis; RAA system, renin–angiotensin–aldosterone system.

expenditure (for instance, exercising at the gym) and non-volitional (or unintentional) energy expenditure[22] (for instance, an immune response against an infection) are introduced. To conclude, a model is presented that explains the appearance of long-standing problems seen in patients with chronic inflammatory diseases and during ageing as a consequence of maladaptive energy regulation.

Two 'selfish' super-systems

The main super-systems involved in energy regulation, the brain and the immune system, can be defined using concepts derived from evolutionary biology and biological anthropology[15,23,24]. Major threats to the individual, such as predators, food scarcity, thirst, extreme temperatures, infectious agents, wounding and haemorrhage are perilous aspects of life under natural conditions (TABLE 1). These threats were dominant during evolution, so can elicit immediate responses from the brain or from the immune system[15,23,24]. Since the responses to these threats demand high amounts of energy[1,25], the possibility of energy shortage is ever-present, particularly because food intake can be minimal or absent when an individual is responding to such threats[2–5]. Energetically, a living organism is a thermodynamically open system[26], so when responding to such threats in the presence of context-associated anorexia, the body depends on stored energy reserves in adipose tissue, muscle and the liver, and on other vital resources such as calcium stored in bone[1]. These energy reserves can be actively released via mechanisms that induce peripheral insulin resistance[27–29], a process that is central to energy distribution by causing the inhibition of energy-rich fuel storage. Similarly, calcium release can be triggered by the sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis acting via cortisol, or by an immune-activated increase in osteoclast activity[30–32], both of which are mechanisms that inhibit calcium storage.

In some potentially harmful situations (TABLE 1), the brain takes control to counter threats, coordinating skeletal muscles, heart, lungs and other organs to achieve this goal. Under these conditions, the brain can be thought of as being selfish, since there is no higher authority within the body to make decisions about energy distribution[29]. The brain demands energy in the form of glucose[33] using pathways specific to itself to induce insulin resistance[29].

Table 1 | **Adaptive responses to common major threats**

Threat	Immediate response(s)	Response systems
Predators	Fight or flight	Brain, SNS and HPA axis
Wounding and haemorrhage	Blood coagulation and blood pressure stabilization	• Brain, SNS, HPA axis and SNS-dependent RAA system • Standby system of blood coagulation
Food scarcity	Foraging	Brain, SNS and HPA axis
Thirst	Water-seeking behaviour	Brain, SNS, HPA axis and SNS-dependent RAA system
Cold	Warming-up and warmth-seeking behaviour	Brain, SNS and HPA axis
Heat	Sweating and cold-seeking behaviour	Brain and SNS
Infection	Immune response to infection	Immune system
Wounding	Inflammatory response	Immune system

HPA axis, hypothalamic–pituitary–adrenal axis; RAA system, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system.

Similarly, the immune system can be thought of as being selfish during the response to infectious diseases or when healing infected wounds, since it takes the highest hierarchical rank in fighting these harmful situations. The immune system also demands energy using pathways specific to itself to induce insulin resistance[28,29,34]. Glucose is the favoured fuel because it can be rapidly metabolized into cellular energy in the form of ATP, and because it is useful under both normoxic and hypoxic conditions[16,17,19,35,36]. A pertinent example of immune system selfishness was provided by observations of the innate immune system of *Drosophila melanogaster*[37]. Similar to insulin resistance in mammals, in *D. melanogaster*, adenosine release is the main factor required for energy redistribution when the innate immune system is challenged[37].

The heart, lungs, kidneys and other organs could arguably also be called selfish because they can claim energy-rich substrates independently of the brain and immune system. Indeed, this statement is true for most organs in the body at the basal level to maintain organ function[25]; even a starving individual can maintain basal function of organs for a long time (~40–60 days)[38]. In contrast to the common major threats listed in TABLE 1, these other organs do not dominate the body because they do not take the highest hierarchical rank during a response. Sometimes these organs can dominate the body in states of chronic disease, for example during chronic heart failure or chronic kidney disease[39,40]; however, these scenarios are not considered to be important forces during evolutionary history. The placenta during pregnancy and mammary glands during lactation can also be considered selfish, but further discussion of these scenarios in healthy reproducing individuals is beyond the scope of this article. Importantly, the common major threats (TABLE 1) should be considered in parallel. For example, one cannot consider the threat of starvation on its own and thereby deduce that the brain is more selfish than the immune system. Depending on the type of threat, either the brain or the immune system dominates.

In the following section, a model is proposed that interrelates the brain and the immune system, in the form of mental memory and immunological memory, respectively, with the role of energy storage organs (FIG. 1).

Memory and energy regulation

Mental memory has evolved to minimize energy expenditure or, in other words, to protect energy stores, and is tuned to ancestral priorities when examined in the context of foraging and other paleolithic tasks[41]. Foraging for food requires an enormous amount of energy; for example, when studied on three randomly selected consecutive days, the Baka hunter-gatherers of southeast Cameroon spent more energy foraging for food than they obtained by eating what they found, creating a negative net energy balance[42]. Such a situation obviously cannot be maintained, and can be prevented by the memory of foraging strategies and of food location[41], thereby decreasing the time required for successful foraging in the wild[43].

In a similar way, immunological memory acts to spare energy reserves. On an individual's first encounter with a pathogen, the immune system takes 14 days to develop a protective response[44]. This process includes shaping the optimum immune response and the clonal expansion of T cells and B cells, which are highly energy-consuming processes[1,18,45]. Notably, the induction of this initial immune response usually happens during a critical period of infection-induced anorexia — that is, cessation of voluntary energy intake caused by the infection, an example of context-associated anorexia. The immune response to a second encounter with the same infectious agent is much faster (3–5 days), as clonal expansion of T cells and B cells can start at an early time-point when the microbial load is low[44]. Usually, this second encounter is associated with only minimal context-associated anorexia, so does not affect energy intake.

Both mental memory and immunological memory are directed towards foreign entities and self. Such activities as tool-making, the invention of language, writing manuscripts and the storage of data on computer hard disks clearly show the energetic advantage of mental memory and its respective storage tools. Likewise, learned tolerance of the immune system towards harmless autoantigens and innocuous foreign antigens on the body surfaces and effector memory against microorganisms is a memory function that spares energy reserves, suggesting that immunological memory has evolved to minimize energy expenditure.

Since the brain and the immune system are vitally important in orchestrating responses to external threats (TABLE 1), the memory functions of these two super-systems can be considered to have an ultimate role: the protection of energy stores. In addition, energy reserves in adipose tissue and skeletal muscles can be considered to represent a 'memory' of the energy state and health status of the body. From this point of view, three major organ systems endowed with a kind of memory exist that are instrumental to energy regulation: the brain, the immune system and the energy storage organs (adipose tissue and skeletal muscles) (FIG. 1a). Together, these organ systems comprise the normal or adaptive energy matrix, an evolutionarily positively selected network that ultimately links mental memory, immunological memory and energy memory with insulin resistance (FIG. 1b).

Necessarily, pathways exist that connect these three forms of memory. For example, the brain and the immune system are connected by cytokines, neurotransmitters and hormones to modulate each other[46]. Another classic example is leptin, which links adipose tissue and the brain[47], and also links adipose tissue with the immune system[48]. Similarly, afferent sensory nerve fibres exist in adipose tissue[49] and skeletal muscles[50], which connect these organs with the brain. The brain also uses vasopressin to regulate adipose tissue function[51]. Another example is IL-6, an important factor in skeletal muscles that interferes with the brain and the immune system[52], and that can also challenge the brain when produced by the activated immune system[46]. Macrophage-derived IL-6 can directly lead to lipolysis in adipocytes[53,54], and the resulting circulating free fatty acids, together with glycerol, stimulate hepatic gluconeogenesis in animal models[55]. Many more examples can be provided, but the general principal remains that such crosstalk serves to integrate the three memory organ systems.

Energy costs in inflammation

Immune cells require energy for housekeeping functions, as well as for a variety of specific tasks such as migration, cytokine synthesis, phagocytosis, antigen processing and other effector functions[45,56]. When immune cells are stimulated *in vitro*, they require ~25–30% more energy than quiescent immune cells[45]. This increase is mirrored in patients with active chronic inflammatory diseases, in whom the energy expenditure of peripheral blood mononuclear cells (PBMCs) increases to 25–30% above the normal level seen in healthy or immunosuppressed individuals[12]. Similar results are also seen in PBMCs from patients with acute infections[12].

An individual with a sedentary lifestyle who is 1.80 m tall and weighs 85 kg requires ~10,000 kJ daily (7,500 kJ of which daily requirement represents the resting metabolic rate)[25] (FIG. 2). The total amount of energy required by the entire immune system in an inactivated state is ~1,600 kJ daily, and this level can increase by 25% during mild activation to 2,000 kJ daily (REF. 1). This amount of energy expenditure is similar to that required by resting skeletal muscles and the brain[1]. During acute infections such as sepsis, the total energy expenditure of the immune system can increase by 30–60%[25,57], whereas chronic low-grade infections, such as chronic hepatitis C in patients with fully compensated liver disease, can lead to an increase in total energy expenditure of 10%[11], illustrating that even low-grade inflammation can lead to extra energy costs.

The range of the pro-inflammatory load in different situations is enormous. When serum IL-6 is measured by the same high-sensitivity ELISA as an estimate of inflammation, the pro-inflammatory load can range from 1–2 pg/ml in healthy young individuals[58] and 2–4 pg/ml in healthy elderly individuals[58], to 6–7 pg/ml in caregivers of patients with Alzheimer disease (a situation of psychological stress)[59], 10 pg/ml in patients with well-controlled RA[60], 100 pg/ml in newly diagnosed patients with RA, and can even climb as high as 10,000 pg/ml in patients with sepsis (R.H.S. unpublished observations). Thus, the level of energy expenditure experienced by an individual can be expected to differ depending on their pro-inflammatory load. The idea that energy expenditure is proportional to the degree of inflammation has been further exemplified in studies in healthy volunteers who were injected with recombinant IL-6 (REF. 13) or lipopolysaccharide[14]. In comparison with untreated active chronic inflammatory diseases or even sepsis, the increased levels of inflammation seen during ageing, in situations of psychological stress and in patients with chronic inflammatory diseases that are in remission are not considered to constitute situations of high energy expenditure. By contrast, in untreated active chronic inflammatory diseases, the overactive immune system dominates energy distribution within the body.

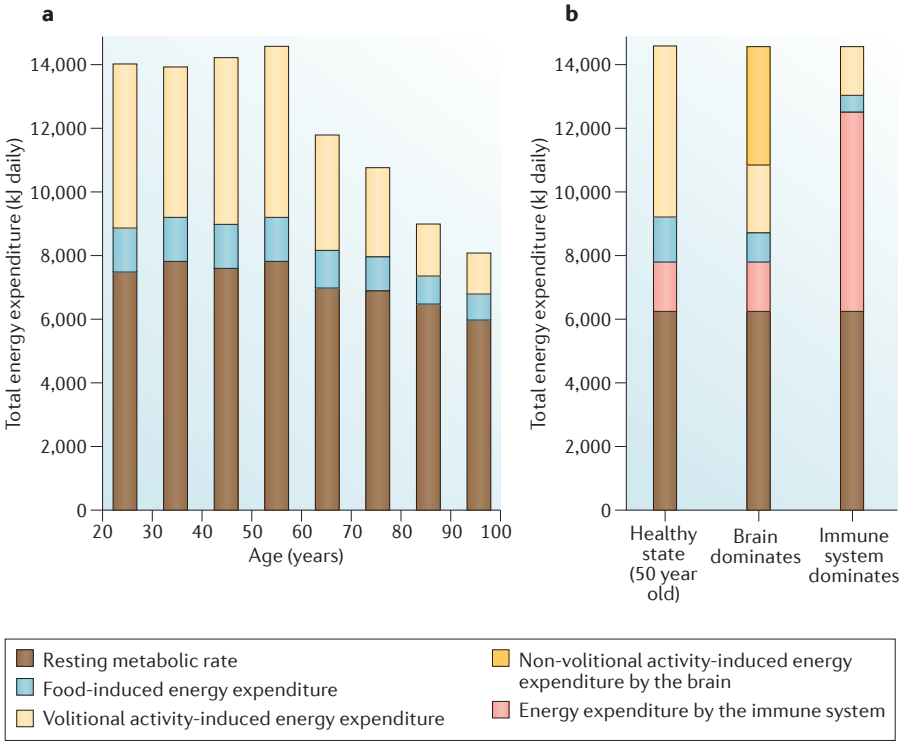

Figure 2 | **Average total energy expenditure for adults under various conditions. a** | Patterns of energy expenditure change as healthy individuals age[77]. The resting metabolic rate (or basal metabolic rate) is the amount of energy expended by an individual in the morning, 30 minutes after awakening, while lying in bed, relaxed, undertaking no physical activity and in thermoneutral conditions after one night of fasting. Food-induced energy expenditure, the thermogenic effect of food, is ~10% of the total energy expenditure under normal conditions. Activity-induced energy expenditure depends on the activity itself and whether it is volitional or non-volitional. **b** | An illustrative example of the average energy expenditure of a healthy 50 year-old individual; an individual with a 'dominant brain' (high levels of psychomotor activity and non-volitional physical activity); and an individual with a 'dominant immune system' (high levels of inflammatory activity and low levels of volitional physical activity). Notably, the energy expenditure of the immune system cannot yet be measured independently of the resting metabolic rate, so in this example the energy expenditure of the immune system is provided according to previous calculations[1].

Energy costs of brain activation

When an individual has a manic episode, psychomotor activity is high and energy expenditure is increased[61,62]. Similarly, energy expenditure can markedly increase in patients with dementia who have high levels of psychomotor activity, leading to cachexia[63]. These are special situations with high levels of psychomotor activity; however, when common forms of brain activation in the context of chronic inflammatory diseases or normal ageing are considered, pain, psychological stress, sleep alterations and anxiety can all become relevant. The effects of smoking should also be considered, as smoking can stimulate psychomotor activity[64,65]. These sequelae are not usually a major focus of treatment strategies, even though the associated psychomotor activity can induce extra energy costs.

An acute state of pain increases energy expenditure by up to 60%, as observed when painful electrical stimuli are applied to the abdominal skin of healthy individuals[66]. In this setting, energy expenditure parallels heart rate, blood catecholamine levels and levels of serum cortisol; thus, pain can increase insulin resistance[67]. Pain-induced increases in energy expenditure are fuelled by many energy sources, although the largest increase is seen in glucose utilization[66]. Similarly, postoperative removal of analgesic medication (resembling a more chronic pain situation over several days), can lead to a high level of pain and an increase in energy expenditure of 15%[68]. For ethical reasons, long-term experimental studies on patients with chronic pain are not possible, but the available evidence indicates that pain entails extra energy costs.

During a period of acute psychological stress, such as during a laboratory stress test, the energy supply to the human brain increases by 12%[69]. Directly following a 10-minute stress experiment, the general energy intake increased by 26% of the normal daily requirements of the brain (570 kJ), and the test induced a state of "cerebral insulin resistance" (REF. 69). Neurodegenerative diseases with high levels of physical activity, such as Parkinson disease, Alzheimer disease and Huntington disease, can be chronically stressful and, in the case of Huntington disease, can increase energy expenditure up to 20%[63]. Thus, the added stress caused by diseases such as dementia might result in extra energy costs. Similarly, the added stress of providing care for a beloved family member increases energy expenditure by 20%[70]. Psychological stress seems to be expensive in terms of energy consumption.

Many of the aforementioned conditions also decrease the quality of an individual's sleep. Normal sleep is accompanied by a 30% decrease in energy expenditure during sleeping time[71], whereas reduced sleeping time and sleep quality can increase energy expenditure by 5–15%[72,73]. In the extreme situation of obstructive sleep apnoea, energy expenditure can increase by as much as 30%[74]. In this situation, it is as if the individual has not reduced energy expenditure at all while asleep. Importantly, energy uptake following sleep disruption (especially at night after an evening meal) can exceed sleep alteration-dependent energy expenditure, resulting in a positive net energy balance[72]. This situation is particularly relevant in obesity when levels of physical activity are low.

Anxiety can also increase energy expenditure, as shown in a study in which 79 male students were investigated for state and trait anxiety[75]. Notably, students who scored highly for anxiety (highest quartile) had a 10% increase in energy expenditure compared with students with a low anxiety score (lowest quartile)[75]. Furthermore, smoking not only increases the level of activity in the central and peripheral nervous systems, but also affects energy expenditure. In a 2014 study, total energy expenditure was increased by ~15% in men who smoked more than six cigarettes per day compared with men who had never smoked[64]. In summary, typical situations associated with psychomotor activation, which can happen in patients with chronic inflammatory diseases or during ageing, can cause extra energy costs.

Non-volitional energy costs

Extra energy expenditure caused by the immune system in the form of inflammation, or by the brain in the form of pain, psychological stress, sleep alterations and anxiety, can create an energy shortage. Reduced supplies of energy-rich fuels are particularly pertinent in situations involving context-associated anorexia[2–5,76]. These extra energy costs are deemed to be non-volitional or unintended. During the process of ageing or in a patient with a chronic inflammatory disease that is in remission, extra energy costs are due to low-grade inflammation[11] and, if present, non-volitional brain-derived energy expenditure. High levels of immune system-induced energy expenditure, such as those seen in patients with newly diagnosed chronic inflammatory diseases or in patients with chronic inflammatory diseases during a flare, can also often be accompanied by brain-derived extra energy costs, in particular due to pain and altered sleep.

Although, under normal conditions in a healthy individual, volitional activity-induced energy expenditure slowly decreases during ageing[77] (FIG. 2a), volitional activity can decrease immediately in a situation in which the brain or the immune system suddenly becomes dominant (FIG. 2b). This change can occur in young or old individuals, but is more problematic in the elderly owing to the natural reduction in volitional energy expenditure and energy intake that occurs as an individual ages[77] (FIG. 2a).

The non-volitional energy expenditure caused by inflammation can be very high[25,57], and a situation of acute energy shortage cannot last for longer than 19–43 days before stored energy reserves are depleted[38]. This time-frame is known as the 'complete energy consumption time' in the presence of complete anorexia, as calculated for an individual infected with influenza virus[32,38]. Physical considerations of energy follow simple mathematical rules of summation and subtraction, as shown in an example of a healthy individual of 50 years of age[77] (FIG. 2b). Using the same example, BOX 1

Box 1 | Calculation of total energy expenditure with non-volitional energy costs

Total energy expenditure (EE in the following equations) is a mathematical sum comprising many parts:

Total EE = resting metabolic rate + food-induced thermogenesis + volitional physical and mental EE

In a situation in which there are high levels of non-volitional activity in the immune system or brain, the equation must be modified:

Total EE = resting metabolic rate + food-induced thermogenesis + volitional physical and mental EE + non-volitional EE

Assuming that non-volitional energy expenditure occurs in the presence of normal levels of total energy expenditure and resting metabolic rate, with a reduced food-induced thermogenesis due to context-associated anorexia[2–5], there will be a reduction in volitional physical and mental activity. In this situation, a reduced portion of total energy is available for volitional activities and, additionally, context-induced anorexia hinders or prevents adequate energy intake to compensate for this loss.

Table 2 | **Activities causing a non-volitional increase in daily energy expenditure**

Non-volitional activity	Extra energy costs*	Refs
Inflammation	25–60%‡	1,57
Chronic low-grade infection§	10%	11
Acute pain	up to 60%	66
Chronic pain	15%	68
Psychological stress	up to 30%	63,69,70
Sleep alterations	up to 30%	72–74
Anxiety	up to 10%	75
Heavy smoking	up to 15%	64

*Extra energy costs are relative to total energy costs in healthy individuals, and are given as a percentage of the basal or total energy expenditure. ‡Range spans mild activation to sepsis. §Such as hepatitis C infection.

explains how a reduced proportion of total energy is available for volitional activities when non-volitional activities occur (TABLE 2).

Non-volitional activities causing energy expenditure cannot be viewed independently, as the causes of non-volitional energy expenditure often accompany each other (for instance, pain is often accompanied by disturbed sleep and pain represents a form of psychological stress). The cumulative percentage increase of extra energy expenditure will therefore not be the sum of the individual percentages mentioned in TABLE 2. Nevertheless, when accompanied by context-induced anorexia, the increased extra energy expenditure for such non-volitional activities should lead to a shortage of energy available for partaking in volitional activities. This energy shortage can lead to undesired sequelae resulting from reduced physical and mental activity[78–80].

Consequences of energy shortage

Although this article cannot explain the growing field of evolutionary medicine in detail (see REFS 15,23,24), one can summarize that, during evolution, homeostatic networks were positively selected for use in short-lived acute energy-consuming responses rather than for use in long-standing chronic inflammatory diseases[15]. Long-standing responses of the super-systems (for example, courtship behaviour, mental memory and immunological memory) were positively selected to support reproduction and to protect energy stores. Although several genetic risk factors that favour the development of chronic inflammatory diseases have been identified in these super-systems, such as *HLA-DR4* as a risk factor for RA[81], these factors are unlikely to have been positively selected for their ability to induce or specifically aggravate such diseases. Instead, these factors increase reproductive fitness in individuals of pre-reproductive and reproductive ages (for example, *HLA-DR4* offers some protection against Dengue haemorrhagic fever[82]), with the resulting fitness benefits at reproductive age expected to be higher than the fitness costs at post-reproductive age[83] (for example, the development of RA). Overall, an individual's lifetime reproductive success will be increased by traits such as this, thereby providing an explanation for why factors that favour chronic inflammatory diseases have not been out-selected during evolution. In fact, under specific environmental conditions, such factors might even have been positively selected under a different somatic context (such as for fitness during reproductive age but not for post-reproductive individuals)[15,83].

The signs and symptoms that often accompany chronic inflammatory diseases are elements of evolutionarily positively selected programmes. These programmes are in no way unfavourable when used for a short period of time; they are adaptive, can be used in various situations when energy is scarce and can help to build the adaptive energy matrix to protect energy stores (FIG. 3a). Utilizing these programmes can provide the body with a sufficient supply of energy-rich fuels and other nutrients, such as calcium, in the presence of threats and in situations in which context-induced anorexia occurs[32].

In previous articles[1,15,29,32,38], I indicated that the signs and symptoms mentioned at the beginning of the article (see Supplementary information S1 (table)) are merely the unfavourable sequelae of chronic disease, but this is not correct. Instead, I propose a new model, in which these signs and symptoms represent positively selected and highly favourable coping mechanisms used by the body in situations of short-lived energy undersupply. These adaptive responses are not designed to be used for long periods of time; in fact, long-term use of these mechanisms will necessarily lead to the development of a maladaptive energy matrix, with concomitant loss of energy reserves. If an energy shortage cannot be overcome, volitional physical and mental energy expenditure markedly decrease for a prolonged period of time (FIG. 3b). The long-term consequences of reduced physical and mental activity include cardiovascular diseases[84], metabolic diseases and obesity, cognitive dysfunction and pain[85,86], neuro-degenerative disease[87,88], psychiatric diseases[89], frailty[90] and other chronic diseases such as cancer[91]. These conditions all constitute risk factors for early death.

Conclusions

In this Perspectives article, I have provided the reader with a framework that accounts for increased energy expenditure caused by psychomotor activity in chronic

Glossary

Context-associated anorexia
Anorexia that is dependent on a particular circumstance, such as sickness behaviour during an infection, mental activation in bipolar disorder or age-related anorexia.

Insulin resistance
A condition of low insulin sensitivity with marked changes to the insulin receptor and to downstream signalling pathways; because insulin is responsible for the storage of glucose and free fatty acids, a lower insulin sensitivity leads to reduced energy storage and increased levels of energy-rich fuels in the circulation.

Pro-inflammatory load
A high level of systemic activity in the immune system, as measured by an increased erythrocyte sedimentation rate, or increased levels of serum C-reactive protein or serum IL-6.

Psychomotor activity
Activity induced by the brain that leads to activation of the skeletal muscles and the heart.

Super-systems
Integrative systems at the top level of homeostatic regulation of the body; examples include the nervous, endocrine and immune systems.

Thermodynamically open system
Systems, such as the human body, that can take up and lose energy, mainly in the form of heat.

State and trait anxiety
State anxiety is how a person is feeling at the time of a perceived threat, whereas trait anxiety is the enduring disposition to feel stress, worry and discomfort.

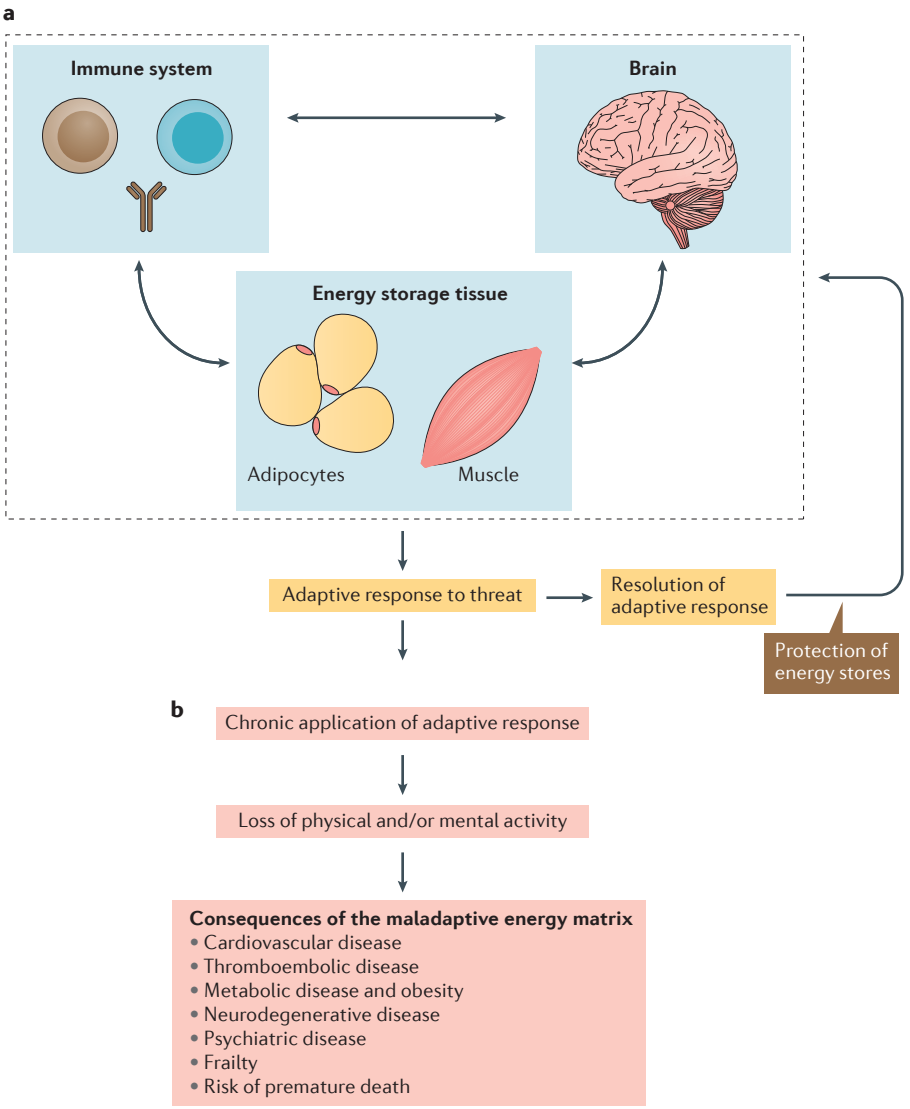

Figure 3 | **The adaptive and maladaptive energy matrices. a** | The adaptive energy matrix represents the evolutionarily positively selected normal or adaptive response to a threat. The brain, immune system and energy storage organs (adipose tissue and skeletal muscles) communicate with each other and induce adaptive responses depending on the prevailing short-term threat. Such adaptive responses are necessary to protect energy stores. **b** | Short-lived, adaptive responses to threats were not positively selected for use in chronic inflammatory diseases or during ageing, so prolonged use of these responses falls outside of adaptive norms. Chronic application of these responses transforms the adaptive energy matrix into the maladaptive energy matrix, leading to disease and premature death. Central to the health problems caused by the maladaptive energy matrix is a loss of physical and mental activity in an individual.

inflammatory diseases and during ageing. Previous models mainly focused on increased energy expenditure caused by a highly active immune system[1], but did not account for energy expenditure caused by psychomotor activity, making these previous models applicable to patients with active chronic inflammatory diseases, but not to patients with chronic inflammatory diseases that are in remission or elderly individuals. In individuals from the last two groups, the proportion of energy expended by the immune system is small, so immune-derived energy shortage cannot explain the appearance of adaptive programmes in these individuals (see Supplementary information S1 (table)): immune system-independent energy expenditure must be involved.

The proposed framework is based on the idea that energy shortage in these groups of individuals depends on increasing energy expenditure caused by high levels of psychomotor activity. For example, pain, psychological stress, sleep alterations and anxiety increase energy expenditure. This framework includes aspects of evolutionary medicine (concepts of selfishness, memory crosstalk and short-term adaptive programmes), energy regulation (energy expenditure in inflammation, energy expenditure in brain activation and the idea of three memory organ systems relevant to energy protection) and neuroendocrine adaptive programmes that are positively selected to overcome short-lived activation of the immune system or brain. The proposed model demonstrates the concept of non-volitional energy expenditure, which reduces physical and mental activity, ultimately leading to an increased risk of cardiovascular diseases, metabolic diseases and obesity, cognitive dysfunction and pain, neurodegenerative diseases, psychiatric diseases, frailty and cancer (FIG. 3).

In the future, studies should aim to quantitatively detect sequelae of chronic inflammatory diseases (see Supplementary information S1 (table)) and to measure energy expenditure, energy intake and physical activity using a variety of techniques. The current goal of achieving disease remission is not ambitious enough. Physicians and pharmaceutical companies should take the next step towards an integrative approach and conduct randomized controlled trials that look beyond immunosuppression.

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