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The allostatic triage model of psychopathology (ATP Model): How reallocation of brain energetic resources under stress elicits psychiatric symptoms

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ABSTRACT

Psychiatric, cardiometabolic, and immune disorders are highly comorbid, and are precipitated by psychological stress. To explain why these conditions co-occur and how stress triggers their pathogenesis, we introduce the Allostatic Triage Model of Psychopathology (ATP Model) that explains psychopathogenesis, and these bidirectional associations through a bioenergetic lens. Stress increases the energy demand on biological systems, which operate on a finite energy budget, increasing the risk of energy scarcity, especially in the brain, which faces high energy needs and limited access to energetic resources. Allostatic processes anticipate stress-induced increases in energy demand and regulate systemic and brain energy allocation from mind-to-mitochondria, a process that we call "allostatic triage". The brain allostatic-interoceptive system generates internal models of systemic and brain metabolism and energy output that are used to produce affective states, which regulate allostasis. In turn, we propose that affect regulates allostatic triage among functional brain networks. Chronic and traumatic stress dysregulates the mitochondrial and brain networks that regulate affect by reducing metabolic efficiency. We propose that stress-induced energy scarcity and affective dysregulation exacerbates allostatic triage to the networks most necessary for short-term survival, at the expense of non-vital processes contributing to long-term optimization and well-being, dysregulating allostasis and driving transdiagnostic disease pathogenesis. Persistent network activation patterns underlying psychiatric symptoms can then become entrenched as psychiatric disorders through activity-dependent neuroplasticity, also known as canalization. Altogether, we propose that stress dysregulates mitochondria, affect, and allostatic triage, impairing allostasis, and driving transdiagnostic pathological states, which are canalized over time into transdiagnostic disease.

Abbreviations: ADP, Adenine diphosphate; AL, Allostatic load; AOL, Allostatic overload; ATP, Adenine triphosphate; ATP Model, Allostatic Triage Model of Psychopathology; CEN, Central executive network; CNS, Central nervous system; DMN, Default mode network; DNA, Deoxyribonucleic acid; EMAL, Energetic model of allostatic load; EPIC, Embodied prediction interoceptive coding model; FGF-21, Fibroblast growth factor 21; GAD, Generalized anxiety disorder; GDF-15, Growth and differentiation factor 15; HPA, Hypothalamic pituitary adrenal axis; ISR, Integrated stress response; MAL, Mitochondrial allostatic load; MDD, Major Depressive Disorder; MIPS, Mitochondrial information processing system; MFN2, Mitofusion 2; P, General psychopathology factor; PFC, Prefrontal cortex; PTSD, Posttraumatic stress disorder; RNA, Ribonucleic acid; ROS, Reactive oxygen species; SN, Salience Network.

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1. Introduction

Stress exposure is a risk and precipitating factor for psychiatric (Bourvis et al., 2017; Daviu et al., 2019; Kasai et al., 2008; Kendler et al., 2004, 1999; Lex et al., 2017; van Winkel et al., 2008), cardiometabolic (Backé et al., 2012; Dimsdale, 2008; Gebreab et al., 2018), and immunological (O'Donovan et al., 2015) diseases, which are bidirectionally related to each other. For example, chronic stress increases the odds of developing major depressive disorder (MDD) by $>$ 3.5 fold (Kendler et al., 1999) and more than doubles the odds of developing hypertension (Liu et al., 2017). These psychiatric and medical illnesses are also bidirectionally linked (Chen et al., 2023; Li et al., 2024; Sun et al., 2024; Wang et al., 2025). While autoimmune disorders (O'Donovan et al., 2015), cardiometabolic diseases, and other medical illnesses increase risk for psychiatric disorders (Atlantis and Baker, 2008; Ha et al., 2017; Speed et al., 2019), psychiatric disorders also increase risk for medical diseases (Galts et al., 2019; Miller and Raison, 2016; Miller et al., 2018; Müller, 2018; Penninx and Lange, 2018). For example, hypertension more than doubles the odds of developing MDD (Gan et al., 2023; Turana et al., 2021), and MDD increases the risk of developing hypertension (Meng et al., 2012; Wu et al., 2012; Zhang and Li, 2024). Are there shared psychobiological processes underlying stress effects on psychiatric and medical disorders and the comorbidity of these disorders? Here, we propose a conceptual model to explain bidirectional relationships among stress, chronic medical diseases, and psychopathology by integrating existing and novel concepts into a bioenergetic model of transdiagnostic stress-induced disease pathogenesis.

What is it about stress that drives multisystemic pathology? Hans Seyle defined stress as "the non-specific response of the body to any demand", but did not clearly define "demand". An alternative model was proposed by Koolhaas et al. (2011) in which the term "stress" is restricted to stimuli that overwhelm the natural regulatory response of the organism (Koolhaas et al., 2011). Building on these foundations, we define demand bioenergetically: stress is any increase in *metabolic* demand that overwhelms the capacity of the stress response to increase output of the energy currency, adenine triphosphate (ATP) to meet the increased energy demand. What is known as the stress response, then, is an energetic response that helps the organism survive periods of high energy demands (Armario et al., 1990; Balasanthiran and Shotliff, 2015; Bobba-Alves et al., 2022; Busillo et al., 2011; Du et al., 2009; Eisner et al., 2018; Hunter et al., 2016; Mizuno et al., 2010; Picard et al., 2014; Selye, 1936; Tran and Wang, 2019; Wang et al., 2025; Wende et al., 2017).

Another key role of the stress response is to facilitate adaptations that increase the capacity of organisms to ensure survival and meet the demands of future stressors (Eisner et al., 2018). Although chronic and traumatic stress can trigger adaptive mechanisms that could arguably enhance short-term survival, they also drive maladaptive recalibrations that promote disease in the longer term (Radley and Herman, 2023). Metabolism and energy output, including behavior, are regulated through an anticipatory process called allostasis (Sterling, 1988). Mitochondrial networks within and between cells (Picard and Shirihai, 2022) have been called the mitochondrial information processing system (MIPS), which regulates allostasis at the cellular level, and interacts with the peripheral and central nervous system (CNS) networks that comprise the allostatic-interoceptive system (Kleckner et al., 2017). The MIPS, therefore, plays a key role in regulating systemic allostasis (Kelly et al., 2024). The allostatic-interoceptive system refers to a brain network including insular nuclei that receive and integrate interoceptive and metabolic information from the peripheral nervous system (Craig, 2009; Critchley and Garfinkel, 2017; Tsakiris and Critchley, 2016), and in conjunction with the anterior cingulate cortex, among other regions, generate affective states that fine tune allostasis (Kleckner et al., 2017; Sennesh et al., 2022). However, stress dysregulates the MIPS and the allostatic-interoceptive network, reducing metabolic efficiency, and increasing the risk of energy scarcity when demand is high.

What happens when despite the additional energy made available by the stress response, energy demand exceeds production capacity? A third major function of the stress response is that during energy scarcity, organisms prioritize and (re)direct available energy to the processes necessary for survival (Bobba-Alves et al., 2022). For example, if an organism faces life-threatening danger, the autonomic nervous system shunts blood flow away from digestion towards skeletal muscles to facilitate the fight or flight response (Cannon and de la Paz, 1911). Organisms also shunt energy from systems that produce better long-term outcomes, such as growth, maintenance, and repair process, as explained in the energetic model of allostatic load (EMAL) (Bobba-Alves et al., 2022). Applying EMAL to the CNS, we propose that stress triages energy away from metabolically expensive, but acutely dispensable (for survival) brain functional network activation patterns, to less expensive networks that mediate attentional vigilance and fear-response behaviors. Henceforth, we call this general principle "*allostatic triage*", which we propose is a major driver of the bidirectional causation between stress-associated peripheral and psychiatric disease. For brevity, we focus on allostatic triage in the CNS here.

Building on Lisa Feldman Barrett's embodied predictive interoception coding model (EPIC) of allostatic-interoceptive system function, we propose that affective states, which reflect the brain's internal model of metabolic efficiency, regulate allostatic triage in the CNS (Barrett et al., 2016; Sennesh et al., 2022). In this model, positive affect represents the organism's perception of high metabolic efficiency and the ability to handle additional metabolic load. This state of plentiful energy resources drives expensive behaviors, such as goal-oriented decision making and problem solving that optimize long-term outcomes in humans and higher animals. On the other hand, negative affect, as observed in MDD, represents the perception of low metabolic efficiency and the inability to handle additional load. We propose that negative affective states triage energy from costly processes and behaviors until conditions improve, as happens with aging (Shaulson et al., 2024).

Extending these fundamental notions to psychopathology, we propose that the normal process of allostatic triage during stress is exacerbated by stress-induced dysregulation of the MIPS and the allostatic-interoceptive network. We propose that dysregulated mitochondrial and allostatic-interoceptive networks drive unreliable body-to-brain and within-brain cascades that uncouple affective states from metabolic efficiency. When affective states no longer precisely represent metabolic efficiency, allostatic triage is exacerbated, allostasis is impaired (Barrett et al., 2016), and risk for psychiatric and medical diseases increases (Fig. 1).

The ATP model (Fig. 1) integrates existing models of cellular and systemic allostatic regulation into a whole-organism predictive framework. By highlighting the energetic competition that occurs within and between systems during stress, the ATP model aims to explain psychopathogenesis, and the bidirectional association of psychiatric disease with cardiometabolic and immune pathology through a bioenergetic lens. We present the ATP model in seven steps. First, we build on established definitions of stress (Koolhaas et al., 2011; Selye, 1950, 1946, 1936) to define it metabolically, and review its role in driving psychopathogenesis. Second, we review EPIC, which explains how metabolic information processing influences all neural activities through affective states (Barrett et al., 2016; Kleckner et al., 2017; Sennesh et al., 2022). Third, we describe the MIPS, its role in the stress response, and how it regulates cellular, systemic, and CNS allostasis, and behavior (Picard and Shirihai, 2022). Fourth, we outline EMAL, which describes how stress-induced energy scarcity drives energy tradeoffs to ensure short-term survival (Bobba-Alves et al., 2022). Fifth, we explain our novel concepts of affect-driven prioritization and CNS allostatic triage and how they mediate stress-induced CNS functional connectivity changes that we propose underlie psychiatric symptoms. Sixth, we explain how the changes in functional connectivity mediated by allostatic triage become "canalized" into psychopathology (Carhart-Harris et al., 2022). In section eight, we integrate these existing models and our

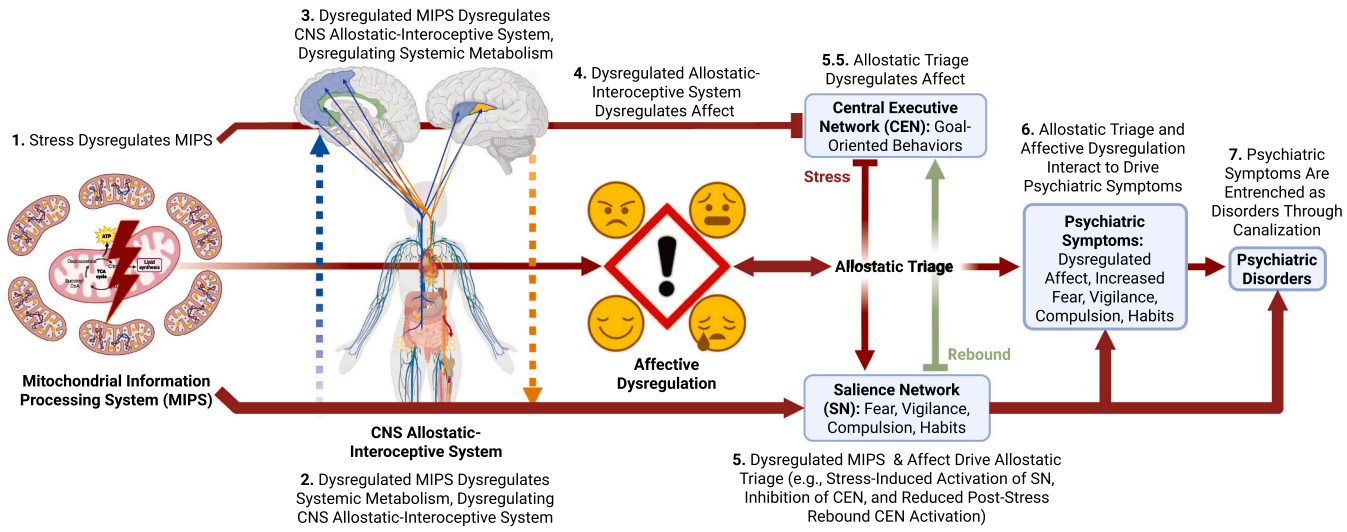

Fig. 1. Simplified illustration of the complete Allostatic Triage Model of Psychopathology (ATP Model) of stress-induced psychopathogenesis in seven steps. **1)** The lightning bolt in the mitochondria indicates stress-induced dysregulation of the MIPS. **2)** The blue dashed arrow going up indicates that dysregulation of the MIPS in the periphery trickles up to indirectly dysregulate the brain allostatic-interoceptive system. **3)** The orange down arrow in step three indicates that dysregulation of the MIPS in the CNS directly dysregulates the allostatic-interoceptive system in the CNS, which contributes to systemic metabolic dysregulation and disease. **4)** The red through arrow leading to the "!" surrounded by four facial expressions representing different affective & emotional states in step four indicates affective dysregulation induced by steps 1–3. The red arrow and inhibition symbol from the MIPS to the CEN/SN indicates independent effects of mitochondrial dysregulation on CEN and SN function. **5)** The red down arrow in step five indicates that steps 1–4 exacerbate allostatic triage from the CEN, which mediates goal-oriented and executive control behaviors, to the SN, which mediates fear, vigilance, compulsive, and habitual cognition and behaviors that are associated with psychopathology, when overactivated. The translucent green up arrow represents reduced rebound activation of the CEN after stress, inhibiting a protective mechanism that limits the deleterious effects of stress on CNS allostatic triage. 5.5) Highlights the bidirectionality between allostatic triage and affective dysregulation. **6)** Affective dysregulation and allostatic triage interact to drive psychiatric symptoms. **7)** Psychiatric symptoms become entrenched as psychopathology through activity-dependent neuroplasticity, which is sometimes called canalization. MIPS: Mitochondrial Information Processing System; CNS: Central Nervous System; CEN: Central executive network; SN: Salience Network. Figure Created on Biorender.com.

novel concepts into the ATP model, discussing the implications of taking an energetic approach to understand the stress→disease cascade. Finally, we outline remaining gaps in the literature, and propose specific hypothesis that must be addressed to fill these gaps and test the veracity of the ATP model.

2. Section 2: Stress-induced energy scarcity drives psychopathology

Considering established definitions of stress from first principles, we ground our definition of stress metabolically, making stress-induced increases in "demand" quantifiable. It's helpful to differentiate between stressors, which are internal or external stimuli that increase metabolic demand, and the stress response, an organism's adaptive response to meet that increased demand. Organisms undergo stress when a stressor overwhelms their capacity to meet the increased metabolic demand, driving adaptations that *impair* or *restrict* function (Koolhaas et al., 2011). The stress response has three general roles: 1) increasing the systemic availability of energetic substrates (Armario et al., 1990; Balasanthiran and Shotliff, 2015; Selye, 1936), and energy production in stress-responsive tissues (Bobba-Alves et al., 2022; Busillo et al., 2011; Du et al., 2009; Hunter et al., 2016; Picard and McEwen, 2018; Tran and Wang, 2019; Wang et al., 2025; Wang et al., 2025); 2) activating adaptive processes that help cells and organisms perceive and respond to immediate and future stressors (Cameron and Schoenfeld, 2018; Eisner et al., 2018; McEwen, 1998; McEwen, 1998; Picard and McEwen, 2018; Sorrells and Sapolsky, 2010); and 3) shunting energetic resources to stress-responsive cells and tissues, and away from growth, maintenance, and repair processes (Bobba-Alves et al., 2022), and non-stress responsive cells (Tsigos et al., 2020), a process that we call allostatic triage and extend for the first time to CNS functional connectivity. When the stress response matches stress-induced increases in energy demand, adaptations improve function, but when insufficient energy is available, adaptations impair or restrict function. We define stress intensity as the stress-induced change in metabolic demand between two points in time, minus the stress-response-induced change in energy availability (stress intensity = Δ energy demand$_{\text{Time 1-Time 0}}$ - Δ energy availability$_{\text{Time 1-Time 0}}$). Thus, stress occurs when stress intensity is positive, driving allostatic triage and functional impairment. Altogether, we ground established definitions of stressor, stress, stress response, and stress intensity bioenergetically, making each quantifiable from first principles.

We refer to stress as a general construct throughout this work. However, clear distinctions exist among acute, chronic, and traumatic stressors (Abbott et al., 1984; Zucchi et al., 2009), which differ among critical factors that increase stress intensity: 1) large increases in the magnitude or chronicity of increased metabolic demand, requiring greater activation of the stress response to facilitate sufficient energy availability; 2) severe perceived consequences of stress including damage or threat to the self, identity, or others, driving anticipatory stress (Koolhaas et al., 2011; O'Donovan et al., 2012; Selye, 1946, 1936); 3) perceived unpredictability (Anisman and Matheson, 2005; Baker and Stephenson, 2000), preventing anticipatory activation of the stress response to meet the increased demand; and 4) perceived uncontrollability (Baker and Stephenson, 2000), preventing behavioral adaptation to attenuate demand. Acute stressors activate the stress response and change systemic physiology and brain functional connectivity in healthy organisms, but the effects are generally adaptive and resolve quickly (Parihar et al., 2011). In contrast, traumatic stressors involving threat to life or physical integrity more often produce deleterious consequences (Keyes et al., 2013; Willard et al., 2016) Importantly, if unpredictable, even repeated mild stressors can evoke prolonged stress responses (Cameron and Schoenfeld, 2018; Glover et al., 2017; Koolhaas et al., 2011; Onat and Büchel, 2015). Moreover, early-life unpredictability (i.e., unpredictable sensory signals and/or parental behavior) is associated with psychopathology independently of exposure to traumatic stressors

(Spadoni et al., 2022), and affects cognitive development and hippocampal signaling in both rats and humans (Davis et al., 2017). Growing evidence also suggests that repeated exposure to unpredictable stressors contributes to systemic metabolic inefficiency, called allostatic load (AL) (Danese and McEwen, 2012). In contrast, predictability and controllability buffer against the deleterious effects of stress (Cohodes et al., 2023). Importantly, other important qualitative and contextual factors are not captured by our definition of stress intensity, and are beyond the current scope to discuss. Altogether, metabolic demand, perceived consequences, predictability, and controllability, determine the adaptations produced by different stressors (Anisman and Matheson, 2005; Baker and Stephenson, 2000; Melo et al., 2020; Zakowski, 1995).

Numerous systems and signaling molecules are part of the stress response, including the sympathetic adrenal medullary axis that is activated within seconds and produces catecholamines (e.g., epinephrine), and the hypothalamic-pituitary adrenal (HPA) axis, which is activated within minutes and produces glucocorticoids (Arango-Lievano et al., 2015; Sapolsky et al., 2000). The stress response also activates the immune system and other diverse cell types, driving the release of immune and metabolic signaling molecules (e.g., cytokines (Garcia-Oscos et al., 2012; Ménard et al., 2017), mitokines, or metabokines (Kang et al., 2021)) to communicate metabolic stress to the CNS and other tissues (Agis-Balboa et al., 2011; Li et al., 2013; Martín-Montañez et al., 2017; Pardo et al., 2018). Within the CNS, stress increases the release of cytokines (Johnson et al., 2004; Wilson et al., 2013), serotonin (Murnane, 2019) and other neurotransmitters (Kelley, 2022; Mateos et al., 2008; Wilson et al., 2014) and neuropeptides (Albrechet-Souza et al., 2021; Itoga et al., 2016; Schreiber et al., 2017), which alter metabolism, plasticity, and the functional connectivity of neural networks. Each of these "stress mediators" modulate metabolism, mitochondrial function, and drive adaptation and allostatic triage (Supplemental Table 1).

Anticipating stress and mounting anticipatory responses enhances survival and attenuates stress intensity, but chronic exposure to unpredictable stressors can drive maladaptive responses and precipitate psychopathology. For example, anticipation of a future threat, real or imagined (i.e., anticipatory stress), activates the stress response and can itself be an endogenously generated stressor. When a threat is imminent, anticipatory activation of the stress response is adaptive, but exposure to real or imagined unpredictable stressors can drive anticipatory activation in the absence of threat (i.e., anxiety), especially in people with preexisting depression and anxiety symptoms (Havranek et al., 2016). Increasing blood glucose and triglycerides in the absence of stress-induced increased demand is metabolically costly because energy is required to both increase and remove them from circulation (Bruce S. McEwen, 1998; M. Picard et al., 2014). Furthermore, persistent stress-induced increases in blood glucose and triglycerides leads to protein and lipid glycation, oxidative and reductive stress, vascular endothelial damage, and insulin resistance, among other deleterious consequences that require additional energy to remediate (Kelley et al., 2022; Vanessa Fiorentino et al., 2013; Wilson et al., 2013). In fact, anticipatory, but not retrospective threat appraisals, mediated the relationship between chronic stress exposure and telomere length in a sample of postmenopausal women, which could occur as a result of repeated and prolonged activation of the biological stress response and increased AL (Kelley, 2022; O'Donovan et al., 2013). Chronic anticipatory activation of the stress response in the absence of a genuine stressor (i.e., false alarms) also dysregulates the MIPS and the allostatic-interoceptive system, perturbing physiology, and we propose, unnecessarily driving allostatic triage (discussed in detail in Sections 3, 4, 5, and 6 below). Altogether, chronic unpredictable stressors can dysregulate systems from mind to mitochondria by driving anticipatory stress that activates the stress response repeatedly and unnecessarily, leading to maladaptations and systemic pathology.

Chronic and traumatic psychological stress are among the strongest known environmental risk factors for psychopathology, including MDD (Kendler et al., 2004), bipolar disorder (Lex et al., 2017), posttraumatic stress disorder (PTSD) (Publishing, 2013; Smoller, 2016), anxiety disorders (Daviu et al., 2019; Kasai et al., 2008), psychotic disorders (van Winkel et al., 2008), and personality disorders (Bourvis et al., 2017). The comorbidity and symptom overlap of many psychiatric disorders may indicate a common etiology and pathophysiology. Indeed, while there are challenges and some debate (Watts et al., 2024), factor analysis of diagnostic and statistical manual of mental disorders-5 symptoms in large data sets yields a general psychopathology factor (p), and two smaller internalizing and externalizing factors, rather than disorder-specific factors (Allegrini et al., 2020; Carhart-Harris et al., 2022; Carver et al., 2017; Caspi et al., 2014; Fissler et al., 2022) and stress exposure is reciprocally linked to p during critical developmental periods (Snyder et al., 2019). While some symptoms are specific to particular psychiatric disorders, the lines between distinct disorders are unclear, and stress is clearly a common driver of psychiatric and transdiagnostic disease and the bidirectional relationships among them.

3. Section 3: CNS allostatic regulation: the EPIC model and affect-driven prioritization

Allostasis was first defined as "maintaining stability through change" (McEwen, 1998; McEwen, 1998; Sterling, 2014, 1988). Energy is the single most important factor for the maintenance of life, and allostasis can also be defined from a metabolic perspective: maintaining bioenergetic stability through stress-induced metabolic perturbations, which has emerged as a major focus of the field (Bobba-Alves et al., 2022; Eisner et al., 2018; Picard et al., 2014). While the concept of allostasis can be accurately applied to numerous biological processes, each of them is fundamentally bioenergetically driven. Therefore, in line with contemporary usage (Bobba-Alves et al., 2022; McEwen and Wingfield, 2010; Picard et al., 2014), we refer to bioenergetic allostasis when using the term "allostasis". Allostatic systems anticipate metabolic and physiological changes and trigger adaptive processes to ensure equilibrium before setpoints are crossed (McEwen and Wingfield, 2010), as opposed to simpler reactive thermostat-like homeostatic responses (e.g., activate if the temperature exceeds 23°C). Allostatic systems must therefore anticipate the bioenergetic costs of daily activities, and future energy output, likely by maintaining an internal representation (i.e., model) of the important features of the systems they regulate (Barrett et al., 2016).

The brain allostatic-interoceptive system anticipates stress and triggers the energy production necessary to enact the appropriate behavioral responses, and reduce other costly behaviors to balance the energy budget before its overdrawn (Barrett, 2017a). For example, an individual may anticipate a future event that requires additional energy such as public speaking, and trigger the stress response to ensure that energy is available before the energy demand increases. However, chronic and traumatic stress, especially when unpredictable and uncontrollable, can alter important physiological and metabolic setpoints, including reducing or increasing the threshold for activation of the stress response, leading to over or under activation, as is observed in psychopathology (McEwen, 2005; McFarlane et al., 2011; Pariante and Miller, 2001; Yehuda et al., 2015, 2004; Young et al., 1991). In this way, prior stress exposure can impair anticipatory allostatic responses to subsequent stressors, increasing risk of energy scarcity and disease.

3.1. *Active inference models of the allostatic-interoceptive system*

Active inference posits that organisms interact with sensory information, including signals from the viscera, immune, and cardiovascular systems, to generate internal models of the interactions between the world, themselves, and their internal milieu. Internal models are experience-dependent inferences of the causes of sensory inputs and are refined by predicting the changes in those sensory inputs when the environment changes, or when behaviors are enacted. Active inference

models were first developed to explain the function of six-layered neocortex broadly (Friston, 2010), but have now been independently applied to the CNS allostatic-interoceptive system by Lisa Feldman Barrett (Barrett et al., 2016; Kleckner et al., 2017; Sennesh et al., 2022), Anil Seth (Seth and Friston, 2016), and Karl Friston (Pezzulo et al., 2015). Understanding these types of models may be fundamental to understanding diverse anticipatory bioenergetic processes, including stress and affect.

The allostatic-interoceptive system receives sensory information that it uses to generate an internal model (a collection of "priors") of systemic and cerebral metabolism and its relationship to behaviors, including endogenous functions. Behavior, be it motor, cognitive, or glandular secretions, are enacted as a test of the model's veracity. If what the model predicts happens, the model is confirmed, and new behaviors are enacted to test the model's next prediction, and so on. Actions are therefore one side of the two-sided coin of active inference and are inexorably compelled in tandem with the model's predictions for the purpose of testing them and updating the model. Each time an action or environmental change alters the incoming sensory information unexpectedly, prediction errors are produced that update the model's priors in real time, leading to a new set of predictions (derived from an updated model), and actions. This describes the basic active inference loop.

Barrett and colleagues proposed the EPIC model (Barrett et al., 2016) based on extensive tract-tracing and functional imaging experiments showing that afferent sensory information from the periphery is received and integrated in the insular cortex, which interacts with visceromotor regions of the anterior cingulate cortex, among other regions, to generate affect, defined as "the expected sensory consequences of allostatic changes within the body's internal milieu" (Barrett et al., 2016). Visceromotor regions produce actions that regulate systemic allostasis, and efference copies (i.e., predictions) that anticipate the sensory outcomes of those actions, that are compared to incoming sensory information to produce prediction errors, which update the model in real-time. Affect is modeled with two axes, one for valence (i.e., positive vs negative), and one for intensity (Barrett, 2017a; Barrett et al., 2016). Altogether, affect is the continuous subjective experience of the predicted sensory consequences of allostatic active inference, and bioenergetically compels or constrains behavior based on energy availability (i.e., state-dependent behavior).

Barrett also proposed the theory of constructed emotion (Barrett, 2017b), defining emotions as socioculturally-dependent cognitive constructions that explain affective states in context (Barrett, 2017b). Contextual information from the external environment and internal bodily states, and cognitive processes including memory, attention, concepts, and categorization, shape the cognitive categorization and concept formation involved in the construction of emotions. We recognize that Barrett's contrast between affect and emotions is distinct from common psychological definitions and normative usage, which often use the terms interchangeably. However, there is a critical difference between an organism's lower-dimensional perception of its allostatic state (i.e., affect) and its interpretation of the causes of that state (i.e., emotion) that is not captured by normative usage. Therefore, we emphasize that affective states regulate systemic allostasis by anticipating and regulating systemic resource allocation as behaviors are enacted and the environment changes, while emotions are constructed through context-dependent, concept-driven predictive coding to explain affective states in context, which guide decision-making and high-order behavior.

3.2. *Affective states regulate behavior according to metabolic efficiency: affect-driven prioritization*

Metabolic allostasis is the foundation of neural computation. In healthy organisms, affect represents the capacity to handle additional metabolic load. If metabolic efficiency is high, affect is positive, and expensive actions such as challenging, but potentially rewarding activities that support long-term allostatic regulation are facilitated. If metabolic efficiency is low, affect is negative, compelling an organism to conserve energy by delaying costly behaviors and triaging resources away from expensive processing tasks until conditions improve. In this way, organisms regulate metabolic stress by controlling their energy output and resource allocation through affective states, a process that we call 'affect-driven prioritization'.

Allostatic regulation likely requires an internal representation of metabolic efficiency at the relevant levels of biological organization (Conant and Ross Ashby, 1970; Pezzulo et al., 2015; Sennesh et al., 2022; Seth and Friston, 2016). Biologically, metabolic efficiency is the rate of energy expenditure relative to the minimum metabolic rate required to sustain life (Sturm et al., 2023); henceforth, we call this 'biological metabolic efficiency'. However, maintaining allostasis itself has a metabolic cost that depends on how precisely internal models of metabolic efficiency fit the incoming sensory data. To account for this additional layer of complexity, we define a new general term: "allostatic metabolic efficiency" as the actual cost of regulating allostasis relative to the cost that would be incurred by a perfectly optimized model. For example, cells must maintain an internal model of cellular metabolic efficiency (Picard and Shirihai, 2022), while the allostatic-interoceptive system must maintain internal models of systemic and/or tissue or region-specific metabolic efficiency. However, metabolic efficiency differs between cells, tissues, networks, and systemically, especially after stress, begging the question: which systems contribute most to affective states? We propose that metabolic efficiency in networks and tissues implicated in expected future behaviors are weighted more heavily and have an outsized impact on affect relative to systemic metabolic efficiency. Altogether, metabolic efficiency, likely in systems implicated in future behavior, drive affective states, which regulate behavior through affect-driven prioritization.

3.3. *Stress dysregulates affect by precipitating an inefficient internal model*

Chronic and traumatic stress, especially when unpredictable, can reduce allostatic metabolic efficiency and drive psychopathogenesis through multiple mechanisms. Chronic stress increases sympathetic nervous system arborization (Capitanio and Cole, 2015; Sloan et al., 2008, 2007), altering HPA axis[11] reactivity (Lowrance et al., 2016), driving "false alarms" and unreliable prediction errors, reducing allostatic metabolic inefficiency (Barrett et al., 2016). Stress also dysregulates mitochondria (Eisner et al., 2018; Picard et al., 2014; Wang et al., 2025; Weger et al., 2020), reducing biological metabolic efficiency, and we propose contributes to the aforementioned (mitochondrially regulated- see Section 3 below) sympathetic nervous system and HPA axis dysfunction (Picard et al., 2014). Altogether, chronic and traumatic stress reduce allostatic metabolic efficiency through the generation of unreliable prediction errors.

Unpredictable stress is a particularly potent generator of unreliable prediction errors. Unpredictable stress leads to a broader distribution of priors for threat detection (i.e., less confidence in the environmental cues and contexts that predict threat or safety) and results in a less confident model of threat avoidance. This, in turn, drives the overgeneralized threat detection, maladaptive attempts at avoidance, and anticipatory stress observed in preclinical stress models (Cameron and Schoenfeld, 2018; Glover et al., 2017), trauma-related disorders (Besnard and Sahay, 2016; Cisler et al., 2024), and anxiety disorders (Fraunfelter et al., 2022). Initially, unpredictable stress drives imprecise internal models, and subsequently, inefficient actions, reducing allostatic metabolic efficiency and impairing allostasis. However, over time, unreliable prediction errors are discounted and internal models can

[1] HPA axis reactivity is increased in MDD and GAD, but may be reduced in PTSD

grow overly precise and insensitive to sensory input (Barrett et al., 2016; Kleckner et al., 2017; Sennesh et al., 2022), resulting in inflexible affective states, a "locked in" brain, and the entrenchment of psychopathology, which is sometimes called "canalization" (Carhart-Harris et al., 2022). Altogether, if EPIC or similar models accurately describe CNS allostatic regulation, stress-induced changes in functional network activation and cognition can be understood in metabolic terms. Further, EPIC explains why stress, viewed bioenergetically, leads to unreliable prediction errors and the rigid cognitive landscapes associated with psychopathogenesis.

4. Section 4: The MIPS Bridges cellular and systemic allostasis

Despite their central role in metabolism, the designation of mitochondria as the "powerhouses of the cell" is insufficient to explain their myriad established functions (Belenguer et al., 2019; Picard and Shirihai, 2022). Mitochondria are living, dynamic, intracellular organisms (Picard and Sandi, 2021) and exhibit accepted principles of social behavior: functional specialization (Johri and Beal, 2012), communication, interdependence between individuals, and behavioral synchronization to achieve collective ends (Picard, 2015; Picard and Sandi, 2021; Picard and Shirihai, 2022). Mitochondria also move between cells, including neurons and immune cells (Borcherding and Brestoff, 2023), and high levels of cell-free mitochondria are observed in systemic circulation with unknown origins and destinations (Dache et al., 2020). The MIPS (Picard and Shirihai, 2022) transforms energy, and thus must receive, integrate, and process information about energy demands, communicate, and alter its function, to control energy flow within organisms and regulate local and systemic allostasis in collaboration with the allostatic-interoceptive system.

Mitochondria have evolved as information integration hubs that act as gatekeepers of metabolic information, and output summary signals that regulate allostasis. The MIPS receives signals from steroid (Du et al., 2009; Gak et al., 2015; Hunter et al., 2016; Sapolsky et al., 2000), serotonergic (Fanibunda et al., 2019), catecholaminergic (Lee et al., 2021; Lim et al., 2021; Mishra et al., 2020; Sandroni et al., 2022), insulin and insulin-like peptides (Bhardwaj et al., 2021; Du et al., 2019; Gazit et al., 2016; Gui et al., 2021), immune (Valença-Pereira et al., 2021), and metabolic factors (Sapolsky et al., 2000), and numerous other signaling molecules (Eisner et al., 2018; Picard et al., 2014; Picard et al., 2014; Picard, 2015), integrates that information within and between mitochondrial networks, and outputs summary signals to regulate cellular and systemic allostasis (Table 1). Through these mechanisms, the MIPS orchestrates key aspects of multiple stress-response systems directly (Goglia et al., 2002; Kelley et al., 2025; Midzak and Papadopoulos, 2016; Miller, 2013; Picard et al., 2014; Picard et al., 2018; Picard and Shirihai, 2022; Velarde, 2014), or indirectly (Goffart and Wiesner, 2003; Kim et al., 2018; Lee et al., 2002, 2008; Lombardi et al., 2019; Wiese and Bannister, 2020), allowing it to govern broad cellular and systemic functions. Altogether, the MIPS plays a dual role of energy producer and information processor, keeping the organism alive, and guiding its behaviors according to its allostatic program, forming the central bridge between local and systemic metabolic information processing (Picard, 2015).

Table 1
Mitochondrial summary signals.

	Function	Summary Signal
1.	**Direct:** Signaling molecule biosynthesis	Metabolites, DNA & RNA precursors, ROS, cf-mtDNA, ions, bases, ATP, heat, small peptides, steroid hormones, catecholamines, monoamines
2.	**Direct:** Energy production, distribution, dynamics	ATP production & distribution, mitochondrial dynamics
3.	**Indirect:** Regulation of nuclear gene expression	Epigenetic regulation by Ca^{2+} signaling, metabolic enzymes, ROS, metabolites

Table 1: The MIPS receives and integrates diverse inputs, and outputs three types of summary signals to regulate cellular and systemic allostasis: 1) Direct production of outputs: including metabolites, precursors for deoxyribonucleic acid (DNA), ribonucleic acid (RNA), reactive oxygen species (ROS), cell-free mitochondrial DNA, ions, gasses, ATP, heat, small peptides, and steroid hormones (Midzak and Papadopoulos, 2016; Miller, 2013), including sex (Velarde, 2014), metabolic (Goglia et al., 2002), and stress hormones (M. Picard et al., 2014); 2) Direct regulation of host cell activity via ATP production and distribution; 3) Epigenetic regulation of nuclear gene expression: Ca^{2+} signaling, metabolic enzymes, ROS and metabolites (Lombardi et al., 2019; Picard and Shirihai, 2022; Wiese and Bannister, 2020). MIPS: mitochondrial information processing system; DNA: deoxyribonucleic acid; RNA: ribonucleic acid; ROS: reactive oxygen species; ATP: adenine triphosphate.

4.1. The MIPS regulates function and behavior across all levels of biological organization

The MIPS regulates the behavior and function of cells, networks, and whole organisms, including the immune system. For example, mitochondrial respiratory capacity regulates adaptive immunity by regulating CD8 + T cell memory development, and innate immunity by controlling the differentiation and cytokine expression of innate immune cells (Karan et al., 2020; Keeney et al., 2023). Mitochondria also regulate macrophage polarization (Trinchese et al., 2024; Weinberg et al., 2015), inflammasome activation (Weinberg et al., 2015), and various other immune functions through energy sensing pathways (Chen et al., 2023), mitophagy (Angajala et al., 2018), fission and fusion events (Angajala et al., 2018; Trinchese et al., 2024), ROS production (Chen et al., 2023; Weinberg et al., 2015) and metabolic intermediates (S. Chen et al., 2023; Trinchese et al., 2024), each regulating different signal transduction pathways critical to immune function (Iwasaki et al., 2020). Mitochondria also regulate cardiometabolic (Zong et al., 2024), endocrine (Jin and Diano, 2018), and other physiological functions (Harrington et al., 2023). Importantly, psychopathology is associated with chronic inflammation (Mellon et al., 2018; Miller and Raison, 2016; Müller, 2018; O'Donovan et al., 2017), which is metabolically expensive, contributing to systemic metabolic load (Bird, 2019; Ganeshan et al., 2019) during stress.

The MIPS regulates adaptive CNS processes, including gene expression (M. Picard et al., 2014; Yang et al., 2001), the production and metabolism of monoamine and catecholamine neurotransmitters (Graves et al., 2020; Lee et al., 2021; Rasbach et al., 2010), aspects of glutamate (Robinson et al., 2020) and gamma-aminobutyric acid production and metabolism (Besse et al., 2015; Cavalcanti-de-Albuquerque et al., 2021), excitability and neurotransmitter release (Kwon et al., 2018, 2016; Sun et al., 2013; Ugur et al., 2017), neuroplasticity (Cheng et al., 2010; Chihara et al., 2007; Courchet et al., 2013; Fukumitsu et al., 2016; Gebara et al., 2021; Kimura and Murakami, 2014; Mattson, 2007; Mattson et al., 2008) and neurogenesis (Adusumilli et al., 2021; Khacho et al., 2019; Khacho and Slack, 2018), and glial cell function and proliferation (McAvoy and Kawamata, 2019), which scale to whole-organism behaviors. In fact, mitochondrial respiratory chain enzyme activities in one striatal network are associated with anxiety-like and avoidance behavior (Rosenberg et al., 2023), hippocampal mitochondrial gene expression is associated with avoidance, and ROS production is associated with pattern separation in stressed, but not control rats (Kelley et al., 2023). Further, experimental manipulation of mitochondria mediates whole organism behaviors, including anxiety and depressive behaviors (Gebara et al., 2021), social dominance (Ghosal et al., 2023; Hollis et al., 2015), and prosociality (Pozo et al., 2023). In humans, peripheral superoxide-sensitive mitochondrial redox environments bioenergetically mediate motor performance (Spooner et al., 2021). Together, these examples exhibit regulation of broad physiological processes and behaviors across all levels of biological organization by the MIPS.

4.2. The MIPS regulates the allostatic-interoceptive system

The MIPS regulates systemic allostasis directly by managing cellular allostasis and through diverse signaling mechanisms, including stress mediators (Supplemental Table 1), and indirectly by regulating the allostatic-interoceptive system. Interoceptive information about systemic metabolism and metabolic stress is communicated to CNS, linking peripheral and CNS mitochondria into the whole organism MIPS. In the CNS, nodes of the MIPS regulate the allostatic-interoceptive system by receiving, metabolizing, and producing signaling molecules (Supplemental Table 1) and managing allostasis within neurons and glial cells that comprise allostatic-interoceptive networks (Jin and Diano, 2018). Importantly, receptors for many stress mediators are highly expressed in the insular and anterior cingulate regions that comprise the allostatic-interoceptive system (Sjöstedt et al., 2020). Therefore, dysregulation in the MIPS dysregulates the allostatic-interoceptive system, reducing allostatic metabolic efficiency, and dysregulating affect. We discuss the consequences of reduced systemic and CNS metabolic efficiency, and affective dysregulation in Sections 4 and 5 below, respectively.

5. Section 5: EMAL: energetic tradeoffs drive disease

Biological metabolic efficiency is reduced in disease states, primary mitochondrial disorders (Niyazov et al., 2016), and after chronic exposure to stress or stress mediators (Sturm et al., 2023). Biological metabolic efficiency depends on at least three important cellular factors (Table 2), in addition to external factors such as the energetic substrates used as inputs for energy production (i.e., glucose, ketones, etc). Chronic exposure to stress or stress mediators drives hypermetabolism and mitochondrial adaptations (Madrigal et al., 2001; Picard and McEwen, 2018) (Supplemental Table 2) necessary to maintain elevated energy output, but that reduce metabolic efficiency (Sturm et al., 2023). Specifically, stress-induced reductions in the ratio of ATP/adenine diphosphate (ADP) relative to the combined cost of metabolism itself and the increased background costs of hypermetabolic states, characterize mitochondrial allostatic load (MAL) (Picard et al., 2014) (Supplemental Table 3). Stress-induced hypermetabolism is necessary to increase energy production, but is chronically maladaptive because it drives MAL, resulting in genetic and epigenetic dysregulation (Flint et al., 2007), telomere shortening (Kawanishi and Oikawa, 2004), and cellular senescence (Wiley et al., 2016). Chronic MAL reduces the capacity for growth and adaptation, and drives dysregulation at higher levels of biological organization, such as inflammation (Picard et al., 2014; Sturm et al., 2023), metabolic disease (Picard et al., 2014), and psychiatric symptoms. In this way, even if the total amount of ATP and the ATP/ADP ratio is increased, hypermetabolic cells use more energy to produce that ATP and for background costs, which can lead to energy scarcity despite increased metabolism (i.e., metabolic inefficiency). Altogether, when cells are less efficient, they have less energy to repair themselves, grow, and flexibly adapt to their environments.

Table 2
Factors mediating biological metabolic efficiency.

1. Source of ATP:	ATP production rates by glycolysis or mitochondrial oxidative phosphorylation
2. Stoichiometry:	ATP produced per unit of reductive substrate (NADPH, FADH2) relative to the amount of ADP in the system (ATP/ADP ratio is more important than total ATP levels)
3. Background Costs:	Rate of ATP consumption for allostasis, growth, adaptation, and housekeeping (e.g., transcription, translation, biogenesis, maintenance, and repair)

Table 2: Three critical factors that contribute to the efficiency of metabolism itself (biological metabolic efficiency). Other factors such as the energetic substrates used as inputs for ATP production also contribute to metabolic efficiency, but are not included here because they are not features of the system itself. ATP: Adenine triphosphate; ADP: Adenine diphosphate; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; FADH2: Reduced form of Flavin Adenine Dinucleotide (FAD)

5.1. MAL drives systemic and CNS metabolic inefficiency

MAL drives dysregulation at higher levels of biological organization because cellular, tissue, organ, and neural network function are regulated by the MIPS. Bruce McEwen described common ways that chronic activation of the stress response alters its dynamics (McEwen, 1998; McEwen, 1998; McEwen and Wingfield, 2010). Chronic or traumatic stress, and MAL (Picard et al., 2014) can reduce or increase thresholds for activation of the stress response, driving repeated activation, a prolonged response, or reduce thresholds, producing an inadequate response (McEwen, 1998). Persistent allostatic states and hypermetabolism results in physiological maladaptations including hypertension, hyperglycemia, hyperlipidemia, and changes to the lipid profile of the brain (Chaichi et al., 2021; Clement et al., 2009; Kelley et al., 2022; Madrigal et al., 2001; Prasad et al., 2019) and other tissues (Miao et al., 2023; Tham et al., 2018), characterizing the shift from allostatic states to AL (Buckwalter et al., 2016; Hilliard et al., 2016; Leslie and Vartak, 2020; McEwen and Wingfield, 2003; Seeman et al., 2001, 1997; Suvarna et al., 2020). Persistent AL drives additional physiological recalibrations, further reducing metabolic efficiency and energy availability for growth, maintenance, and repair, characterizing the shift to allostatic overload (AOL) (Bobba-Alves et al., 2022). AOL is associated with alterations to receptors and chaperones for energetic substrates and stress mediators (Boks et al., 2016; Wang et al., 2018; Xie and Bu, 2019), circadian changes to HPA and sympathoadrenal-medullary axis function (Fava et al., 2019; Sapolsky et al., 2000), increased hemoglobin A1c (Fava et al., 2019; Seeman et al., 1997; Suvarna et al., 2020), chronic inflammation (Buckwalter et al., 2016; Hilliard et al., 2016; Seeman et al., 2001, 1997; Suvarna et al., 2020), arterial stiffening to maintain elevated blood pressure, and the structural remodeling of brain circuits and anatomy (Bobba-Alves et al., 2022), features of cardiometabolic, autoimmune, and psychopathology. MAL characterizes cellular metabolic inefficiency (Picard et al., 2014), and AL and AOL characterize systemic metabolic inefficiency (McEwen, 2015), both forms of biological metabolic efficiency. Importantly, MAL, AL, and AOL contribute to allostatic metabolic inefficiency, dysregulating affect. When affective states become decoupled from biological metabolic efficiency, affective allostatic regulation is impaired, exacerbating biological metabolic inefficiency, a positive feedback loop driving disease.

5.2. Metabolic inefficiency drives disease pathogenesis

Biological metabolic inefficiency drives disease pathogenesis because it reduces the reserve metabolic capacity of cells and organisms, increasing the chances of energetic scarcity and the necessity of deleterious energetic tradeoffs when energy demand is high. Bruce Ames proposed “Triage Theory” which explains that organisms triage micronutrients, including essential vitamins and minerals, to the processes most necessary for survival when resources are scarce (Ames, 2006). EMAL proposes that the same is true for energetic resources; when energy is scarce, or predicted to be scarce by the allostatic-interoceptive system, organisms allocate energetic resources to the processes predicted to be necessary for survival, at the expense of growth, maintenance, repair, and other costly functions in other domains. During scarcity, the finite energy budget of an organism must be distributed competitively among physiological functions according to their metabolic costs and perceived necessity. Reduced energy resource allocation to maintenance and repair leads to the accumulation of damage, further reducing efficiency and impairing function, while reduced allocation of energy to growth impairs flexible adaptation to the environment. Altogether, energy tradeoffs drive and follow from metabolic inefficiency, and reduce phenotypic plasticity, driving transdiagnostic disease

pathogenesis.

MAL limits phenotypic flexibility. The integrated stress response (ISR) (Costa-Mattioli and Walter, 2020) is activated by factors of MAL, and globally limits gene transcription and protein translation, apart from a restricted set of genes that are crucial for acute stress adaptation. Furthermore, ISR activation alters systemic allostatic regulation through the mitochondrially-mediated nuclear production of "mitokines" such as fibroblast growth factor 21 (FGF-21) (Flippo and Potthoff, 2021; Restelli et al., 2018) and growth and differentiation factor 15 (GDF-15) (Wang et al., 2021), which are released into systemic circulation and signal metabolic stress to the CNS and other tissues. Both acute (Gouspillou et al., n.d.) and chronic stress can increase mitokine levels, which can activate the HPA axis (Cimino et al., 2021; Ryan et al., 2018) in support of allostasis. Mitokines generally exert protective effects, but we propose that chaotic release of stress mediators, like mitokines, reduces allostatic metabolic efficiency, as discussed above. We hypothesize that the limited breadth of gene expression and phenotypic flexibility that follows from chaotic or chronic ISR activation, entrenches inflexible maladaptive phenotypes at higher levels of biological organization. Indeed, transdiagnostic psychiatric and systemic disorders are associated with AL (Bersani et al., 2020; Kelley, 2022; Lenart-Bugla et al., 2022; McEwen, 2003; Mellon et al., 2018; Miller et al., 2018; Seeman et al., 2001), MAL (Amorim et al., 2025; Becker et al., 2022; Blalock et al., 2024; Hummel et al., 2023; Jiang et al., 2024; Lushchak et al., 2023; Ni et al., 2024; Peoples et al., 2019), and ISR activation (Korneeva, 2022; Zhang et al., 2022). Thus, consistent with EMAL, we propose that AL, MAL and ISR activation drive transdiagnostic disease pathogenesis by inducing metabolic inefficiency, energy scarcity, and subsequently, phenotypic inflexibility.

6. Section 6: CNS allostatic triage: affect-driven prioritization of brain functional connectivity

Applying EMAL to CNS functional networks, we propose a general principle of brain function: allostatic triage regulates brain functional connectivity during energy scarcity according to metabolic cost and survival value. Specifically, allostatic triage leads to the redistribution of brain metabolic resources from metabolically expensive networks optimized for long-term outcomes to the least expensive networks that can ensure short-term survival during energy scarcity. As discussed above in Section 3, affect is generated by the allostatic-interoceptive system from internal models of metabolic efficiency. Integrating EPIC and EMAL, we hypothesize that affect defines the setpoint above which allostatic triage occurs, a process that we call affect-driven prioritization.

Why must the brain triage resources rather than simply increasing energy production? Energy is a finite resource, and the brain is particularly sensitive to metabolic stress. All biological activities are dependent upon energy metabolism, but the human brain is the most expensive organ, using 20 % of oxygen and 25 % of glucose (Erbsloh et al., 1958; Magistretti and Allaman, 2015; Magistretti and Pellerin, 1999; Zhu and Thompson, 2019) despite it being just ~2–3 % of the total body mass (Erbsloh et al., 1958; Magistretti and Pellerin, 1999). While the cardiovascular system is also disproportionally expensive, the brain extracts oxygen (30 %) more slowly compared to the heart (80 %) or muscle (90 %), resulting from its comparatively low capillary density, unique sensitivity to pH changes, hyperglycemia and hyperoxemia, and brain-specific requirements to maintain the entropy change of mitochondrial oxidative metabolism (e.g., the O_2/CO_2 ratio) (Buxton, 2010, 2024, 2021). Due to these limitations, the brain continuously operates at or near its maximal metabolic capacity and can only increase its overall cerebral metabolic rate of oxygen by 10–30 % during intense increases in demand, although some grey matter regions can increase by up to 40 % (compared to a 10 fold increase in muscle) (DiNuzzo et al., 2024). Therefore, brain energy production is restricted by a hard upper limit on its access to energetic resources, making it particularly sensitive to systemic and CNS metabolic inefficiency, which can quickly lead to energy scarcity when demand is high (Buxton, 2021; DiNuzzo et al., 2024).

What is the metabolic value of triaging energetic resources between brain networks? There is a hierarchy of metabolic costs in the brain. Most of the brain's energy is devoted to intrinsic activity (Zhang and Raichle, 2010), which exerts constant demand, while task-dependent activation is the most variable. The number of neurons in a network increases the metabolic cost of CNS network activation (Arshavsky, 2023), but the preponderance of evidence in humans suggests that synaptic density (Yu et al., 2023) and the number of metabotropic neuromodulator receptors (Castrillon et al., 2023) are the primary determinants of CNS metabolic cost. Indeed, cortical activation typically involves synaptically dense integration hubs (Yu et al., 2023) and is more bioenergetically expensive than subcortical activation, and the most evolutionarily expanded cortical regions are the most costly (Mosharov et al., 2025). Signaling in evolutionarily expanded regions, including the prefrontal cortex (PFC), and networks including the central executive (CEN, also called the frontoparietal network) and default mode networks (DMN), which have the highest number of neuromodulator receptors, have the greatest blood perfusion (Farahani et al., 2025), use up to 67 % more glucose (Castrillon et al., 2023), and show the highest levels of mitochondrial enzyme activity (Mosharov et al., 2025) compared to phylogenetically older and less complex attentional and sensory-motor networks. Several neuromodulator receptors enriched in the most evolutionarily expanded networks (e.g., 5-HT_{2A}, muscarinic receptors) are activated by stress (Baik, 2020; Glavin, 1985; Murnane, 2019), strongly overlap with mitochondrial enzyme activity (Mosharov et al., 2025) and blood perfusion (Farahani et al., 2025), alter mitochondrial and cellular metabolism (Fanibunda et al., 2019; Graves et al., 2020; Lim et al., 2021; Mishra et al., 2020), and facilitate complex cognition (Castrillon et al., 2023; Grossman and Cohen, 2022). Indeed, experimental evidence from individuals with inherited mitochondrial disorders exposed to stress-induced increases in energy demand, supports the hierarchical triage of metabolic resources from evolutionarily expanded regions mediating complex cognition to older regions mediating sensory, vigilance, and fear-related processes (Bo et al., 2025). Altogether, phylogenetically younger neuromodulator receptor-rich networks that mediate complex executive and self-referential behaviors are more metabolically costly than networks mediating sensory, attention, vigilance, fear, habits, and vital functions (Castrillon et al., 2023; Tomasi et al., 2013), and are more susceptible to allostatic triage during energy scarcity.

According to EPIC, affect predicts the ability of a healthy organism to handle additional stress or metabolic demand without losing function. Activation of the stress response alters affect by changing predictions about energy expenditure and availability. However, chronic and traumatic stress reduces metabolic efficiency and dysregulates affect. We propose that dysregulated affective states still drive allostatic triage such that the negative affect observed in MDD (bottom dark blue dashed line in Fig. 2), will elicit allostatic triage at a lower level of energy demand than if the same individual was in a state of strong positive affect (top light blue line in Fig. 2). We hypothesize that during energy scarcity, the available energy is first triaged between networks within the task-dependent activation category, but as stress grows in intensity and/or chronicity, energy must also be triaged away from growth (i.e., neuroplasticity), maintenance, and repair processes, depending on their predicted survival value in context, further reducing brain metabolic efficiency and phenotypic flexibility over time (Fig. 2). Altogether, we propose that allostatic triage occurs in healthy organisms during high demand but becomes pathological when it's governed by dysregulated affective states. To illustrate allostatic triage, we discuss examples of stress-induced and psychopathology-associated differences in CNS functional connectivity in relation to their energetic costs below.

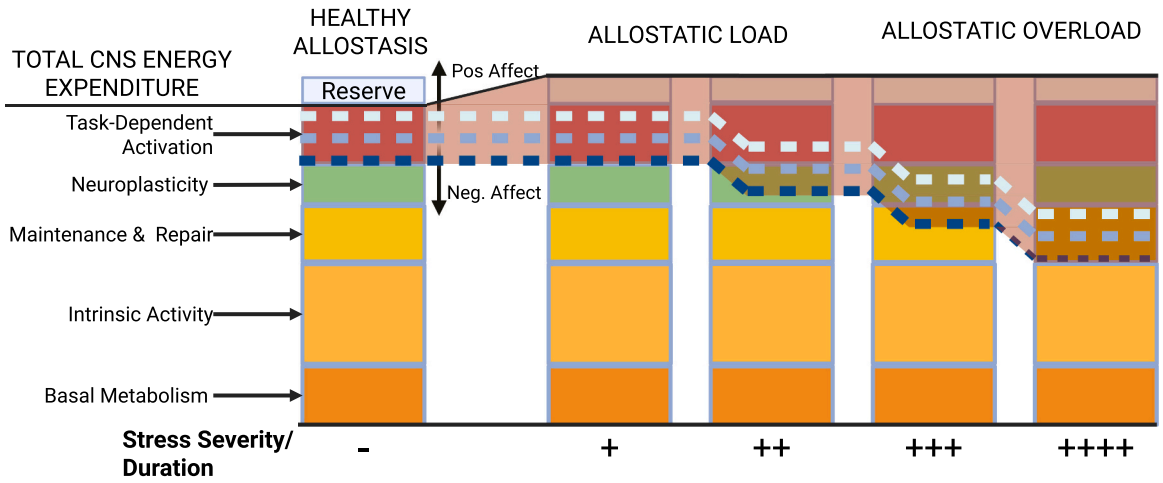

Fig. 2. Hypothetical ATP Model of CNS allostatic triage based on EMAL. Each colored box represents a different category or "bucket" of energy use in the CNS. Increased task-dependent neural activation (red box) is required for cognitive activities that produce the behaviors necessary to respond to stressors, and in the context of increased energy demand (i.e., stress) and insufficient energy production, can necessitate allostatic triage from other networks within that category, or when extreme, from other categories (other colored boxes). Moving from left to right on the figure, the level of bioenergetic demand on the CNS increases, starting with mild stress (- or healthy allostasis) to moderate to intense stress (+, ++ or allostatic load), and extreme stress and energetic demand (+++, ++++ or allostatic overload). The red shaded area indicates which categories are being triaged to support additional resource allocation to task-dependent activation based on the level of demand. Affect, which is derived from the internal model of the predicted bioenergetic state of the organism, is represented by the three different shades of blue dashed lines. We propose that affect determines the setpoint (i.e., the level of energetic demand) at which allostatic triage begins to occur (i.e., affect-driven prioritization) Negative affect, representing the prediction that energy efficiency is low or uncertain (bottom darkest blue dashed line), causes triage at lower levels of stress. Positive affect represents the prediction that energy is abundant and results in reduced triage as stress increases (top lightest blue dashed line). Importantly, allostatic triage need not first triage energy from neuroplasticity followed by maintenance and repair, and so on, in that order. Rather, energetic resources are likely triaged from multiple buckets simultaneously, a limitation of presenting this figure in two dimensions. ATP Model: Allostatic Triage Model of Psychopathology; CNS: Central Nervous System; EMAL: Energetic Model of Allostatic Load. Figure created on Biorender.com.

6.1. Stress and psychopathology alter CNS functional connectivity

Acute stress and stress mediators generally shift CNS activation patterns towards phylogenetically older, less metabolically expensive networks, and alter signaling within and between phylogenetically younger and more expensive networks. For example, norepinephrine and glucocorticoids shift activation from cortico-striatally mediated goal-oriented behavior towards lateral striatally-mediated habits and compulsions (Schwabe and Wolf, 2011), which are less metabolically costly. At the network level, acute stress activates the salience network (SN), which plays a major role in attentional vigilance and threat detection, and the expression of anxiety, fear, and habitual and compulsive behaviors that are associated with psychopathology. Acute stress also activates the DMN, and the CEN, but these effects are complex and differ by the protocol used (van Oort et al., 2017). Some stress paradigms show reduced CEN activation and function, while others show increases or shifts in activation and function within the CEN (van Oort et al., 2017). For example, acute stress-induced cortisol release shifts neural resources within the CEN from circuits underlying cognitive flexibility (Plessow et al., 2011; Shields et al., 2016) to those underlying goal shielding (Plessow et al., 2011), which refers to maintaining one's focus on a goal by avoiding other goals, a possible bioenergetic tradeoff. Altogether, acute stress and stress mediators alter CNS functional connectivity and function consistently with allostatic triage, though more evidence is needed to fully understand these processes. We hypothesize that allostatic triage is one driver of the effects of acute stress on CNS functional connectivity, especially in the context of metabolic inefficiency.

Pre to post human imaging data in chronic stress paradigms is limited, but the available evidence suggests that chronic stress drives persistent resting state SN activity (McCutcheon et al., 2019), and increased vigilance, habitual, and compulsive behaviors. Chronic stress also modifies CEN functional connectivity (Hermans et al., 2017, 2014; McCutcheon et al., 2019) and impairs broad executive functions (Bloemen et al., 2018). Interestingly, after stress resolves, healthy organisms may show increased rebound activation of the CEN, which may support recovery from stress, but this effect may be impaired after chronic or intense stress (Hermans et al., 2017, 2014). Chronic stress is also associated with impaired DMN network connectivity (Zeev-Wolf et al., 2019). Importantly, brain state transitions are metabolically expensive (Gu et al., 2018), and additional activation energy may be required to transition out of chronic stress-induced functional connectivity patterns, suggesting that stress-induced maladaptive states could become entrenched over time as psychiatric disorders. Altogether, diverse forms of chronic stress increase SN functional connectivity, vigilance, habits, and compulsions, but alter CEN connectivity and reduce executive function (Girotti et al., 2018; Hermans et al., 2017), echoing the transdiagnostic features of psychopathology (Bloemen et al., 2018; Snyder, 2013).

Psychiatric disorders are associated with both transdiagnostic and disorder-specific differences in CNS functional connectivity. The SN is expanded in MDD and connectivity changes in the SN predict affective symptoms (Lynch et al., 2024). There are also differences in SN functional connectivity in schizophrenia (Chen et al., 2016; Pietrzykowski et al., 2022), PTSD (Akiki et al., 2018) and GAD (Xiong et al., 2020), which, like MDD (Li et al., 2021) also exhibit differences in CEN connectivity (Akiki et al., 2018; Coussement et al., 2022), and deficits in executive function. DMN activity is increased in MDD (Scalabrini et al., 2020), though there is ongoing debate, with studies showing both downregulation and upregulation, depending on the analysis techniques used (Scalabrini et al., 2020). Altered DMN functional connectivity has been observed in Schizophrenia (Manoliu et al., 2014), PTSD, and GAD, and GAD is also associated with reduced DMN cortical volume (Bashford-Largo et al., 2022). Activity across all three networks has also been used to predict heterogeneous presentations of PTSD using machine learning approaches (Nicholson et al., 2020). Altogether, while existing data paint a highly nuanced picture of brain connectivity in psychopathology that is beyond the scope of this work to comprehensively review, two networks and their associated behaviors and cognitive functions emerge as transdiagnostic features of chronic stress and

psychopathology: 1) increased SN connectivity and vigilance, habitual, and compulsive behaviors, and 2) altered CEN connectivity and impaired cognitive flexibility, goal-oriented cognition, and executive function.

To illustrate the potential role of allostatic triage in driving psychopathogenesis, we highlight 1) and 2) above. We hypothesize that altered CEN functional connectivity and impaired executive function results from allostatic triage within nodes of the CEN, and from the CEN to other networks, including the SN, and from the downregulation of compensatory activation after stress resolves (Fig. 3). Critically, most regions of the SN are less metabolically expensive than those of the CEN (Castrillon et al., 2023; Farahani et al., 2025; Mosharov et al., 2025). Accordingly, Fig. 3 highlights our general principle that in the context of predicted energy scarcity and metabolic inefficiency, negative affective states exacerbate allostatic triage from expensive networks that optimize long-term outcomes, such as the CEN, to less costly networks with high survival value, such as the SN (Fig. 3). Importantly however, the predicted outcomes of circuit and network activation, and the resulting behavioral states are also crucial determinants of brain functional connectivity. Thus, the ATP model does not necessitate that energetic resources are exclusively triaged from more expensive to less expensive networks. Rather, we propose that the allostatic-interoceptive system drives allostatic triage according to the predicted outcomes of network activation (e.g., survival value), and only to the (predicted) extent necessary to maintain allostasis. Altogether, we hypothesize that stress-induced pathological allostatic triage generally impairs CEN

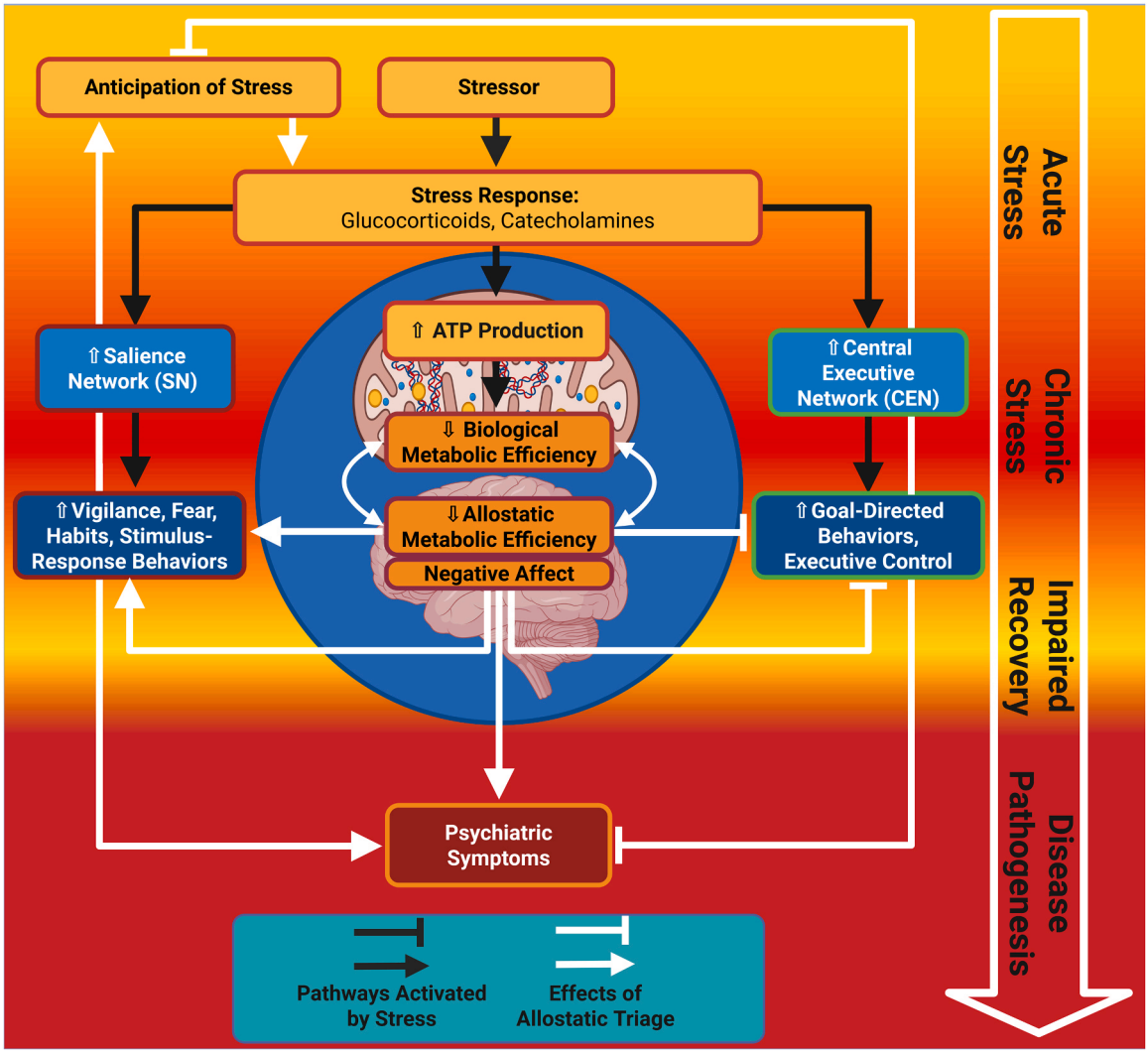

Fig. 3. Illustrative example of chronic stress-induced allostatic triage from the central executive network (CEN) and goal-directed and executive functions to the salience network (SN) and vigilance, fear, habitual, compulsive, and stimulus-response behaviors. We propose that this process results from stress-induced reductions in biological metabolic efficiency (i.e., the efficiency of metabolism itself) and allostatic metabolic efficiency (i.e., the efficiency of allostatic regulation), and is regulated by affective states, which represent internal models of metabolic efficiency, a process that we call affective prioritization. Critically, allostatic triage is exacerbated by the affective dysregulation caused by chronic stress. Arrows represent activation and blunted lines indicate inhibition. Black indicates the normal effects of stress and white indicates the effects of allostatic triage. The background color indicates stress intensity with yellow/orange indicating mild or acute stress, light red indicating intense or chronic stress, and dark red indicting stress-induced disease pathogenesis. The shift from light red back to yellow indicates recovery, which may be impaired after chronic stress. The bidirectional white arrows between biological and allostatic metabolic efficiency indicate the mutual dependence of both processes. The white arrow and blunted inhibition symbol from reduced allostatic metabolic efficiency to increased vigilance, fear behaviors, habits, etc, and increased goal directed behaviors and executive control indicate allostatic triage from expensive executive functions that optimize long-term outcomes to less costly behaviors that ensure short-term survival. The white arrows and inhibition symbols from negative affect to vigilance and fear behaviors, and goal-directed behaviors, respectively, during "impaired recovery", indicates that the process of rebound enhancement of the CEN after stress is impaired after chronic stress-induced allostatic dysregulation, driving psychiatric symptoms. Importantly, the CEN and SN are represented here as illustrative examples, but we propose that allostatic triage occurs among all functional brain networks, depending on their predicted outcomes and metabolic costs. Figure created on BioRender.com.

function, and leads to SN overactivation, driving general features of psychopathology. However, we hypothesize that stressor and disorder-specific changes in functional connectivity emerge from allostatic triage applied to the specific patterns of network activation predicted to best optimize survival versus long-term outcomes for each individual in context, especially when those predictions are unreliable and the changes are maladaptive.

7. Section 7: Canalization of psychopathology: changes in CNS functional connectivity become entrenched through canonical mechanisms of neuroplasticity

Stress and allostasis alter CNS plasticity (McEwen and Gianaros, 2011), and AL is associated with structural changes in the brain (Lenart-Bugla et al., 2022). Indeed, persistent stress-induced changes in network and circuit activation may be stabilized over time through canonical mechanisms of neuroplasticity, producing psychiatric disease phenotypes. Some anatomical features of psychopathology, like a larger SN, appear stable and "trait-like", but persistent changes in the patterns of network activation can predict affective symptoms, suggesting that dynamic changes to the SN track with symptoms (Lynch et al., 2024). Further, childhood trauma exposure is associated with a smaller hippocampus and a trend towards larger amygdala volume (Logue et al., 2018) which are risk factors for developing PTSD (Gilbertson et al., 2002), and trauma exposure and PTSD in adulthood may further reduce hippocampal volume (Bremner et al., 2021; Zheng et al., 2021), suggesting that in some cases, even gross anatomical differences can emerge from the neuroplasticity induced by traumatic stress.

Neuroplasticity in some brain networks and contexts may represent a dispensable biological function that is triaged away from some networks and towards others in the context of bioenergetic scarcity according to network activity (Fig. 2, Fig. 3). This is not a new concept; canonical Hebbian neuroplasticity (i.e., long term potentiation (LTP)) applied to consistently expressed brain activation and behavioral patterns may lead to the entrenchment of those patterns and reduced behavioral and phenotypic plasticity (i.e., phenotypic stabilization). This process of phenotypic stabilization has been described as "canalization" by Robin Carhart-Harris, in line with Waddington's original use of the term (Carhart-Harris et al., 2022; Waddington, 1942). During energy scarcity, we propose that energy is triaged from the expensive CEN to the less costly SN, which drives psychiatric symptoms when overactive. Changes in brain activation patterns are expensive (Gu et al., 2018). Therefore, if there is less post-stress rebound activation of the CEN (Hermans et al., 2017, 2014), we might expect those patterns to become canalized over time into psychopathological phenotypes.

8. Section 8: The allostatic triage model of psychopathology (ATP model)

Each of the prior sections introduced an established principle, or a novel, but well-supported proposal that we integrated into the ATP model Section: 2) Stress-Induced Energy Scarcity: Stress overwhelms the capacity of the stress response to meet stress-induced increases in demand, driving energy scarcity; 3) Affect-Driven Prioritization: affective states represent predicted metabolic efficiency and regulate neural network activation and behavior based on predicted resource availability; 4) MIPS Bridges Cellular and Systemic Allostasis: the MIPS regulates allostasis, function, and behavior across all levels of biological organization, directly, and indirectly by regulating the allostatic-interoceptive system; 5) EMAL: Bioenergetic Tradeoffs: stress induces energy scarcity, requiring the reallocation of resources (i.e., allostatic triage) from metabolically expensive processes that optimize long-term outcomes (i.e., growth, maintenance, and repair) to processes required to maintain short-term survival; 6) Dysregulated CNS Allostatic Triage: stress and metabolic inefficiency drive allostatic triage, and when chronic, impair the affect-driven prioritization of CNS functional network activation, driving persistent allostatic triage from energy-demanding complex cognition, to less expensive networks optimized for survival, driving psychopathogenesis; 7) Canalization: stress-induced network activation patterns and the resulting psychiatric symptoms become entrenched through canonical mechanisms of neuroplasticity. Chronic changes in CNS functional connectivity induced by pathological levels of allostatic triage are essentially maladaptive changes to the functional setpoints of CNS connectivity, echoing established stress-induced shifts in other physiological setpoints (B. S. McEwen, 1998; McEwen, 2005). By fixing the brain into a specific state that is bioenergetically resistant to change, entrenched activity patterns drive psychopathogenesis through canalization.

Each of these principles, other than our novel concept of affect-driven allostatic triage, is well-established in the literature. In Section 6, we provide evidence supporting differences in the metabolic costs of CNS functional network activation, and for the limited access to metabolic resources in the CNS, setting the stage for resource scarcity during stress. Furthermore, recent work on functional network activation in primary mitochondrial disorders (Bo et al., 2025), supports our proposal of an energetic hierarchy in the brain and the prioritization of essential functions including affective responses, while downregulating complex cognition during stress-induced energy scarcity, and especially in the context of pre-existing metabolic inefficiency. The evidence cited in Section 3 supports the idea that affect regulates systemic allostasis (affect-driven prioritization), but the effects of affect on the allostatic triage of CNS functional connectivity have not been directly investigated. Altogether, if our hypotheses are confirmed (Table 3), our novel concept of the affect-driven prioritization of CNS allostatic triage may bridge the gaps between stress, mitochondrial dysfunction, affective dysregulation, energy scarcity, and transdiagnostic disease pathogenesis.

Importantly, peripheral dysregulation is not necessary for affective dysregulation and allostatic triage, but we propose that it is one pathway that contributes to affective pathology and pathological allostatic triage. Importantly, if psychopathogenesis is first driven by CNS metabolic dysregulation alone, the ATP model predicts that over time, peripheral pathology becomes more likely to develop, driving transdiagnostic disease progression.

8.1. *Specific hypotheses, future directions, and remaining questions*

The ATP model advances our understanding of psychopathogenesis

Table 3
Hypotheses of the allostatic triage model of psychopathology (ATP Model). AL: Allostatic Load, CNS: Central Nervous System, MAL: Mitochondrial Allostatic Load.

H1.	Preexisting peripheral (AL) and/or CNS metabolic inefficiency (MAL), and increases in biological energy demand such as acute inflammation will increase the experience of negative affect during stress
H2.	Affect will closely represent biological metabolic efficiency in healthy organisms, likely within the biological systems and CNS networks implicated in expected future behaviors
H3.	Allostatic Triage: when stress-induced energy demand exceeds the energy production capacity of the CNS, energy will be triaged to the least expensive regions and networks expected to ensure short-term survival, and away from more expensive regions and networks that may produce better long-term outcomes
H4.	Affect-Driven Prioritization: Affective intensity predicts the degree of stress-induced triage of CNS network functional connectivity (e.g., highly negatively valanced states will produce greater triage compared to less negatively valanced states)
H5.	In psychopathology and chronic disease states, affect will become less associated with biological metabolic efficiency (reduced allostatic metabolic inefficiency), but will continue to predict allostatic triage in the CNS
H6.	Triage-Driven Canalization: Persistent allostatic triage from one network or circuit to another will predict the persistent changes in CNS functional connectivity that develop over time in the process of psychopathogenesis (i.e., allostatic triage predicts which networks are canalized)

by integrating the distinct models presented above with our novel concept of affect-driven CNS allostatic triage. The ATP model does not contradict any major model or treatment for psychiatric disease; rather, the ATP model reframes existing evidence and treatments through a bioenergetic lens by integrating established models through our novel concept of affect-driven CNS allostatic triage. Abundant evidence strongly supports each component model, but no existing model spans all levels of biological organization or can fully explain transdiagnostic disease pathogenesis bioenergetically. While the hypotheses in Table 3 are already supported by abundant evidence, we provide testable specific hypotheses of the core ATP model to summarize the investigations necessary to fully confirm its veracity, particularly the core concept of affect-driven allostatic triage.

A deeper investigation of the mechanisms underlying the ATP model will support its further development from a conceptual framework into a genuinely predictive model, and the advancement of the field beyond nonspecific concepts like "mitochondrial dysfunction" and "affective dysregulation", towards a more nuanced understanding of these processes (Monzel et al., 2023). Further, a deeper understanding of the mechanisms underlying the ATP model may yield novel and improved therapeutic approaches, and lead to new ways to foster preventative approaches to resilience that address transdiagnostic disease before it develops. Specifically, the ATP model suggests that treatment approaches focused on 1) normalizing stress-induced physiological dysregulation; 2) improving metabolic efficiency; 3) reducing the extraneous metabolic cost of dysregulated immune function; 4) updating internal models of metabolic efficiency that drive affective states; and 5) increasing energy availability, may be useful primary or adjunct therapies for psychiatric disorders and their co-morbidities. Such approaches may include psychedelic therapies, which may improve mitochondrial metabolic efficiency (Fanibunda et al., 2019; Fissler et al., 2023; Kelley et al., 2022), reduce inflammation (Flanagan and Nichols, 2022, 2018), and normalize stress-induced alterations to the stress response (Galvão et al., 2018; Jones et al., 2023; Lewis et al., 2023), exercise or movement therapies (Björkman and Ekblom, 2022; Goldstein et al., 2018; Neylan et al., 2025), dietary interventions (Fisk et al., 2020; Murphy et al., 2004; Ricci et al., 2020), novel psychotherapeutic or movement therapies focused on improving the veracity of internal models that drive affective states, pharmacological or dietary supplements that increase energy availability (Bakian et al., 2020; Toniolo et al., 2018), or combinations of each of the aforementioned treatment strategies.

Additional unanswered questions related to the specific mechanisms underlying the ATP model and its component models remain, though the veracity of the core ATP model itself does not depend on specific answers to these inquiries. Among the most important questions is one that remains unanswered in EPIC: what exactly is affect a representation of? Does affect only represent systemic biological metabolic efficiency, or is it weighted more heavily towards the CNS, or the CNS regions and networks needed to respond to current or future stressors (Lockhart et al., 2020; Monzel et al., 2024)? Similarly, what signals or physiological states drive affective states? For example, does the allostatic-interoceptive system model details about systemic or CNS metabolic efficiency by monitoring systemic biomarkers of mitochondrial stress, like lactate or mitokines (Clairis et al., 2024), or is the electrophysiological information carried by vagal afferents described in the EPIC model sufficient? Relatedly, is the affect-driven prioritization of allostatic triage general, as illustrated by the affect-dependent thresholds illustrated in Fig. 2 (blue dashed lines), or do specific affective or emotional states drive allostatic triage towards specific attractor states that are predicted to best optimize outcomes?

Altogether, if our hypotheses are supported, partly or in full, the ATP model will improve our understanding of psychopathogenesis and the relationships between psychiatric and medical diseases. By framing psychopathogenesis and transdiagnostic disease as an energetic, dynamic process, the ATP model may align with the lived experience of patients more closely and suggest novel therapeutics (Monroe and Simons, 1991).

CRediT authorship contribution statement

Concept and design: DPK conceived of the ATP model with GS, JF, MP, KV, and AOD. Literature review and data collection: DPK performed this task with SPS, GS, MP, AS, and AOD. Drafting the manuscript: DPK drafted the manuscript with SPS, GS, MP and AOD. Critical revisions: DPK, SPS, ASL, MP, JW, GS, AS, KV, TN, ERB, and AOD. Statistical analysis: N/A. Administrative, technical, or material support: N/A. Supervision: AOD, MP, TN, JW.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106419.

Data availability

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

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