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The energetic cost of allostasis and allostatic load

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Abstract

Chronic psychosocial stress increases disease risk and mortality, but the underlying mechanisms remain largely unclear. Here we outline an energy-based model for the transduction of chronic stress into disease over time. The energetic model of allostatic load (EMAL) emphasizes the energetic cost of allostasis and allostatic load, where the "load" is the additional energetic burden required to support allostasis and stress-induced energy needs. Living organisms have a limited capacity to consume energy. Overconsumption of energy by allostatic brain-body processes leads to *hypermetabolism*, defined as excess energy expenditure above the organism's optimum. In turn, hypermetabolism accelerates physiological decline in cells, laboratory animals, and humans, and may drive biological aging. Therefore, we propose that the transition from adaptive allostasis to maladaptive allostatic states, allostatic load, and allostatic overload arises when the added energetic cost of stress competes with longevity-promoting growth, maintenance, and repair. Mechanistically, the energetic restriction of growth, maintenance and repair processes leads to the progressive wear-and-tear of molecular and organ systems. The proposed model makes testable predictions around the physiological, cellular, and sub-cellular energetic mechanisms that transduce chronic stress into disease risk and mortality. We also highlight new avenues to quantify allostatic load and its link to health across the lifespan, via the integration of systemic and cellular energy expenditure measurements together with classic allostatic load biomarkers.

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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.

Keywords

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1. Introduction

The fundamental distinguishing feature between life and death is the flow of energy. Compared to the living human body, the dead body harbors the same DNA sequence and molecular composition, the same number of cells, and the identical anatomical arrangement of organs. The dead body, however, lacks energy flow. Energy fuels our ability to sense and feel, our behaviors, the thinking process, and the consciousness through which we perceive and respond to the world around us (Shulman et al., 2009). As a result, the living human experience, including stress responses (Picard et al., 2018a), consumes a considerable amount of measurable energy (Kraft et al., 2021). Yet, we know remarkably little about the mechanisms that sustain and guide energy consumption and, specifically, how bioenergetic disturbances contribute to disease risk and mortality (Wallace, 2010).

A topic of paramount importance to biomedical sciences concerns the mechanisms by which psychological factors promote states of health and disease (Cohen et al., 2019). Living organisms evolved the ability to anticipate internal and environmental perturbations, and in turn mobilize adaptive physiological recalibrations to minimize deviations, a phenomenon termed *allostasis* (Sterling and Eyer, 1988). Building on this concept, McEwen and Stellar proposed that the chronic activation of allostatic systems leads to maladaptive recalibrations that end up "wearing out" the organism's organ systems. This phenomenon was termed *allostatic load* (McEwen and Stellar, 1993).

Over the last few decades, the allostatic load model (McEwen, 1998) has evolved and guided research on the stress-disease cascade. This model provides an integrative theoretical framework to conceptualize and measure chronic stress, including the central role of the brain in transducing subjective experiences into biological changes (McEwen, 2006) and the availability of environmental energetic resources that support allostasis (McEwen and Wingfield, 2003). The internal, biological basis for the "wear-and-tear" of allostasis over time as it becomes allostatic load, however, still remains as a major knowledge gap in the stress-disease cascade. Understanding the manifestations of allostatic load and overload at multiple levels of biological complexity (organismal, cellular, sub-cellular) has the potential to help clarify *why* allostatic load is damaging. What is it about the allostatic load primary mediators (e.g., stress hormones, cytokines, metabolites) that disrupt health-sustaining biological and physiological functions? *When does adaptive allostasis become allostatic load and overload?* We argue that a more complete allostatic load model is achieved by understanding the interplay of allostasis and allostatic load with the fundamental biological constraints related to energy transformation and allocation within the brain-body unit.

1.1. Limits to energy transformation impact health

At any given time, cells can transform only a finite amount of energy (Niebel et al., 2019). The biophysical limit to sustainable energy transformation constrains both *cellular behavior,* such as how rapidly cells can divide (Yang et al., 2021), and *human physiology,* such as how long one can run or how well one can reproduce (Pontzer, 2018). Stress-related physiology under the control of the nervous system is also naturally energy-dependent (Thayer and Sternberg, 2006). As a result, among living organisms, including humans, energy flow drives function and sets the boundaries of adaptive capacity. The constant requirement for energy to power life-sustaining cellular and physiological activities explain why deficits in available energy can impair health and contribute to various disease states (Picard et al., 2016).

The requirement for energy to sustain human health is illustrated perhaps most clearly in individuals with rare mitochondrial disorders. *Mitochondria* are small intracellular organelles that transform energy using oxygen and food substrates (Lane, 2022). People with mitochondria that cannot efficiently transform energy suffer from multisystem disease and die prematurely (Gorman et al., 2016; Kaufmann et al., 2011), highlighting the central role of mitochondria, and energy more generally, in human health (Picard, 2022). If we want to better understand health, resilience, and disease risk, we must therefore understand how the body's limited energetic resources are allocated and distributed between competing processes.

In this narrative review and perspective paper, we discuss the energetic basis of allostasis, allostatic states, allostatic load, and allostatic overload. We describe how limits to energy consumption or expenditure may establish a threshold wherein adaptive allostasis turns into damaging allostatic states, allostatic load, and allostatic overload. We draw from three bodies of complimentary literature – cell biology, human physiology, and psychology – to illustrate how the increased energy expenditure known as *hypermetabolism* may represent the linchpin of the stress-disease cascade. In turn, this energetic view of stress and health illuminates potential mechanisms of stress resilience and vulnerability, advancing the science of allostatic load.

2. The allostatic model of the stress-disease cascade

The *Nomenclature* section defines key historical terms developed to pinpoint specific stages of the allostatic load model of the stress-disease cascade. Here we summarize the progression across these stages.

When living organisms experience real or imagined stressors, a set of anticipatory *allostatic responses* are triggered to cope and promote survival. As these stressors persist, the resulting allostatic responses are sustained over time, becoming under- or over-activated. The normal regulatory set-points and/or dynamic range are consequently altered, transitioning transitory allostatic responses to *allostatic states* (Koob and Le Moal, 2001). Allostatic states, as originally outlined by McEwen, can take different forms including repeated activation, lack of habituation, prolonged response, and inadequate response (McEwen, 1998). Persistent activation of allostatic states incurs additional energetic costs and triggers more lasting cellular and physiological recalibrations – such as hyperglycemia, elevated blood lipids,

and elevated circulating stress mediators (cortisol, catecholamines, etc) – that constitute *allostatic load*. When sustained over time, allostatic load triggers compensatory functional and structural recalibrations causing progressive dysregulation among the organism's physiological network. Well known physiological examples include the stiffening of the arteries to sustain high blood pressure, the downregulation of hormone receptors on target tissues to counteract overstimulation, and the remodeling of the brain circuitry and anatomy in response to neurochemical factors. Over time, these end stage recalibrations lead to the breakdown of communication and of regulatory systems, termed *allostatic overload* (McEwen and Wingfield, 2003). At the cellular level, allostatic overload manifests in molecular changes, like the accumulation of damage and accelerated aging, culminating in the onset and progression of disease, and ultimately premature death. Importantly, this stress-disease cascade progressing from adaptive allostasis, to maladaptive allostatic states and allostatic load, and finally to allostatic overload activates a large spectrum of *energy-consuming* processes (Fig. 1).

3. What is the purpose of allostasis?

Energy is the driving force of life, but also is a limited resource. As mentioned above, living organisms operate under energetic constraints imposed by their ability to transform energy (Yang et al., 2021). The behaviors of their cells, tissues, and organs, like the brain and immune system, are bound and limited in scope by how much energy they can transform at any given moment. This constraint has forced the evolutionary selection of organisms optimized for energy efficiency that can sustain life at the lowest amount of energy expenditure possible (Makarieva et al., 2008). By maximizing energetic efficiency, organisms can allocate energy to fuel adaptative processes and other health- and longevity-promoting functions, including basic processes such as maintanance and repair, to more complex ones including growth, reproduction and cognition.

From this energetic perspective, the evolution of likes and dislikes, feelings and emotions, and approach/withdrawal behaviors arose to minimize the energetic cost of life (Damasio, 2018). We tend to like things that give or save us energy (e.g., palatable food and warm clothes, respectively), and dislike things that cost us energy (e.g., cold rain). These and other dimensions of physiological regulation allow organisms to anticipate and avoid energetically costly exposures, in favor of more "comfortable" (i.e., energy saving) conditions that minimize physiological perturbations (Sterling, 2020). Below we discuss allostasis and its relation to the human mind.

3.1. Anticipation, allostasis, and adaptation

On a daily basis, the imperative to maximize energetic efficiency exists in a direct tradeoff with our natural instincts to anticipate, prepare, and adapt to stressors. Through anticipation, allostasis prepares the organism for upcoming challenges, thereby increasing the future probability of survival (Weiner, 1992). Consider a person facing a potential predator. Upon the *perceived* threat of an attack, an evolutionary selected allostatic defense response immediately kicks into action. The release of catecholamines and cortisol is triggered,

increasing breathing and heart rates, activating sweating, and liberating glucose and lipids in the bloodstream.

The adaptive value of this *integrated* allostatic or stress response is clear: (i) the elevated breathing and heart rates increase blood pressure and oxygen delivery to all vital organs that would require rapid energy delivery should 'fight-or-flight' (or 'tend-and-befriend' (Taylor et al., 2000)) responses be necessary; (ii) the sweat response preemptively cools down the body to prevent overheating expected from the heat released during muscle contraction and brain activity; and (iii) the mounting hyperglycemia/hyperlipidemia ensures that energy substrates are readily available in our blood for energy transformation within the brain's mitochondria, to power the planning and execution of the fight-or-flight response. A beautifully coordinated, whole-body response to a potential threat and anticipation of endpoints.

Allostasis is anticipatory, which means that the above-described cascade can occur whether or not the threat ultimately materializes. Indeed, the human mind is among the most potent triggers of wasteful allostasis. Self-preservation (Dickerson and Kemeny, 2004) and the self-sustained adverse psychological states, in the form of preservative cognitions like worry and rumination (Brosschot et al., 2005), directly drive energy-dependent allostatic responses. From an evolutionary point of view, the existence of anticipatory and future-oriented behaviors suggests that allostatic mechanisms are more advantageous than the alternative that consists of reacting and producing emergency responses only after the stressor has happened (Bredemeier and Berenbaum, 2008). Emergency responses, such as healing wounds and fighting infection (because one was unable to run fast enough), have a higher energetic cost and are potentially harmful. By anticipating the future, allostasis therefore puts the organism in the best possible state to face current and upcoming challenges.

The brain is central to anticipatory allostatic responses (McEwen, 2006). As a threat-detecting master, the brain is an organ specialized in reacting, anticipating, and ruminating. These processes optimize behavior by minimizing uncertainty (Friston, 2010). Uncertainty is fundamentally costly because it leads to larger deviations from the optimum. Not knowing what the future holds precludes the ability to anticipate change, producing larger, more energetically costly deviations to correct. Adequately predicting future exposures lowers uncertainty, allowing an organism to (theoretically) perfectly prepare and adapt optimally to upcoming challenges.

Optimal adaptation means the lowest degree of perturbation, which requires the least amount of energy expenditure to correct deviations (Nijhout et al., 2017). As a result, the brain integrates inputs from multiple senses and compares them against memories of past experiences to predict future exposures. By doing so, it minimizes the deviation between the state of the organism and reality. This idea is captured by the free-energy principle (Friston, 2010), which provides a framework to understand the existence and function of future-oriented energy-saving strategies used by allostasis. Allostasis minimizes the energetic costs associated with uncertainty, possibly explaining why allostasis is adaptive and why it evolved in the first place (Sterling, 2020). Allostasis likely exists because, in the long-term, it conserves energy.

4. Allostasis costs energy

Although allostasis sustains health in the long-term by ensuring preparedness and minimizing the energetic cost of adaptation, *it itself costs energy* in the short-term (Thayer and Sternberg, 2006). Allostasis imposes an *energetic load* on the system. As this cost persists and rises, it contributes to allostatic states and allostatic load. Here we propose that the *load* in allostatic load is the additional energetic burden that the organism must bear to adapt and survive. Excess energy consumption above one's optimum is defined as *hypermetabolism*. In this section we review the limited quantitative evidence that stress-induced allostasis and acute responses to mental stress consume excess energy and trigger hypermetabolism.

4.1. Experimental studies in laboratory animals and in humans

The idea that psychological or mental stress, and the resulting allostatic processes, influence energy expenditure goes back almost a century (Christie, 1935; Whitehorn et al., 1930). The hypermetabolic effects of acute and chronic stress, and some potential mechanisms, have been examined in both laboratory animals and humans.

Most studies have addressed the link between stress and energy expenditure by a technique called indirect calorimetry, where oxygen consumption (ideally in parallel with carbon dioxide production to increase precision) is measured from the expired breath (Mehta et al., 2015). In birds, one study found that acute stress from noise exposure (15 min) increased energy expenditure by ~15 %, the magnitude of which correlated with the elevation in blood corticosterone (Jimeno et al., 2018). Similarly, restraint stress (3 h) in rats increased energy expenditure by ~20–25 % (Harris et al., 2006), whereas milder chronic unpredictable stress (3 weeks) increased energy expenditure by a more modest ~12 % (Garcia-Diaz et al., 2007). Overall, these and other animal studies show that non-injurious experimental mental stressors reliably activate allostatic processes that increase the energetic cost of living in animals.

Allostasis from acute psychological stress also increases energy expenditure in humans. For example, healthy men solving Ravens matrixes (combination of detailed observation and abstract reasoning) exhibited up to a ~9 % increase in total body energy expenditure, whereas performing mental arithmetic under time pressure (12 min) increased energy expenditure by ~13 % (Carroll et al., 1986). In another study, mental arithmetic under time pressure (15 min) caused a ~28 % increase in energy expenditure (Sawai et al., 2007). Similarly, mental arithmetic (8 min) with rising time pressure and involving elements of competition (an observer taking scores, a leader board, and performance incentive) and punishment (losing points, brief loud aversive sound with failure), increased energy expenditure by ~37–42 % (Balanos et al., 2010; Carroll et al., 2009), suggesting the potential escalating effect of psychological stress/threat on the energetic cost of allostasis. In line with this idea, one study found that a longer version (30 min) of the stressful combination of mental arithmetic and Stroop's color-world conflict test increased energy expenditure by ~67 % (Delarue et al., 2003). While most studies only evaluated men, two studies showed similar effects in women. Healthy women performing a combination of mental arithmetic and Stroop's color-world conflict test (15 or 30 min) exhibited a 39–45 %

increase in energy expenditure (Seematter et al., 2002, 2000). Just as in rodents and birds, mental stress consistently increases whole-body resting energy expenditure in humans by ~9 %–67 %, depending on stressor intensity and duration.

4.2. Non-experimental studies

Non-experimental studies of human psychological traits and stress hormones also provide converging evidence for the hypermetabolic effects of allostasis and allostatic load. For example, young men with high trait anxiety were found to have ~14 % higher energy expenditure than those with low anxiety (Schmidt et al., 1996). On the other hand, individuals who regularly engage in relaxation practices like yoga, which dampen arousal and allostatic processes, may consume up to ~15 % less energy at rest (Tyagi et al., 2014). Thus, both default arousal-generating (i.e., threat) and calming (i.e., safety) psychological states (Brosschot et al., 2017) can influence energy metabolism.

Hormones also directly influence energy expenditure. Basal circulating levels of both catecholamines (Hollstein et al., 2020) and cortisol (Damjanovic et al., 2009; Haase et al., 2016), which reflect the activation of two major stress axes contributing to allostasis and allostatic load, positively correlate with how much energy the body-brain unit consumes to sustain life over a 24-hour period. Moreover, experimental administration of catecholamines and glucocorticoids is sufficient to trigger hypermetabolism (Ratheiser et al., 1998; Tataranni et al., 1996). In the context of clinical hypermetabolism, such as in burn patients, blocking adrenergic signaling can mitigate hypermetabolism (Nunez--Villaveiran et al., 2015), providing direct evidence that primary stress mediators can contribute to physiological hypermetabolism. Based on laboratory stress studies, at least a third of the hypermetabolic effects of acute psychological stress may be attributable to sympathetic nervous system activation and to the elevation in heart rate (Sawai et al., 2007), providing initial clues about the origins of hypermetabolism during stress. In fact, *whole-body energy expenditure can be understood as the integrated cost of the major stress systems*, including glucocorticoid signaling by the hypothalamic pituitary-adrenal (HPA) axis, adrenergic signaling by the sympathetic-adrenal-medullary (SAM) axis, and other stress response pathways. Psychological stress alone, therefore, is sufficient to increase energy expenditure in humans, possibly through well-known allostatic mediators.

4.3. Sources of hypermetabolism and mental activity

Whether stress-related elevations in energy expenditure arises from mental activity or peripheral physiological processes is not entirely resolved. The long history of interest in the cost of mental activity (Sourkes, 2006) has largely concluded that the energetic cost of mental operations is less than our intuition would suggest. Brain energy consumption increases only marginally during deliberate mental activity (Raichle, 2015; Sokoloff, 1977). This increase likely arises from the fact that the brain, despite its relatively small size representing < 2 % of body weight, consumes ~20–24 % of the body's total energy expenditure at rest (Mink et al., 1981; Wang et al., 2010). One explanation for the cheap, nearly free, cost of mental activity is that the brain appears to compensate for task-evoked energy expenditures. Imaging studies have shown that local task-evoked increases in brain activity in specific areas – which are typically less than 5 % in magnitude (Raichle and

Mintun, 2006) – are offset by decreases in activity in other brain areas. As a result, specific mental operations yield only a modest global increase in brain activity and energy consumption (Shulman et al., 2014). The fact that stress-induced hypermetabolism cannot be explained by increased brain energy consumption implicates other multi-system, brain-body processes. Next, we return to energy expenditure at the organism level and discuss the partitioning of energy costs across transitions from allostasis to allostatic load.

5. Allostasis and stress-induced energy expenditure (ASEE)

From an accounting perspective, the energetic costs of allostasis are added on top of other costs that sustain the organism. The human energy expenditure literature generally distinguishes between three main sources of energetic costs (Careau et al., 2021). First, the *basal metabolic rate* (BMR) includes the cost of all vital operations that regulate and maintain physiological functions: breathing to sustain blood flow and ensure the availability of nutrients systemically, neural activity that allows cognition and anticipation, plus physiological functions including hematopoiesis (i.e., the production of blood cells in the bone marrow) and many others. Second, the *thermic effect of food (TEF)* that refers to the energy required for digestion. Third, the *activity-related energy expenditure (AEE)* that sustains the demands of waking life, including movement, talking, listening, climbing stairs, typing on the computer and other daily activities. Finally, *thermoregulation* – the energy required to maintain body temperature – is generally grouped together with BMR or AEE. Together, these costs add up to an individual's *total energy expenditure (TEE)* (Pontzer et al., 2021), reflecting how much energy it costs an organism to stay alive.

On top of the life- and behavior-sustaining energy costs are the energy costs of stress-induced allostatic states, allostatic load, and allostatic overload. We term this component *allostasis & stress-induced energy expenditure* (*ASEE*). To position the additional energy costs associated with allostatic load within this energy landscape, we divide energy expenditure into different categories and consider the concept of the energy reserve.

The *energy reserve* component does not relate to physical energy storage forms such as adipose tissue or material access to food. It reflects the portion of the energy *transformation* capacity or budget that isn't normally utilized to sustain life, but that is available as a buffer when needed (Morava and Kozicz, 2013; Picard et al., 2014). For example, engaging in multi-day athletic performances or pregnancy increases energy expenditure integrated over periods of sustained effort above baseline TEE (Thurber et al., 2019). This indicates that additional energetic resources are available above TEE, although there certainly is a constraint or limit to the organism's total energy budget (Thurber et al., 2019). Similarly, cells isolated in vitro and within the organism operate at sub-maximal metabolic rates, maintaining a "spare" or reserve bioenergetic capacity (Marchetti et al., 2020). Here also, there is a limit to the capacity of different cell types to dynamically transform and consume energy, as in the human organism. We posit that the portion of the organism's finite energy budget consumed by ASEE can tap into the limited reserve capacity.

Together, these energetic components add up to the *total energy budget*, reflecting the total amount of energy available to the organism over time (Fig. 2). Note that for most humans

living in urbanized civilizations, the total energy budget is not limited by environmental supply as originally described by McEwen and Wingfield from an evolutionary or animal ecology perspective (2003), although digestive capacity may be limiting in extreme contexts (Thurber et al., 2019). Rather, the total energy budget appears set by internal energy transformation systems, including glycolysis and mitochondrial oxidative phosphorylation (Mookerjee et al., 2017), and physical limits to energy dissipation rates (Niebel et al., 2019; Yang et al., 2021).

5.1. Spending down the total energy budget

An organism's total energy budget can be spent at different rates. A useful analogy for this concept is the modern smartphone. A smartphone has a given battery charge that can be consumed more or less rapidly depending on the amount of ongoing internal processing. Keeping a phone "on" costs energy, such that the battery goes down, albeit slowly. The energy required to keep a phone "on" is the cost of vital functions. On "airplane mode", the phone consumes less energy, and the battery lasts longer. In normal mode, powering the antenna and searching for signal, keeping apps running, and the readiness to receive incoming messages are classically allostatic processes in nature. Now add texting, talking, and streaming. Like stressors, these demands activate internal energy-consuming processes, draining the battery's energy more rapidly. These additional activities are analogous to allostatic states and allostatic load, representing the added energetic cost of chronic (over) activation of allostatic processes (i.e., ASEE), consuming energy at a higher rate than would be required just to keep the device on.

In keeping with the smartphone analogy, allostatic overload represents the material degradation over time whereby the device begins to wear out, run out of memory storage, slow down processing speed, and malfunction. The mechanical analogy does not fully encompass the complexity of living processes within the human organism, where endogenous repair processes and recalibrations always take place. Nevertheless, the *escalating load of activities draining a finite amount of available energy* appropriately captures the energetic cost of activities during allostatic load.

5.2. The cost of adaptation wasted

As described above, by preparing the organism for future exposures, allostasis effectively reduces the total energetic costs associated with novelty, surprise, and damage repair that stressors engender. But when anticipated threats do not materialize, the organism pays the cost of allostasis *without* reaping the potential long-term benefits. The cost allostasis is then wasted as futile hypermetabolism.

Futile stress responses may be particularly (or uniquely) prevalent in humans. Humans have highly developed cognitive abilities, enabling us to autonomously initiate allostatic cascades by imagining or sustaining potential threats (i.e., anxiety, ruminating, worrying) for periods of time longer than necessary (Brosschot et al., 2005, 2017; Dickerson and Kemeny, 2004). As an interesting link between futile mental activity and energy, rumination appears to be the strongest psychological predictor of *fatigue* (Querstret and Cropley, 2012), the subjective experience of energy deficiency. Allostatic responses mobilized unnecessarily

lead to the waste of limited energy resources; the regulatory systems shift unnecessarily, wasting precious energy. This waste in turn drives the overconsumption or redirection of energy above one's optimum, promoting damaging hypermetabolism.

6. Why is hypermetabolism damaging?

Having established that the constellation of allostatic processes costs energy, the next logical question is why expending more energy is damaging to health. *How does elevated energy expenditure, or hypermetabolism, during allostasis contribute to allostatic load and allostatic overload over time?* To address this question, we consider three related bodies of literature.

6.1. Energy expenditure scales with the rate of aging and lifespan in animals

First, there exists evolutionary-conserved, cross-species relations whereby animals with higher metabolic rate age faster and die younger (Gillooly et al., 2001). For every minute of life, smaller animals such as flies, shrews, and mice spend significantly more energy per unit of body weight to sustain life than their larger counterparts like baboons, elephants, and whales (Rolfe and Brown, 1997; West et al., 2002). In parallel, smaller animals also have much shorter lifespans: flies live days, shrews live less than a year, mice live 2–3 years, whereas elephants and whales can live around and over a century (Healy et al., 2014). Faster breathing animals who exhibit comparatively higher energy expenditure – or *relative hypermetabolism* – also erode their telomeres faster (Whittemore et al., 2019) and tend to have predictably shorter lifespans.

6.2. Hypermetabolism predicts mortality in humans

Second, among otherwise healthy individuals, those with higher energy expenditure exhibit a 25–53 % increased mortality rate over 20–40-year follow up periods (Jumpertz et al., 2011; Ruggiero et al., 2008). Higher resting heart rate – which generally scales linearly with metabolic rate (Green, 2011) – also was associated with a 80–90 % increased risk of death over a 12-year follow up (Nauman et al., 2011). In clinical populations with equivalent diagnoses (e.g., cancer, diabetes, and renal disease) patients with hypermetabolism also are more likely to die than those with normal resting metabolic rate (Steyn et al., 2018; Vazeille et al., 2017; Yao et al., 2018). Thus, physiological states that chronically elevate energy expenditure – which we propose is a consequence of allostatic load and overload – induces a more "mouse-like" state that predicts earlier mortality.

6.3. Stress signaling triggers hypermetabolism and accelerates cellular aging in vitro

All tissues and cell types express receptors for canonical stress hormones allowing them to respond to hormonal stimulation within minutes to hours. Consequently, glucocorticoids can be used in vitro to model HPA axis signaling and chronic "psychosocial" or neuroendocrine stress. In neurons and other cell types, glucocorticoid signaling induces robust bioenergetic and mitochondrial recalibrations (Bobba-Alves et al., 2022; Du et al., 2009), and sustained exposure drives mitochondrial biogenesis (i.e., the production of new mitochondria) and the number of mtDNA copies per cell (Bobba-Alves et al., 2022), which are hallmarks of increased energy expenditure. In a long-term model of chronic glucocorticoid stress, energy

expenditure was increased by ~60 % (Bobba-Alves et al., 2022), reflecting ASEE and robust hypermetabolism.

Over time, hypermetabolic cells under allostatic load also show signs of allostatic overload. This includes an accelerated rate of telomere shortening, epigenetic aging, and decreased cellular lifespan (Bobba-Alves et al., 2022). Thus, cells age faster and are more likely to die when their ASEE is elevated by stress exposure. This observation is consistent with the cross-species allometric scaling of metabolic rates and aging biology (i.e., animals with higher energy expenditure age faster), and with the prospective human studies linking hypermetabolism to increased mortality (people with higher energy expenditure die earlier) reviewed above. These in vitro results complement physiological results in whole organisms and mechanistically link glucocorticoid signaling, hypermetabolism, and the molecular wear-and-tear that underlie biological aging independent of complex physiological processes.

7. The energetic model of allostatic load (EMAL)

Above we have described the energetic cost of allostasis and how the organism's total energy budget is allocated. We also have discussed how imagined threats drive cognitive, physiological, and cellular allostatic responses, increasing allostasis and stress-related energy expenditure (ASEE). When sustained, this leads to allostatic load, which burns an increasing fraction of the energy budget above baseline TEE – like an overactive phone rapidly draining its battery. Additionally, we have presented three lines of evolutionary, population-based, and in vitro evidence that hypermetabolism is health damaging and accelerates aging. The EMAL integrates these notions, predicting that allostatic load and allostatic overload develop and become health-damaging when the total energy budget becomes overspent, or "bankrupt", and forced to *"steal"* from other cellular and physiological process processes (Fig. 3).

Overall, if energy expenditure was a direct driver of allostatic overload and aging, the sequence leading from allostasis to allostatic states, allostatic load, and eventually overload (e.g., accelerated telomere shortening) could be understood as follows: stress-induced allostasis and allostatic load processes makes the human body more "mouse-like", triggering hypermetabolism and thereby accelerating the rate of energy expenditure to make it more akin to that of a shorter-lived, rapidly aging organism.

Some assumptions central to this model require validation and rigorous empirical testing. The first is that there is a fixed total energy budget (Pontzer, 2018). But individuals can sustain abnormally high total energy expenditure (e.g., endurance athletes) for days to weeks (Thurber et al., 2019) and some disease states trigger hypermetabolism (Guo et al., 2021), bringing into question the absoluteness or fixity of total energy expenditure. The concept of an energetic reserve addresses this point. The second assumption is that the relative energetic costs of each component are stable over time and that energy tradeoffs only occur over absolute thresholds. Functional tradeoffs at the cellular (Niebel et al., 2019; Yang et al., 2021) and organismal levels (Urlacher et al., 2019) could arise not just at a fixed arbitrary value in energy expenditure, but from a combination of energetic, hormonal, and behavioral

factors that triggers a biological reprioritization of certain processes over others (see next section). The entire reserve capacity, therefore, may not need to be fully spent before ASEE costs impinge upon and "steal" energetic resources from GMR processes. Finally, stress disrupts sleep, which may occur early in the sequence of events leading to allostatic load and overload (Kim and Dimsdale, 2007). Sleep disruption could thus increase the cost of vital functions, manifesting in elevated energy expenditure during sleep, or elevated basal metabolic rate during wakefulness (Shechter et al., 2013). Thus, the components shown in Fig. 3 are not independent from one another but likely interact in complex bi-directional ways.

7.1. Energy tradeoffs: When allostasis becomes allostatic load and allostatic overload

When the whole budget becomes spent, additional energy costs from mounting allostatic processes can only be met by redirecting energy from other processes. In these tradeoffs, the most urgent processes divert or steal energy from less urgent ones. Pro-survival allostatic and stress-related processes come with some level of evolutionary-endowed biological urgency (Weiner, 1992). Therefore, we posit that they force tradeoffs and steal energy from less immediately required processes. This process of energy reallocation is similar to how excessive exercise can cause tradeoffs with reproductive or immune functions (Pontzer, 2018), how excessive immune activation can curtail growth in children (Urlacher et al., 2018), and how glucocorticoid stress responses or mitochondrial defects slows down division in cells (Bobba-Alves et al., 2022; Sturm et al., 2021). One must first survive immediate threats to later grow, think, and behave. Therefore, the evolutionary-shaped urgency to mobilize stress pathways position ASEE costs as physiological priority.

The prioritization of stress responses may explain why survival and adaptation-driven ASEE can divert energy resources from non-immediately essential processes. Non-immediately essential growth, maintenance, and repair processes include those contributing to lifespan and longevity. Examples of *GMR* processes include the formation of immune cells in the bone marrow and the maintenance of memory lymphocytes (Pearce et al., 2013), the elimination of defective cells of cancerous potential or the removal of waste products from the brain (Iliff et al., 2012), the formation of new neurons and other cell types from stem cells (Brunetti et al., 2021), and the maintenance of DNA integrity via telomere maintenance and DNA repair (Schumacher et al., 2021). Unlike the acutely life-sustaining processes such as the beating heart, breathing, and neuroendocrine regulation of glycemia, one can survive variable periods of time (days to weeks) without hematopoiesis, autophagy, neurogenesis, nor DNA repair.

In relation to aging, GMR processes include all molecular events that combat thermodynamic decay and maintain the integrity of life, such as cell division, DNA and other molecular repair pathways, antioxidant defenses, etc. These processes prevent the accumulation of damage and errors in DNA and other cellular components over time, which are hallmarks of aging (Abascal et al., 2021; Lopez-Otin et al., 2013).

GMR processes are energetically costly because they rely on energy-dependent enzymes and molecular operations. Within the cytoplasm, mitochondria, the nucleus, and other organelles, the enzymes of GMR such as telomerase and antioxidant enzymes consume high-energy

intermediates (e.g., ATP) to preserve the integrity of molecules, generate new proteins and DNA, and to build new cellular components (e.g., mitochondrial biogenesis). Growth, maintenance, and repair delay or prevent the accumulation of age-related damage. The suppression of GMR processes by ASEE-driven energy tradeoffs could therefore account for the health-damaging "wear-and-tear" effects of chronic stress.

The chronic tradeoff between ASEE and GMR could manifest in two main quantifiable ways. An organism could develop observable hypermetabolism, measurable directly over periods of minutes, hours, and/or days as an elevated resting or total energy expenditure. Alternatively, and more insidiously, the organism could divert energetic resources away from GMR, potentially *without elevating total energy expenditure*. In this second scenario, our model predicts that subcellular energy tradeoffs would only be measurable by the molecular sequelae of halting or slowing of GMR, including DNA damage, telomere shortening, oxidative stress, epigenetic drift, and reduced hematopoiesis (Han et al., 2019). The energetic model of allostatic load reframes these traditional age-related markers as indicators of impaired GMR processes and therefore, as potential indicators of ongoing deleterious energetic tradeoffs.

7.1.1. Evidence of energy tradeoffs hampering GMR—Previous observations are consistent with the proposed EMAL. As reviewed above, increased energy expenditure and secondary markers of halted GMR in humans have been linked to accelerated biological aging, increased mortality, and shortened lifespan. At the cellular level, the breakdown of regulatory systems and damage accumulation manifests as telomere instability and accelerated shortening rate (Choi et al., 2008; Sturm et al., 2021). Moreover, in humans chronic psychosocial stress and other toxic environmental exposures that lead to allostatic load also accelerate telomere shortening (Epel et al., 2004; Puterman et al., 2016; Rentscher et al., 2020). Thus, energetic tradeoffs may explain the cellular manifestations of allostatic load and allostatic overload.

Direct mechanistic evidence that allostatic processes are prioritized over GMR mainly comes from in vitro studies where cellular-level energetic tradeoff accelerates biological aging. For example, impaired mitochondrial energy production capacity leading to energetic stress triggers the costly secretion of extracellular signaling molecules, forcing a tradeoff with cell growth pathways, and culminates in a reduction of cell size and division rate (thus reducing growth-related costs) (Mick et al., 2020; Sharma et al., 2021; Sturm et al., 2021). Similarly, glucocorticoid-exposed cells that engage in costly molecular operations involving the production and release of cytokines divide less rapidly, show evidence of molecular damage to the mitochondrial genome, and exhibit higher mortality, potentially reflecting energetic tradeoffs hypermetabolism (Bobba-Alves et al., 2022).

Physiologically, energy is acutely redirected to fuel neuroendocrine cascades, including, but not limited to, the HPA-axis and sympathetic nervous system, which suppress immune functions and cytokine production in the long-term. Allostasis and stress-induced energy costs appear to be prioritized over other processes that usually protect us from infections (Cohen et al., 1991; Kiecolt-Glaser et al., 1984) and promote wound healing (Kiecolt-Glaser et al., 1995; Walburn et al., 2009). Based on our model, this would occur because mobilizing

acute stress responses is more acutely vital than accelerating epithelialization, surveilling pathogens, or preserving telomeres. The EMAL model proposes that the suppression of immune surveillance and wound healing, as well as anti-aging cellular strategies, for examples, take a backseat under the pressure of mounting ASEE consume a growing portion of the energetic budget.

The EMAL model also makes two predictions. The first states that the physiological systems that most require constant renewal and repair to sustain their functions, such as immune cells with high turnover rate, or portions of the brain with high levels of neurogenesis (e.g., the hippocampus), exhibit preferential vulnerability to the forced tradeoff of the limited energy resources for ASEE. The second prediction is that vulnerability is exacerbated during developmental and lifespan stages where growth energy costs are higher-than-average, such as during childhood (Pontzer et al., 2021). When applied to developmental trajectories, this model may help to understand the embedding of stressful experiences, particularly around sensitive periods of development (when energy costs are the highest), and the preferential vulnerability of specific organ systems, like the immune and nervous systems.

8. Allostatic load across levels of biological complexity

Allostatic load has traditionally been conceptualized as a whole-body process, but it is important to recognize that it transcends levels of biological complexity. At the scale of the organism, multi-organ physiological allostatic processes occur in parallel with cellular allostatic load processes, coordinated by the brain. The human brain plays a central role in the integration of interoceptive and sensory perceptions (Kleckner et al., 2017), in addition to the anticipation, initiation, and maintenance of allostasis (McEwen, 2006). Costly brain-body physiological endocrine and immune processes, among others, are coordinated by stress hormones that transmit the perception of a potential danger to all cells in the organism. These responses entail multi-organ physiological processes, but the cellular and intracellular details of these events remain poorly understood.

Two main situations can be envisioned to explain the evolutionary development of allostatic load. If allostatic load existed only among brain-body organism and was absent from isolated cells, it would likely indicate that, on the evolutionary scale, allostasis was an innovation of multicellular, thinking and feeling creatures. However, if allostatic load naturally took place at the cellular level – in the Petri dish without a brain – it would be consistent with the notion that allostatic mechanisms are ancient, evolutionary conserved mechanisms, and that their origin likely predated the evolution of the brain (Sterling, 2020).

The cellular glucocorticoid experiments described above unambiguously demonstrate and isolate the anticipatory nature of energy-dependent cellular allostatic recalibrations. In these experiments, where there is only a single cell type without a brain nor real injurious threat, cellular responses can be isolated from systemic psychophysiological, brain-body processes, reflecting *cellular allostatic load* (CAL). Given our goal to better understand the forces underlying human health, the existence of cellular allostatic load broadens our perspective by illustrating how every cell can sense and respond to stress mediators and develop micro-allostatic responses. In response to endocrine and metabolic stressors, sub-cellular

organelles, like mitochondria, also can exhibit structural and functional recalibrations reflecting allostatic load, a phenomenon known as *mitochondrial allostatic load* (MAL) (Picard et al., 2014). Thus, systemic (AL), cellular (CAL), and mitochondrial (MAL) allostatic load reflect the same set of evolutionary-conserved, energy-consuming, adaptive strategies to optimize health across levels of biological complexity (Fig. 4).

8.1. Cellular bioenergetic recalibrations to life stress in humans

If chronic life stress and the resulting systemic allostatic load produced a sustained elevation in energy expenditure, the adaptive response in the healthy organism would consist in increasing the cellular energy producing capacity. Accordingly, a series of studies on mixed white blood cells has reported that cellular oxygen consumption (a good estimate of energy expenditure) was elevated in women with a history of early life trauma (Boeck et al., 2016; Gumpp et al., 2020). Cellular energy consumption was correlated with trauma severity and circulating cortisol levels (Boeck et al., 2018; Gumpp et al., 2020), consistent with the notion that more severe trauma and activation of the HPA axis mediate these effects. When examining immune cells of 3–6-year-old children, higher maternal allostatic load during pregnancy also predicted higher mitochondrial content – and, therefore, greater energy production capacity – pointing to the potential transfer of the energetic load of stress across generations (Gyllenhammer et al., 2022). Other studies, although not all (Lindqvist et al., 2018; Picard et al., 2018b), have reported elevated numbers of mitochondrial DNA copies per cell (mtDNAcn, (Picard, 2021)) in the blood of individuals with early adversity and psychopathology (Cai et al., 2015; Tyrka et al., 2016). Together, these results point to immune bioenergetic recalibrations and mitochondrial allostatic load in response to chronic life stress (Picard et al., 2014), calling for precise, longitudinal studies in specific cell types (Brasanac et al., 2022; Rausser et al., 2021).

8.2. Implications for allostatic load from organelle to organism.

The conservation of allostatic load across several levels of biological complexity, from organelle to organism, is enlightening in three main ways. First, it gives insights into the nature and origin of allostatic load – not as a modern invention of brain-bearing bodies, but as an evolutionary-conserved natural phenomenon across living creatures. Second, it highlights the many potential mechanisms for hypermetabolism – physiological, behavioral, cellular, and subcellular. These highlighted mechanisms can then help us build more accurate causal interdisciplinary models for the transduction of chronic stress into disease risk, aging, and mortality. Third, an understanding of allostatic load across levels of complexity may eventually illuminate ways in which we can intervene to enhance resilience and promote health. In theory, interventions to mitigate the adverse effects of systemic allostatic load on human health could be targeted to any of these levels to offset the damaging effects of hypermetabolism and energy tradeoffs.

9. An energetic view of resilience-promoting behaviors

The EMAL provides a mechanistic lens through we can view allostasis and underscores a few important insights of interest to brain-body scientists. First, this model provides a hypothesis to understand why some behavioral and psychosocial factors promote resilience

to chronic stress. For example, *exercise* is among the best described factors that buffers against the deleterious effects of psychological stress on cellular aging (Loprinzi and Frith, 2019; Puterman et al., 2010). Besides increasing the pool of well-functioning mitochondria (Neufer et al., 2015), thereby enhancing reserve capacity and the total energy budget, exercise increases physiological efficiency (Careau et al., 2021). In other words, the trained organism can perform life-sustaining activities in its daily life more efficiently (i.e., at a lower energetic cost). Although exercise costs energy acutely, the trained organism presumably undergoes adaptive responses that subsequently allow it to sustain life with lower basal energetic costs. This phenomenon is termed *metabolic compensation*, which might arise from reduced costs in other domains such as reproduction, stress physiology, and inflammation (Pontzer, 2018). Thus, the effective energy "saving" afforded by physical activity and exercise may act by either expanding the organism's energy reserve or by improving efficiency, thereby freeing a portion of the total energy budget for GMR (Fig. 5). Similarly, the health-promoting intervention (and lifespan extending, in animals) of calorie restriction also may reduce energy expenditure (Redman et al., 2018).

In the context of the energetic model of allostatic load, other factors known to modulate allostatic load deserve further research, most notably, the social regulation of allostasis (Schulkin, 2011; Sterling, 2012). Social support and social dynamics (Sapolsky, 2005; Snyder-Mackler et al., 2020) impact health and lifespan and can buffer against the deleterious effects of chronic stress exposure (Saxbe et al., 2020). In animal studies, sociality affords energetic cost savings in response to physical challenges (Culbert et al., 2019; Mortola, 2021) and social threats (Millidine et al., 2009). Sociality and social support, therefore, could confer health protective effects because they improve metabolic efficiency, or because they reduce another component of the energy budget in a way that protects GMR. Further research is needed to test these possibilities.

In humans, little is known about the effects of social allostatic load on energy expenditure. Given the tight embedding of our physiology and social contexts (Saxbe et al., 2020; Schulkin, 2011), future studies should quantify the influence of socioeconomic status, discrimination, social isolation and social support, and other prosocial forces on energy expenditure. Both energy-saving and energy-draining effects of positive and negative social interactions, respectively, should be considered (Hall and Merolla, 2019). We anticipate that precise measures of basal metabolic rate and total energy expenditure (Mehta et al., 2015; Speakman et al., 2021), ideally also with experimental stress studies, will help to precisely quantify the psychobiological energetic tradeoffs among key components of the total energy budget.

10. Applying the energetic model of allostatic load (EMAL)

If the EMAL is (partially) correct, it should be possible to demonstrate that chronic stress is damaging *because* it increases the cost of living or steals energy from GMR processes. A translational combination of cellular, animal, and human studies will be required to fully examine and refine portions of the model. If validated in humans, there would be direct implications for the design of health-promoting and resilience-building interventions.

For example, a new class of interventions could be designed with the explicit goal to reduce the adverse effects of stress by *directly targeting energy expenditure*. The therapeutic goal would be to prevent hypermetabolism or promote "normometabolism". A successful outcome would consist of optimizing metabolic efficiency during daily life and upon stress exposure. For example, in the intensive care unit setting – a naturally stressful environment where hypermetabolism predicts mortality – using energy expenditure to design individualized care improved patient outcomes (De Waele et al., 2021). Energy expenditure, we argue, represents a more integrative, and possibly more accurate, measure of optimal physiological functions than individual molecular markers can reflect. The EMAL suggests that incorporating measures of energy expenditure and metabolic efficiency could increase the sensitivity and specificity afforded by approaches focused on traditional organ-specific allostatic biomarkers. This could in turn help to evaluate the effectiveness of existing interventions in reducing allostatic load, or the magnitude of physiological dysregulation more generally.

For example, the beneficial or adverse effects of new drugs could be evaluated globally on their overall energetic cost of life, not just a specific molecular marker or organ system (see Fig. 4). Based on the EMAL, if a new medication increased basal or total energy expenditure, this would indicate that while the target pharmacological effects may be achieved (e.g., symptom suppression), the drug has induced a broader set of off-target, or secondary, energetically costly deviations from the organism's optimal state. If the drug lowered energy expenditure *without adverse side effects*, this would indicate a favorable organismal response to the treatment.

The proposed model also predicts that reducing ASEE frees up energy for longevity-promoting GMR. Therefore, reducing ASEE should allow organisms to thrive – i.e., to adapt and age optimally. Living creatures almost universally have a beginning and an end. It therefore seems unlikely, and possibly unwise, that decay and aging should be eliminated. Striving to ensure that all necessary energetic resources are available for GMR (as we do at a gross level with nutrition), however, should optimize one's development, growth, healthspan and lifespan. Equipped with a conceptual model and tools to examine the energetic underpinnings and molecular manifestations of GMR processes, investigators can design quantifiable and testable cross-sectional and longitudinal hypotheses.

Besides exercise and social factors that may promote energy efficiency, other approaches could contribute to minimize ASEE and hypermetabolism. For instance, mindfulness and meditation practice may represent effective means of improving metabolic efficiency and promoting restoration. Early studies directly measuring energy expenditure through oxygen consumption during meditation reported up to ~40% reductions in metabolic rate (Benson et al., 1975; Wallace et al., 1971). Relative to controls, advanced yoga practitioners also exhibited a stable 15% lower basal resting energy expenditure (see (Tyagi and Cohen, 2013) for a systematic review). In the most extreme cases, the surprising level of metabolic efficiency achieved during meditation appears to exceed that naturally achieved during sleep states, when allostasis and ASEE costs dramatically subside and GMR processes are expected to be active. This body of literature calls for well-controlled studies to quantify modifiable psychosocial states influence energy expenditure, both acutely and chronically.

Overall, interventions that improve the organism's energetic efficiency, such as exercise, calorie restriction, and meditation are currently among the most promising interventions to reduce the wear-and-tear of stress, and to promote health across the lifespan. Based on energetic principles, the beneficial effects of these interventions could lie in either: (i) their ability to expand energetic reserves, thereby increasing the total energy budget of a person; or (ii) by increasing the efficiency of vital and activity-related energy costs, such that life can be sustained at a lower basic energy cost. Both possibilities converge upon an expanded reserve capacity that protects GMR processes from the forced, punctual energetic tradeoffs with stress-induced allostasis. This expanded reserve capacity, in turn, should optimize the organism's resilience and ability to live a long, healthy life.

11. The parallel between energetic and psychological coping resources

The discussion above has centered mostly on the biological and physiological underpinnings of the EMAL, without directly addressing its link with human psychology. In this final section, we attempt to establish some preliminary theoretical connections between the limits to energy expenditure, energetic tradeoffs with health-promoting processes, and psychological stress theory.

The cost-benefits of energetic expenditure discussed above are similar in spirit to psychosocial models of approach-withdrawal behaviors that are part of transactional models of stress. In situations of acute stress, organisms must decide whether the specific situation threatens their personal well-being and survival. Consequentially, in this transactional model (Lazarus and Folkman, 1984), the decision to mount a stress response and subsequent allostatic load is determined by the demands of the encounter relative to the person's judgment of whether the threat supersedes their coping resources. This appraisal can be conceptualized from our energetic framework since the body and brain must recalibrate biological and physiological activities according to their evaluation of the adaptative value of stress responses. Just as cognitive contextualization is an energetically expensive endeavor, so too is the transactional decision to activate allostatic processes or not given the energy and effort required.

In human stress reactivity studies, stress-induction paradigms that use *social-evaluative threats* to trigger psychophysiological stress responses are routinely used to assess allostatic stress responses (Dickerson and Kemeny, 2004). Stress reactivity occurs specifically in situations that diminish one's control and where the prospect of being negatively evaluated, rejected, and/or shamed are contextually manipulated (Dickerson et al., 2004). In addition to this allostatic process, humans are motivated by strong needs to preserve their social selves and will expend considerable energy to do so. The motivation towards preserving one's *social self* vis-à-vis others' evaluations involves complex interactions among cognitive appraisals, affective processes, and physiological responses (Dickerson et al., 2004, 2008; Gruenewald et al., 2004). Our energetic model, together with work around social allostasis (Saxbe et al., 2020; Schulkin, 2011), illustrates how social forces push energetic levers within the organism.

Much of the stress literature centers on uncontrollability as a central determinant of over-reactivity that contributes to allostatic load. Here, we propose a reframe that focuses on the energetic level that contributes to the cost-benefit transactional analyses that shapes stress and coping responses. For example, changes in mitochondrial energy production capacity in specific brain regions may modulate social behaviors (e.g., dominant vs subordinate (Hollis et al., 2015)), and brain signatures of energy metabolism may account for situational stress and state anxiety related to self-efficacy in humans (Strasser et al., 2019). This concept that *behavior and psychological states are regulated by energy* (Filiou and Sandi, 2019; Morella et al., 2022) compliments work on 'homeostats' and 'allostats' that use thermostats as an analogy for thresholds that regulate allostasis and allostatic states (Goldstein and McEwen, 2002).

Some outstanding challenges include: (i) determining to what extent mitochondrial and organismal energetics play an instructive role on psychological experiences in humans; and (ii) how psychological states influence energetics across levels of biological complexity. We propose that the psychosocial and behavioral factors that can increase energy reserves (e.g., physical activity, social support, caloric restriction, sleep quality, sense of purpose) or promote efficiency (e.g., exercise training, meditation – see below) will need to be investigated in relation to individual differences in coping and stress reactivity.

12. Conclusion

We have outlined an energetic model of allostatic load (EMAL) to account for the stress-disease cascade in humans. Every biological process costs energy. Consequently, the anticipatory allostatic processes induced by real and imagined threats consume the organism's limited energetic resources. Because of evolutionary-acquired cellular and physiological energy constraints, allostasis and stress-induced energy expenditure can divert energy away from GMR processes. Thus, we propose that *the physiological transition between adaptive allostasis and maladaptive allostatic load is the point at which stress-induced energy costs compete with health-sustaining and longevity-promoting growth, maintenance, and repair*.

The proposed model opens several testable questions regarding the energetic basis of resilience or susceptibility to stress. Studies specifically designed to test these hypotheses should examine, beyond current models based exclusively on molecular biomarkers, how much added value sensitive and specific measures of energy expenditure contribute to predict meaningful health outcomes. Empirically, these measures could be applied at both the (sub)cellular and whole-body levels, leveraging approaches from both mitochondrial science and human energetics. Importantly, an energetic understanding of the allostatic load theory and of the stress-disease cascade emphasizes the interplay of mind and body processes, and how their interactions rely on energy to survive and thrive across the lifespan.

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Nomenclature

Allostasis

The activation of energy-dependent, anticipatory recalibrations (i.e., allostatic responses) to maintain stability of vital functional parameters (Sterling and Eyer, 1988). Allostasis is epitomized as “stability through change”.

Allostatic responses

Molecular, organellar, cellular, inter-cellular, physiological, behavioral, and cognitive processes that consume energy, and which are mobilized in anticipation of potential threats and enviromental perturbations.

Allostatic states

Energy-dependent patterns of allostatic responses mobilized in response to chronic stressors, leading to sustained activity and recalibration of inter-connected physiological systems (Koob and Le Moal, 2001).

Allostatic load

The added energetic cost and biological ‘wear-and-tear’ that neural, endocrine, metabolic, cardiovascular, immune, and other allostatic states impose on the organism during chronic stress, which in synergy with unhealthy behaviors, contribute to stress-related diseases (McEwen and Stellar, 1993).

Allostatic load index

Numerical value calculated from the number of neuroendocrine (e.g., cortisol), immune/inflammatory (e.g., cytokines), metabolic (e.g., glyco-lipid profiles), and cardiovascular (e.g., blood pressure, heart rate variability) (Seeman et al., 1997) biomarkers that show either sub-clinical (e.g., high-risk percentiles) or clinical deviations (Beckie, 2012; Juster et al., 2010; Kerr et al., 2020).

Allostatic overload

Long-term energy-dependent functional and/or structural dysregulation and breakdown that arise as consequences of chronic allostatic load, leading to accelerated aging, disease onset and progression, and increased mortality risk (McEwen and Wingfield, 2003).

Energy expenditure

The amount of energy expended or consumed to perform molecular, cellular, physiological, and mental operations required to sustain life and support allostasis in living animals (Rolfe and Brown, 1997). This is also known as “metabolic rate”, which in animals is mostly fueled by the aerobic (i.e., oxygen-consuming) transformation of food substrates in mitochondria.

Cellular allostatic load

The added energetic cost and biological 'wear-and-tear' that allostatic mechanisms impose on the *cell* during chronic stress, including the bioenergetic, transcriptional, inflammatory, morphological, signaling, and other cellular behaviors induced by the signaling action of even single stress mediators (Bobba-Alves et al., 2022).

Mitochondrial allostatic load

The added energetic cost and biological 'wear-and-tear' that allostatic mechanisms impose on mitochondria during chronic stress, including the molecular, structural, and functional recalibrations that mitochondria undergo in response to metabolic, endocrine, biochemical, and other stressors (Picard et al., 2014).

Energetic model of allostatic load (EMAL)

Theoretical model highlighting the measurable energetic costs allostasis and stress-induced energy expenditure (ASEE), which force energetic tradeoffs with health- and longevity-promoting growth, maintenance, and repair (GMR) processes, culminating in the accelerated wear-and-tear of the organism.

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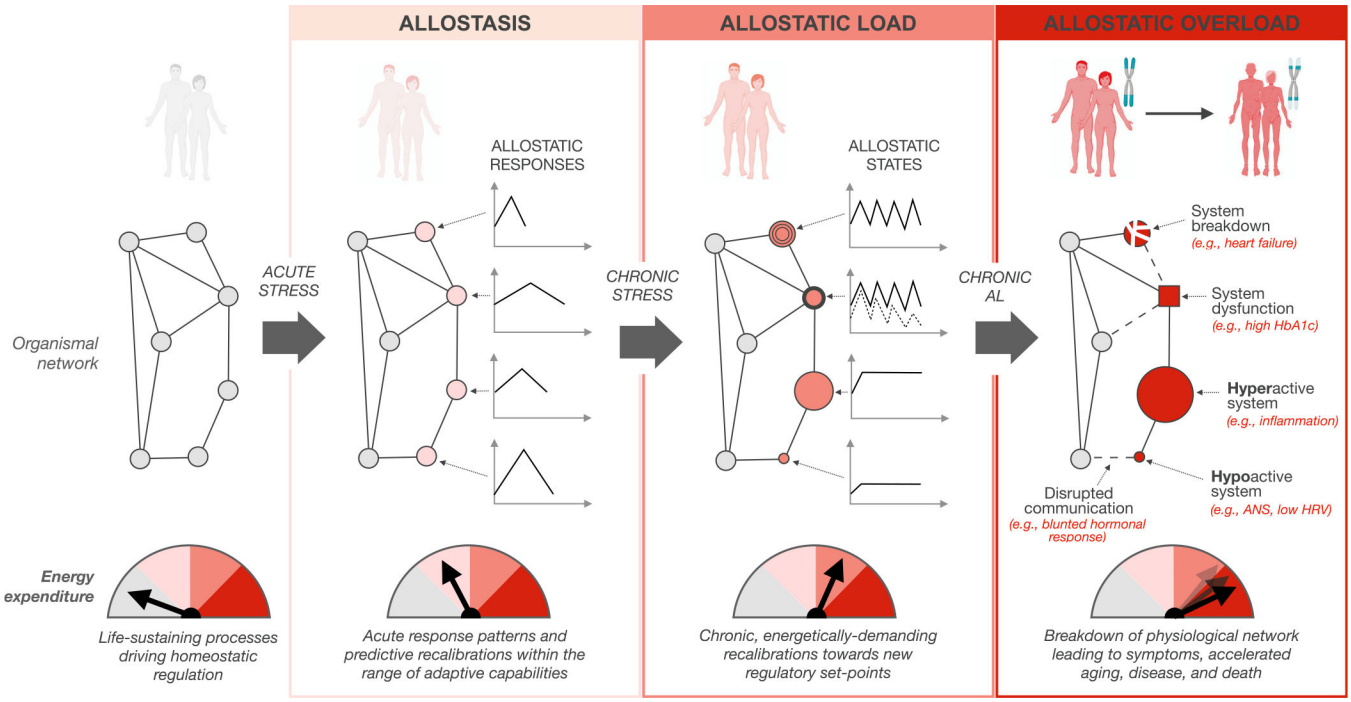

Fig. 1.

The energetic underpinnings of the allostatic load model of the stress-disease cascade. Real or imagined stressors trigger an energy dependent cascade progressing from adaptive allostasis to allostatic states and allostatic load, to allostatic overload, ultimately manifesting as an increased disease risk and accelerated rate of aging. The physiological network, illustrated as nodes and edges, depicts the constant communication (edges) between cells, tissues, organs, and systems (nodes) within the human body under the influence of biopsychosocial and environmental forces. The change in appearance of nodes illustrates the dysfunction, breakdown, and hypo- and hyper-activation of organ systems in response to allostatic load and overload. Dashed lines illustrate impaired communication between organ systems. These changes manifest as measurable circulating biomarkers that eventually become clinical signs and symptoms. The allostatic states are adapted from McEwen's proposed allostatic load time-course (McEwen, 1998). *Abbreviations*: *PSNS*, parasympathetic nervous system; *AL*, allostatic load; *HRV*, heart rate variability; *HbA1c*, glycated hemoglobin.

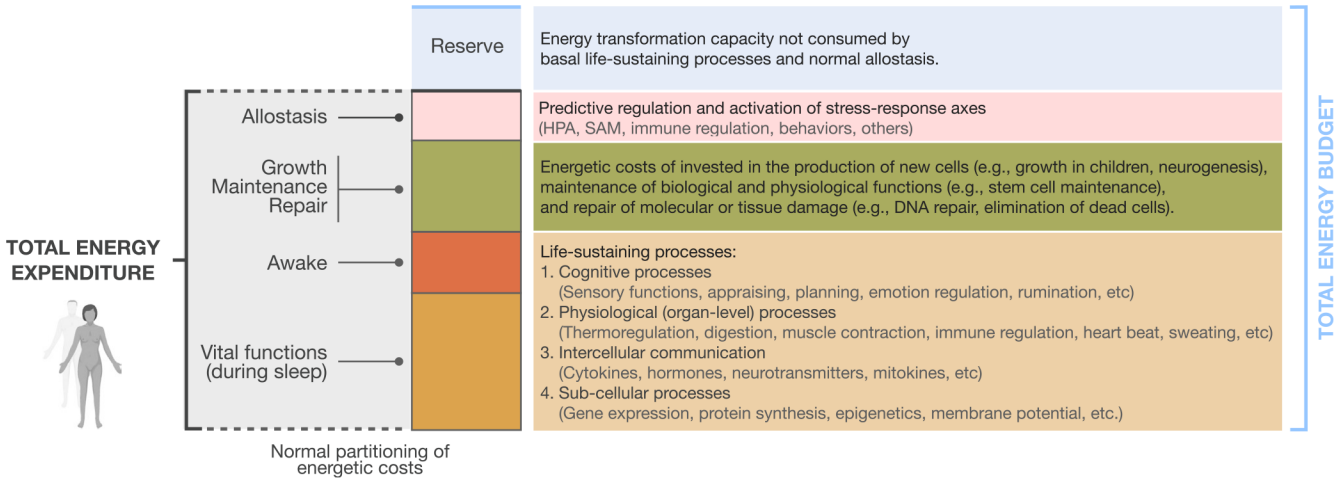

Fig. 2.

Theoretical partitioning of total energetic resources in the organism. Integrated over long periods of time, the human body can transform a finite amount of energy per unit of time, derived from the oxygen we breathe and the food we consume. Based on limited available evidence, we reason that vital regulatory and predictive allostatic processes consume a non-negligible portion of the total energy budget. Growth, maintenance, and repair (GMR) processes are essential to replace damaged molecules and cells, and to offset the natural decay of matter over time (i.e., to overcome the inevitable second law of thermodynamics that states that everything is bound to increase in entropy). The leftover portion of the energy budget is the reserve capacity, which is hypothesized to exist as a buffer for allostasis, and the increasing energetic demands of allostatic load in the organism.

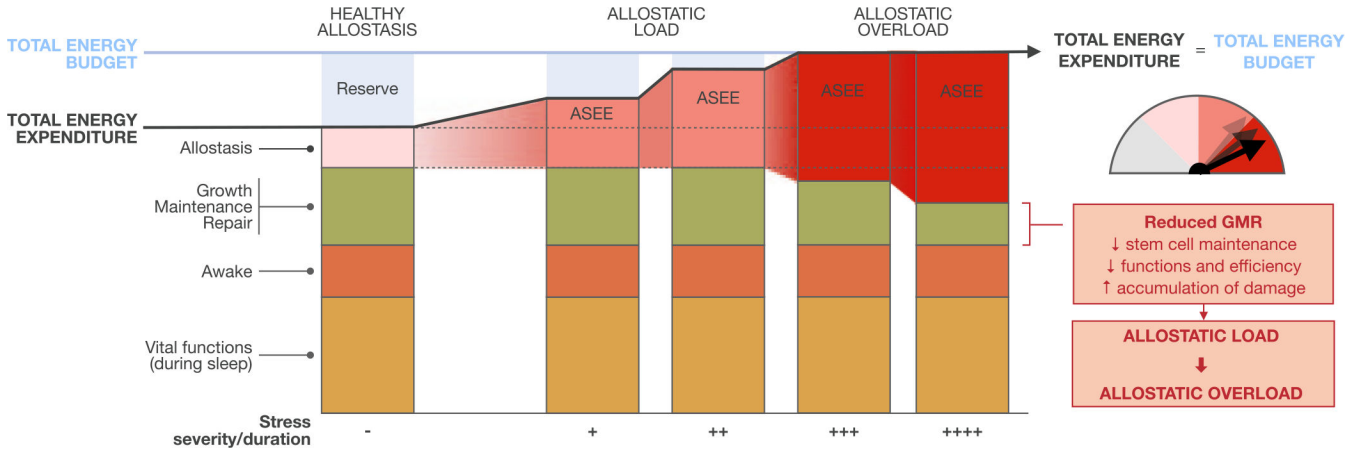

Fig. 3.

The energetic model of allostatic load (EMAL). This figure illustrates the effects of stress-induced allostasis on the partitioning of energy costs within the organism, and the transition from allostasis to allostatic load and overload. Real or imagined stressors increase allostasis and stress-induced energy expenditure (ASEE), which consumes the reserve portion of the organism's total energy budget. When this excess energetic cost exceeds the reserve capacity, it impinges on growth, maintenance, and repair (GMR) processes that are required to sustain health and prevent the entropic decay of cells and systems. As a result, the compression of available resources constrains GMR processes, accelerating the decay of structures leading to allostatic overload marked by the 'wear-and-tear' of cellular and physiological systems. Taken together, allostatic load and allostatic overload arise when the energetic costs of stress-induced allostasis supersede or the organism's available energetic reserve, or when they are prioritized over GMR owing to some other evolutionary mechanism.

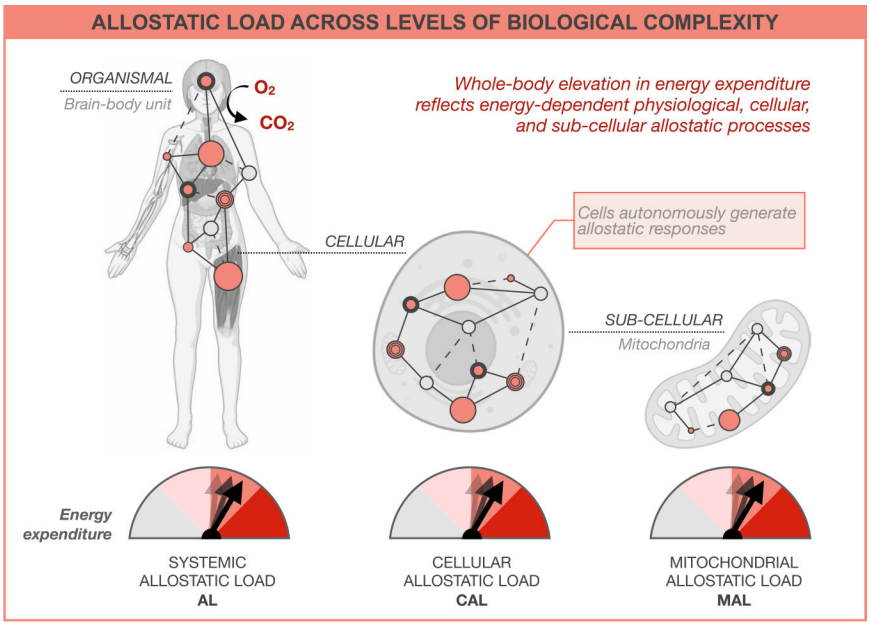

Fig. 4.

Allostatic load across levels of biological complexity. The added energetic cost and biological 'wear-and-tear' that brain-body allostatic states impose on the organism during chronic stress is a more complex expression of the same process that also take place in cells, and in sub-cellular organelles, such as the energy-transforming mitochondria. See *Nomenclature* for definitions.

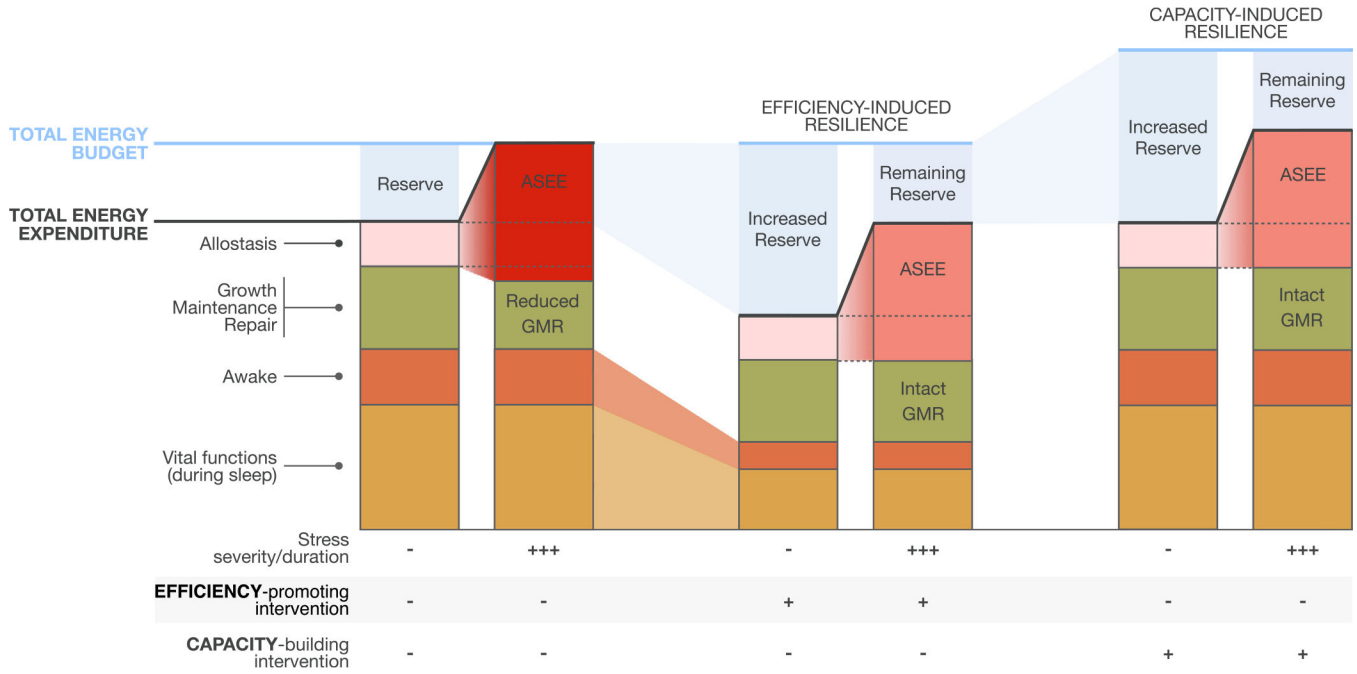

Fig. 5.

Potential influence of resilience-promoting interventions on the total energy budget and partitioning of energy costs within the organism. Illustrated are two types of hypothetical scenarios for resilience-promoting interventions. Compared to the situation (*left*) where allostasis and stress-induced energy expenditure (ASEE) bankrupts the total energy budget and steals energy from growth, maintenance and repair (GMR), resilience to the same stressor can arise from either a reduction in basal metabolic costs (metabolic compensation, *middle*) or increase the total energy budget (*right*). The shifting of the threshold for allostatic overload can increase the ability of the organism to tolerate chronic stress with less of the damaging effects of allostatic overload.