Neuroscience and Biobehavioral Reviews 184 (2026) 106608

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

# A metabolic framework for reward: Redefining dopamine and opioids as physiological agents

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ARTICLE INFO

*Keywords:*
Metabolic Optimization
Reward
Dopamine
Opioids
Homeostasis
Allostasis
Motivated Behavior
Reinforcement
Learning

ABSTRACT

Energy efficiency is a foundational principle of life and evolution. In living organisms, any reduction in metabolic burden frees resources that can be allocated to other vital functions. Optimizing the balance between metabolic expenditure and gain is thus a core computation of the brain, enabling animals to survive and thrive. Yet despite its centrality, this principle has not been systematically integrated into accounts of reward and motivation. Instead, reward is typically modeled as a subjective signal of pleasure or value, leaving unclear its biological function. From a metabolic perspective, however, reward and motivated behavior primarily serve a fundamental biological role: optimizing the body's metabolic economy. Drawing on interdisciplinary evidence, we demonstrate that dopamine and opioids, traditionally regarded as agents of reward and motivation, should be redefined as physiological regulators. Dopamine upregulates, whereas opioids downregulate, physiological processes through cellular and network-level modulation. This countervailing regulation enables rapid coordination across systems and scales, thereby enhancing the metabolic efficiency of homeostasis. The physiological roles of dopamine and opioids reveal a metabolic mechanism underlying behavior and learning: motivation and reinforcement are not directly encoded by neuromodulator release but emerge from its metabolic consequences, with behavior initiated by physiological needs and reinforced through their resolution. Ultimately, the metabolic framework reframes reward not as a subjective experience but as a biologically grounded and quantifiable function, where behavior and learning operate most basically in the service of metabolic optimization.

## 1. Introduction

Energy regulation is a fundamental challenge to biological systems, with every behavior, physiological process, and neural computation carries an energetic cost (Theriault et al., 2023a). Energy efficiency is therefore a central principle of adaptation, shaping morphology, physiology, and behavior across species (Niven and Laughlin, 2008a; Pontzer, 2015a; Sterling and Laughlin, 2015a). To manage the body's energetic budget, the brain does more than react to external rewards or threats, it continuously coordinates physiological and behavioral adaptations to optimize the balance between metabolic expenditure and gain (Barrett, 2017; Waterson and Horvath, 2015). This view shifts reward from a subjective signal of pleasure or value, to a biological computation that improves metabolic efficiency.

Traditionally, dopamine and opioids are viewed as reward-related neurotransmitters, encoding pleasure and facilitating motivated behavior (Becker and Meisel, 2007; Fields and Margolis, 2015; Schultz, 2013; Van Ree et al., 2000). Dopamine has been linked to motivation (Leyton, 2010; Salamone, 1994; Salamone and Correa, 2012) and 'wanting' (Berridge, 2009, 2007, 1996; Davis et al., 2009; Robinson et al., 2005), as well as the anticipation of reward (Barbano and Cador, 2007; Korb et al., 2020). Opioids have been associated with the hedonic sensation of 'liking' (Berridge, 2009; Berridge and Robinson, 2016; Davis et al., 2009; Leknes and Tracey, 2008; Peciña et al., 2006; Peciña and Berridge, 2005).

Yet, growing evidence challenges this view, showing that the functions of dopamine and opioids extend well beyond reward signaling (Askham, 2024; Iversen and Iversen, 2007; Van Steenbergen et al., 2019). Both systems are involved in unpleasant experiences (Inglis and Moghaddam, 2008; Latagliata et al., 2014; Liberzon et al., 2002; Margolis and Karkhanis, 2019), such as stress (Abercrombie et al., 1989; Hulse and Coleman, 1983; Nabeshima et al., 1985; Thierry et al., 1976) and pain (Alderete et al., 2025; Altier and Stewart, 1999; Navratilova et al., 2015b; Taylor et al., 2016), as well as salient (Dum and Herz, 1987; Ungless, 2004) or unexpected events (Bali et al., 2015; Valdés-Baizabal et al., 2020). Moreover, dopamine plays a role in motor control

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https://doi.org/10.1016/j.neubiorev.2026.106608
Received 4 October 2025; Received in revised form 8 February 2026; Accepted 12 February 2026
Available online 13 February 2026

(Joshua et al., 2009; Volkow et al., 2001), cognition (Nieoullon, 2002), and sleep-wake cycles (Monti and Monti, 2007), while opioids contribute to pain modulation (Cahill et al., 2003; Fields, 2000). Taken together, these observations indicate that dopamine and opioids subserve a broader function that cannot be reduced to pleasure or reward alone.

Here, we propose a metabolic framework of reward that unifies these diverse roles and offers a coherent explanation for seemingly contradictory findings. In this account, dopamine and opioids are not agents of reward but neuromodulators with complementary and opposing effects on regulating bodily systems: dopamine upregulates physiological processes, while opioids downregulate them. This reciprocal mechanism allows the brain to balance and optimize energetic demands across multiple systems and scales, coordinating physiological responses with behavioral strategies. By situating reward within a broader metabolic account, this framework recasts the diverse roles of dopamine and opioids across physiology, affect, and behavior as expressions of a unifying metabolic mechanism.

### 1.1. A novel metabolic mechanism of motivated behavior

The brain is constantly working to regulate physiology throughout the body (Theriault et al., 2025; Zhang et al., 2025a, 2025b). Physiological states fluctuate dynamically as the body adapts to meet internal demands and external challenges, such as spikes in plasma glucose after feeding or increases in oxygen demands under stress. While these perturbations are common and beneficial, they are metabolically costly (Ingraham et al., 2019; McEWEN, 1998; McEwen and Wingfield, 2003). To minimize these energetic costs, negative feedback mechanisms trigger physiological and behavioral responses that restore balance and conserve energy (Saper and Lowell, 2014). For example, when glucose levels rise, the secretion of insulin serves to clear glucose from the plasma (Czech, 2017; Rahman et al., 2021). When cortisol levels rise, a negative feedback mechanism inhibits the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus (Calogero et al., 1988) and adrenocorticotropic hormone (ACTH) from the pituitary (Roelfsema et al., 2016). This downregulates the hypothalamic-pituitary-adrenal (HPA) axis, decreasing the mobilization of oxygen and glucose to tissues (Argyropoulos, 2002; Vassilakopoulos et al., 1999), thus limiting unnecessary expenditure. Together, these feedback mechanisms illustrate how the brain controls the energetic burden of dynamic physiological demands. Optimization of energetic efficiency through centrally coordinated control requires a mechanism that can both orchestrate diverse peripheral demands and translate their energetic consequences into reinforcement guiding future action selection. Dopamine and opioids are well positioned to serve this role, thereby linking autonomic control with motivation and reward.

Dopamine and opioids are proposed to function as domain-general metabolic regulators within this brain-body regulatory axis, with dopamine upregulating physiological responses and opioids serving as deactivators, suppressing excessive activity once the disturbance is resolved. This is a closed regulatory loop: efferent signals modulate peripheral physiology, and the resulting peripheral consequences are conveyed back to the brain via interoceptive pathways that update central representations of physiological demand and energetic cost (Barrett and Simmons, 2015a; Theriault et al., 2025; Zhang et al., 2025a, 2025b). In this framework, motivated behavior arises from these energetic consequences. Dopamine-driven physiological upregulation elicit a metabolic effort. We define the increase in energetic burden of a physiological response as *Metabolic Effort*, which may be subjectively experienced as demand that drive *motivation* to resolve it. Opioid-driven downregulation reduces metabolic effort and returns physiological activity toward baseline. We define the reduction in energetic burden of physiological downregulation as *Metabolic Relief*, which can be experienced subjectively as hedonia (Fig. 1). Thus, it is not dopamine or opioid neurotransmission per se that determines motivation and reward; rather, energetic consequences generated systemically in the periphery are weighted centrally by dopamine and opioids.

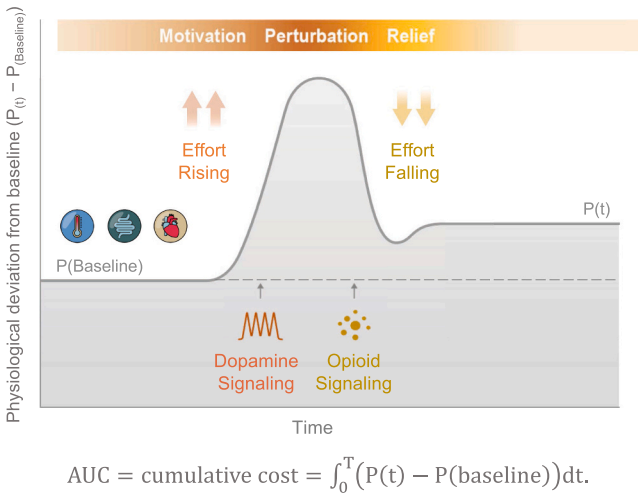



**Fig. 1.** Dopamine and opioids act as physiological agents: dopamine upregulates and opioids downregulate physiology, together coordinating energetic efficiency. The energetic costs of a physiological response accumulate over time as a function of its amplitude and duration (Bobba-Alves et al., 2022; Picard et al., 2014; Pontzer, 2015b). These costs can be calculated as the incremental area under the curve (AUC) by summing the disturbance values across time. A lower AUC reflects reduced metabolic effort (Ingraham et al., 2019; McEWEN, 1998; McEwen and Wingfield, 2003; Peters et al., 2020). Dopamine signaling upregulates physiological activity away from baseline, thereby increasing the cumulative metabolic effort and energy expenditure. Subjectively, the rising metabolic effort is experienced as motivation to act. Opioid signaling downregulates physiological activity toward baseline, thereby reducing the cumulative metabolic effort and ongoing energy expenditure. Subjectively, the reduction in metabolic effort is experienced as relief. Icons illustrate example physiological domains of P(t): thermoregulation, digestion, sympathetic output; more generally, in this framework physiological upregulation of any system in the body, including in the brain, is proposed to increase motivation insofar as it increases metabolic effort.

This model positions dopamine and opioids as complementary regulators of physiology whose metabolic consequences give rise to motivation, reward, and adaptive behavior, providing the basis for the framework we develop below.

To establish the metabolic framework of reward, we review evidence from three domains. First, we integrate multidisciplinary findings showing that dopamine and opioids act as physiological regulators, with roles in core processes such as digestion, respiration, and immune function, highlighting dopamine's activating and opioids' deactivating functions. Next, we outline how neuropathology of dopamine and opioid systems produces systemic metabolic consequences, further underscoring their role in energy balance. Finally, we revisit reinforcement learning, a domain traditionally framed around maximizing reward value, and reinterpret it as metabolic optimization, where computations of energy conservation provide the basis for learning adaptations in both motivated behavior and physiological regulation. Taken together, this perspective reframes reward not as a subjective experience but as a biologically grounded and quantifiable function, where benefit is defined in its most fundamental form- energetic gain. The metabolic framework of reward offers an evolutionarily relevant account of adaptive behavior, linking neuroscience, physiology, and metabolism by showing how metabolic regulation through dopamine and opioids shapes affect, cognition, and action.

## 2. Dopamine and opioids regulate physiology

Converging evidence from diverse physiological domains reveals

that dopamine and opioids are integral regulators of multiple bodily systems. Specifically, dopamine consistently upregulates, whereas opioids downregulate physiological activity across systems (Table 1).

### 2.1. Dopamine upregulates physiology, with downstream effects on affect and behavior

Dopamine exerts broad up-regulatory effects on neural excitability and plasticity. At the cellular level, excitatory dopaminergic function is mediated through D1-like receptors (D1 and D5). D1-like receptors are G-protein-coupled receptors (GPCRs) stimulating adenylate cyclase, thereby increasing the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) (Traficante et al., 1976; Vallone et al., 2000). Dopamine binding to these receptors promotes neural excitation by potentiating glutamatergic signaling by enhancing α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor efficacy and membrane expression, facilitating depolarization through increased inflow of Na+ and Ca2 + (Greengard et al., 1999; Yang, 2000). Beyond these short-term effects, D1-like receptor signaling facilitates gene expression and plasticity by engaging intracellular phosphorylation cascades (Greengard et al., 1999; Jones-Tabah et al., 2022; Nagai et al., 2007). Unlike D1-like receptors, dopamine D2-like receptors (D2, D3, and D4) inhibit adenylyl cyclase, reducing cAMP levels (Vallone et al., 2000), and leading to neural hyperpolarization through modulation of K+ and Ca2 + ion channels (Congar et al., 2002; Keja et al., 1992; Pillai et al., 1998). This precludes a simple characterization of dopamine as uniformly excitatory. However, D2-like inhibitory signaling primarily serves self-regulation of dopaminergic signaling rather than systemic downregulation. Specifically, in dopaminergic terminals, presynaptic D2 autoreceptors implement an inhibitory cascade that suppresses further dopamine release, thereby maintaining dopaminergic signals within an effective dynamic range (Ford, 2014; Missale et al., 1998). At the circuit level, D2 receptors, enriched on the indirect pathway of the basal ganglia, limit striatal output to the motor cortex, thereby constraining excessive activation, sharpening selection among competing action representations and supporting robust control of motor output (Calabresi et al., 2014; Keeler et al., 2014). Thus, the D2-like cellular inhibition potentially serves as a self-regulatory arm of the dopamine system, stabilizing dopaminergic function and fine-tuning of neural circuit activity and behavioral output. Moreover, although D2-like receptors engage inhibitory intracellular cascades, their signaling can nevertheless contribute to systemic physiological upregulation, including HPA activation (Belda and Armario, 2009), inducing hypothermia and yawning (Collins et al., 2007), and orexin activation (Harada et al., 2024). Altogether, dopamine receptor–coupled intracellular cascades collectively constitute a broader physiological architecture that supports systemic upregulation of physiology.

At the circuit level, dopamine projects excitatory efferents along the mesolimbic and mesocortical pathways (Deutch et al., 1987; Robbins, 1997), and systemically through the activation of key visceromotor nuclei located in the brainstem, hypothalamus, and forebrain. These nuclei, which are responsible for elevating arousal throughout the body and brain (Oishi and Lazarus, 2017; Qu et al., 2008), are activated by monoamines, including dopamine (Eban-Rothschild et al., 2016; McCann et al., 1993; Smith, 1976), thereby initiating a broad range of physiological responses. Specifically, dopamine projections from the ventral tegmental area (VTA) stimulate acetylcholine release from the pons and basal forebrain (Moore et al., 1999), serotonin release from the raphe nuclei (Digiovanni et al., 2008), and orexin release from the lateral hypothalamus (Bubser et al., 2005; Harada et al., 2024). In the periphery, these nuclei upregulate the sympathetic nervous system (Haas et al., 2008; Herat et al., 2019; Sakurai, 2007; Williams et al., 2001) and the HPA axis (Cecchi et al., 2002; Kjaer et al., 1994; Kuru et al., 2000; Morilak et al., 2005), and increase glucose and oxygen availability in the circulation (Cho et al., 2017; Jones, 2020; Motelow

**Table 1**
A cross-disciplinary review demonstrates that dopamine upregulates and opioids downregulate diverse physiological processes.

| Process | Dopamine elicits perturbations | Opioids level perturbations |
|---|---|---|
| Energy expenditure and digestion | Dopamine enhances gastrointestinal motility (Zizzo et al., 2010) and coordinates intestinal peristalsis (Hong-Nian Liu et al., 2018; Zheng et al., 2021).<br>Dopamine raises basal metabolic rate via sympathetic activation ( Folgueira et al., 2019; Smit et al., 1995), enhancing calorie burning and nutrient use.<br>Suppressing dopamine inhibits feeding (Hommel et al., 2006; Labouèbe et al., 2013; Mebel et al., 2012; Palmiter, 2008).<br>Ghrelin, a hunger hormone, enhances dopamine signaling in the nucleus accumbens (Cone et al., 2015).<br>Dopaminergic neurons encode motivation to eat (Hauber and Fuchs, 2000; Liu et al., 2017; Volkow et al., 2017) and feeding (Chen et al., 2014). | Opioids decrease the frequency and strength of peristaltic contractions in the intestines, slowing gastrointestinal transit ( Burks et al., 1988; Galligan and Burks, 1982; Shahbazian et al., 2002).<br>Feeding induces endogenous opioids release throughout the brain (Tuulari et al., 2017).<br>Injection of the opioid agonist morphine into the periaqueductal gray (PAG) inhibits feeding (Jenck et al., 1987). |
| Respiration | Brainstem dopamine enhances respiratory rhythm (Lalley, 2005; Lalley and Mifflin, 2012).<br>Dopamine increases respiratory rate and depth through sympathetic activation (Hedner et al., 1982; Lalley, 2009, 2008).<br>A decrease in oxygen levels triggers dopamine release in the carotid body (Welsh et al., 1978). | Opioids act on brainstem neurons to suppress respiration, preventing over-excitation (Hajiha et al., 2009; Olsen et al., 2021; Phillips et al., 2012).<br>Opioid agonists suppress the cough reflex (Schumacher et al., 2015).<br>Opioids reduce sensitivity to rising $CO_2$ levels (Takeda et al., 2001; White and Irvine, 1999). |
| Fluid balance | Dopamine enhances blood flow to the kidneys, facilitating fluid filtration and excretion ( Carcoana and Hines, 1996; Murphy et al., 1987).<br>Dopamine promotes diuresis in the renal tubules of the kidneys, increasing sodium and water excretion (Marwaha and Lokhandwala, 2003; Siragy et al., 1989).<br>Dopamine promotes fluid excretion through renin (Asico et al., 1998), aldosterone ( Gordon et al., 1983), and vasopressin (Li et al., 1998; Muto et al., 1985).<br>Dopamine initiates drinking ( Dourish, 1983; Syed et al., 2016) and increases water intake, whereas blocking its signaling inhibits drinking (Fitzsimons and Setler, 1975). | Opioids reduce kidney filtration and fluid excretion via renal vasoconstriction ( Burchardi and Kaczmarczyk, 1994).<br>Opioids reduce urine output (Bankir, 2001; Nielsen et al., 1995) via vasopressin ( Brown et al., 2000; Taylor et al., 1996).<br>Opioid agonists inhibit water intake (De Caro et al., 1979; Spencer et al., 1986), leading to dehydration and thirst ( Morita et al., 2001). |
| Immune function | Dopamine activates T cells ( Levite et al., 2001), B cells ( McKenna et al., 2002), Natural Killer (NK) cells (McKenna et al., 2002; Zhao et al., 2013), dendritic cells (Prado et al., 2012), and macrophages ( Gaskill et al., 2012).<br>Dopamine up-regulates cytokine secretion (including TNF-alpha, IL-6, IL-10) from T-cells (Levite, 2016; Ritchie et al., 1996). | Opioids directly suppress cell-mediated immunity, affecting T cells, B cells, macrophages, and NK cells ( Boland et al., 2014; Rouveix, 1992), which express opioid receptors (Chuang et al., 1995; Sharp and Eisenstein, 1996).<br>Opioids promote apoptosis in immune cells (Singhal et al., 2002). |

(*continued on next page*)

**Table 1** (*continued*)

| Process | Dopamine elicits perturbations | Opioids level perturbations |
|---|---|---|
| | Dopamine receptors D1 and D5 are expressed on immune cells ( McKenna et al., 2002; Nakano et al., 2008), upregulating immune responses and cytokine production (Osorio-Barrios et al., 2018; Zhao et al., 2013). Dopamine leads to norepinephrine release ( Harrison et al., 1963), which increases neutrophil and macrophage recruitment to wounds and infection (Gosain et al., 2006). | Opioids suppress antibody production (Dinari et al., 1989; Weber et al., 1987). |
| Body temperature | Dopamine activate heat loss by exciting warm-sensitive neurons (Lee et al., 1985; Scott and Boulant, 1984). Dopamine induces vasodilation ( Kullmann et al., 1983; Reitsamer et al., 2004). Dopamine agonists induce temperature shifts, including hypothermia (Collins et al., 2007; Varty and Higgins, 1998) and hyperthermia (Nagashima et al., 1992). By increasing sympathetic outflow, dopamine promotes thermogenesis (Rothwell et al., 1982). | μ-opioid receptors in the preoptic area (POA) inhibit heat-loss mechanisms, such as sweating and vasodilation (Gordon et al., 1984; Yakimova et al., 1996). Opioids suppress vasodilation or vasoconstriction thermoregulatory responses in the hypothalamus (Ikeda et al., 1997; Kurz et al., 1997). μ and δ opioid receptor antagonists delay the upregulation of body temperature after hypothermia (Da Silveira Scarpellini et al., 2009). Opioids agonists inhibits shivering (Alfonsi et al., 1998; Kurz et al., 1993). |
| Arousal | Dopamine upregulates arousal ( Andretic et al., 2005; Oishi and Lazarus, 2017; Qu et al., 2008) and down-regulates sleep (Cho et al., 2017; Eban-Rothschild et al., 2016; N. E. Taylor et al., 2016). Dopamine neurons in the ventral tegmental area (VTA) activate the HPA axis, upregulate corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and eventually cortisol release from the adrenal cortex (Di et al., 2020), preparing the body for action (Alexander et al., 2011; Belda and Armario, 2009). | Opioids suppress the HPA axis (Brunton et al., 2005; Zis, 1985). Activation of μ-opioid receptors in the parasympathetic nucleus ambiguus leads to bradycardia (slow heart rate) (Irnaten et al., 2003). Opioidic drugs lead to excessive and improved sleep (Caldwell et al., 2002; Tang et al., 2019). Opioids have anxiolytic and calming effects (Colasanti et al., 2011; Kabli et al., 2014; Millan and Duka, 1981; Saitoh et al., 2004; Varty et al., 2008). Opioids suppress brain function (Bagley and Ingram, 2020; Li and Van Den Pol, 2008), and neurotransmitter release (Jaferi and Pickel, 2009; Schroeder et al., 1991), including inhibition of Locus Coeruleus norepinephrine signaling ( Kreibich et al., 2008; Travagli et al., 1995). |
| Sex | Dopamine activates sexual motivation and behavior (Meisel et al., 1993; Pfaus, 2009; Wersinger and Rissman, 2000), specifically copulation (Agmo and Fernandez, 1989; Garcia et al., 2010; Hull et al., 2004; Melis et al., 2003; Pfaus et al., 1990) and penile erection ( Sanna et al., 2011; Succu et al., 2007). Dopamine antagonists impair sex behaviors (Baum and Starr, 1980; Pehek et al., 1988). | Opioid release is stimulated by sexual behavior (Paredes, 2014; Szechtman et al., 1981). Opioid agonists suppress sexual behavior ( Garduño-Gutiérrez et al., 2013; Pfaus and Gorzalka, 1987; Van Furth et al., 1994). In rodents, morphine (a μ-opioid receptor agonist) suppresses erection ( Gomez-Marrero et al., 1988) and naloxone (a μ-opioid receptor antagonist) increases mounting and ejaculation (Fuentes et al., 2005). |

and Blumenfeld, 2014; Smythe et al., 1984; Solis Jr. et al., 2017), ensuring that the body responds effectively to anticipated demands, such as stress or physical exertion.

Through the mesolimbic pathway, dopamine activates additional visceromotor regions, such as the central amygdala, hypothalamus, and nucleus accumbens, and brainstem, further upregulating physiological responses, and modulates motor function (Mann and Claassen, 2024; Salamone et al., 2015; Salamone and Correa, 2012). Through the mesocortical pathways, dopamine upregulates neural excitability (Jones, 2020), thereby modulating attention (Anderson et al., 2016; Franken et al., 2005; Nieoullon, 2002), perception (Garcia-Rill et al., 2016; Waschke et al., 2019), and cognitive performance (Seamans and Yang, 2004). Thus, widespread dopaminergic pathways can prepare the organism for action physiologically, behaviorally, and cognitively.

Dopaminergic projections from the VTA have been widely implicated in reward and motivation, including enhanced sensitivity to salient stimuli, behavioral reinforcement, and learning (Arias-Carrión et al., 2010; Ferguson et al., 2020; Heymann et al., 2020). These include the amygdala (Hasue and Shammah-Lagnado, 2002), nucleus accumbens (Bergamini et al., 2016; Skibicka et al., 2013), hippocampus (Broussard et al., 2016; Murty and Adcock, 2014; Tsetsenis et al., 2023), and prefrontal cortex (Lewis, 2000; Noble et al., 2024). However, this circuitry, and its involvement in motivation and reward is proposed to be mediated, at least in part, by dopamine's physiological function: dopaminergic activity can upregulate systemic autonomic and endocrine responses via these VTA projections, thereby generating motivational drive and shaping behavior and learning.

Notably, canonical targets of VTA dopamine (i.e., the amygdala, nucleus accumbens, brainstem, hypothalamus, and prefrontal cortex), are core nodes of an allostatic–interoceptive control system (Kleckner et al., 2017; Zhang et al., 2025a, 2025b), where they are continuously monitoring the internal milieu (i.e., interoception (Barrett and Simmons, 2015a; Berntson and Khalsa, 2021)) and generating visceromotor predictions that modulate the autonomic and endocrine pathways (i.e., visceromotor control) (Barrett and Simmons, 2015a; Kleckner et al., 2017; Theriault et al., 2025; Zhang et al., 2025a, 2025b). *Allostasis* is the regulatory process where the brain improves its ability to manage metabolic efficiency by anticipating physiological demands and implementing useful physiological and behavioral adaptations in advance (Barrett and Simmons, 2015a; Schulkin and Sterling, 2019; Sterling, 2012). Research establishes that neural control of allostasis is not localized to a dedicated set of nuclei; rather, allostasis constitutes a primary organizing function of the brain, distributed across multiple interacting neural systems (Theriault et al., 2025). Recent 7 Tesla functional magnetic resonance imaging work characterizes this system as a distributed architecture. Cortical visceromotor regions, including the anterior cingulate cortex and ventral anterior insula, integrate prior knowledge to generate visceromotor predictions that are conveyed to subcortical and brainstem nodes implementing autonomic and endocrine regulation, including the hypothalamus, amygdala, hippocampus, ventral striatum, and brainstem nuclei such as the periaqueductal gray, parabrachial nucleus and nucleus tractus solitarius (Zhang et al., 2025a,

2025b). Monoamine nuclei, including the VTA, are integral to the allostasis–interoception network, showing strong connectivity with its cortical and subcortical regions (Theriault et al., 2025; Zhang et al., 2025a, 2025b).

This suggests substantial overlap between classic reward circuits and visceromotor control circuits, with reward-related effects potentially operating through modulation of visceromotor processes. Indeed, dopaminergic pathways have been shown to modulate interoceptive processing by responding to metabolic signals conveyed to the VTA via hypothalamic inputs (Labouèbe et al., 2013; Wallace and Fordahl, 2022), which in turn regulate VTA function (Fadel and Deutch, 2002). In parallel, dopaminergic projections also modulate visceromotor output, via the amygdala, nucleus accumbens, hippocampus, and cortex (Barbas et al., 2003; Barrett and Simmons, 2015b; Hoover and Vertes, 2011). Notably, this circuitry regulates a wide range of autonomic and endocrine processes, including those not traditionally thought to be reward-related like immune function (Lubianiker et al., 2026). Taken together, this evidence indicates that the mesocorticolimbic reward circuitry participates directly in the implementation of allostasis regulation. Within this framework, reward is not an additional function layered onto physiological control, but is computed from metabolic considerations, such that actions that improve metabolic efficiency are preferentially reinforced and learned.

The metabolic rationale that guides motivation and reward, also extends to affect, and particularly to valence, challenging the role of dopamine in encoding positive valence. A longstanding contradiction in the literature is that dopamine can enhance both positive and negative affect (Rutledge et al., 2015; Sharot et al., 2009), driving both approach toward appetitive stimuli such as food (Kiyatkin and Gratton, 1994; Phillips et al., 2003; Salamone et al., 1994; Thanarajah et al., 2019), and aversion from negative stimuli such as threat or distress (Cabib and Puglisi-Allegra, 2012, 1996; Keller et al., 1983; Richard and Berridge, 2011). This bidirectional pattern contests the view that dopamine encodes hedonic valence. Instead, these behaviors converge in serving a common metabolic function: restoring homeostasis in response to a physiological need. Supporting this, dopamine transmission increases during states of deprivation (e.g., hunger, thirst) (Aitken et al., 2016; Hsu et al., 2020), and blocking dopamine prevents animals from seeking food or water even when physiologically deprived (Keller et al., 1983). Without dopamine, the organism fails to detect and respond to internal metabolic disturbances. Thus, dopamine's primary function may be to signal metabolic effort, while affect and behavior arise as adaptive strategies to minimize it (Shenhav, 2024).

### 2.2. *Opioids downregulate physiology, with downstream effects on affect and behavior*

Complementing dopamine, opioids are proposed to serve a regulatory, calming function. Once perturbations are addressed, opioids are released to downregulate the physiological, affective, and behavioral responses that were initiated to address them. This process limits unnecessary metabolic costs and conserves energy.

The endogenous opioid system is a widely distributed neuromodulatory network composed of multiple families of opioid peptides synthesized from three principal precursor molecules: proopiomelanocortin (POMC), proenkephalin, and prodynorphin (Höllt, 1983; Le Merrer et al., 2009). Enkephalins and dynorphins are synthesized broadly across visceromotor regions, with prominent expression in the striatum and nucleus accumbens, amygdala, hippocampus, hypothalamus, periaqueductal gray, spinal cord, and brainstem nuclei. POMC-derived peptides, including β-endorphin, are synthesized in more restricted neuronal populations, notably within visceromotor nuclei of the arcuate nucleus of the hypothalamus, the nucleus tractus solitarius, and the pituitary (Höllt, 1983; Le Merrer et al., 2009). Opioid peptides are released both locally and via long-range projections to limbic, hypothalamic, and brainstem targets, giving rise to overlapping peptide systems that span motivational, affective, and autonomic domains (Höllt, 1983; Le Merrer et al., 2009).

There are three main types of opioid receptors in the central nervous system: μ, δ, and κ (Höllt, 1983; Le Merrer et al., 2009; Mansour et al., 1987). When opioids bind to all three receptor types, they activate inhibitory G-proteins that inhibit adenylate cyclase, reducing the conversion of ATP to the second messenger cAMP. This inhibition restricts downstream second-messenger processes (Heijna et al., 1992a; Obermeier et al., 1996) linked to metabolism and neural activation. The suppression of cAMP alone reduces metabolic activity, as cAMP activates protein kinase A (PKA), which governs key metabolic pathways such as glycogenolysis (glycogen breakdown) and lipolysis (fat metabolism) (Hurley et al., 2006). Moreover, opioid binding opens potassium channels and closes calcium channels, hyperpolarizing neurons, reducing neurotransmitter release (Alreja and Aghajanian, 1993; Heijna et al., 1992b; Moises et al., 1994; Torrecilla et al., 2002), and cognitively impairing attention and focus (Arnsten et al., 1983, 1981; Jacobson et al., 2018). Opioid receptors μ, δ, and κ are broadly expressed across cortical, subcortical, and brainstem regions including the prefrontal cortex, amygdala, hippocampus, striatum, hypothalamus, periaqueductal gray, nucleus accumbens, and bed nucleus of the stria terminalis, indicating that opioidergic signaling is anatomically positioned to regulate peripheral physiology. Opioid receptors are also expressed by peripheral neurons, as well as by neuroendocrine, immune, and ectodermal cells (Edinoff et al., 2021). This widespread anatomical distribution positions the opioid system as a distributed architecture capable of modulating multiple nodes of the allostasis–interoception system, underscoring its role in physiology.

Like opioid receptors, dopamine D2-like receptors also inhibit adenylyl cyclase, reducing cAMP levels (Vallone et al., 2000), and leading to neural hyperpolarization (Congar et al., 2002; Keja et al., 1992; Pillai et al., 1998). Yet, shared intracellular coupling does not facilitate shared systemic function. Whereas D2-like signaling is implicated in systemic physiological upregulation (Belda and Armario, 2009; Harada et al., 2024), opioid receptor signaling is associated with terminating or dampening physiological responses, including suppressing the HPA axis (Brunton et al., 2005; Zis, 1985), cell-mediated immunity (Boland et al., 2014; Rouveix, 1992), respiration (Hajiha et al., 2009; Olsen et al., 2021; Phillips et al., 2012), digestion (Burks et al., 1988; Galligan and Burks, 1982; Shahbazian et al., 2002), and urine output (Bankir, 2001; Nielsen et al., 1995).

By suppressing physiological over-excitation, opioids can also dampen affective states, calming affective responses to both positive and negative stimuli. The most prominent example of this is the widely accepted role of opioids in modulating pain. Opioids downregulate the subjective experience of pain (Corder et al., 2018; Inturrisi, 2002; Leknes and Tracey, 2008) via both peripheral and central mechanisms. Peripherally, by activating $G_i$-coupled receptors, opioids counteract the excitability of nociceptors, sensory neurons that are activated by damaging stimuli, and produce a peripherally mediated analgesia (Julius and Basbaum, 2001; Machelska, 2007). In the central nervous system, mu receptor activation in the midbrain mediates opioid-induced analgesia by stimulating descending inhibitory pathways that act on the periaqueductal gray and nucleus reticularis paragigantocellularis, ultimately activating descending inhibitory neurons (Basbaum and Fields, 1984, 1978; Fields, 2004; Pathan and Williams, 2012). The downregulation of pain, on both peripheral and central levels, positions opioids as central agents in analgesia and pain management (Bagley and Ingram, 2020; Fields, 2007; Kalso et al., 2004; Leknes and Tracey, 2008; Stein, 2018; Zubieta et al., 2001). In addition to pain, opioids also downregulate anger (Burns et al., 2014), fear (Nummenmaa and Tuominen, 2018), and anxiety (Colasanti et al., 2011; Tenore, 2008). The anxiolytic effects of GABAergic drugs, such as benzodiazepines, are partially mediated by the activation of opioid receptors μ, κ, and δ (Ågmo and Belzung, 1998; Primeaux et al., 2006). Opioids also modulate positive affect. For example, opioids are released in the thalamus,

caudate, and anterior insula following emotional experiences like laughter (Manninen et al., 2017; Sun et al., 2022), downregulating the intensity of positive affect (Martikainen et al., 2013) and returning the emotional responses to baseline. Moreover, opioid drugs downregulate a sense of pleasure during typically enjoyable activities, such as sex (Argiolas and Melis, 2013; Leyton and Stewart, 1992).

Behaviorally, opioids were shown to downregulate behavior, including drinking (De Caro et al., 1979; Summy-Long et al., 1983, 1981), feeding (Jenck et al., 1987), drug intake (Chen et al., 2013; Margolis et al., 2008), and sexual activity (Pfaus, 2009; Pfaus and Gorzalka, 1987; Vanfurth et al., 1995). Furthermore, κ-opioid receptor agonists suppress exploratory behaviors such as rearing, sniffing, and hole-poking behaviors in rats, while its antagonists in the ventral striatum counter these effects (Gray et al., 2001). This downregulation occurs after perturbations are resolved, conserving energy and avoiding unnecessary expenditure. For example, physical activity triggers the release of endogenous opioids (Harber and Sutton, 1984), known as "runner's high" (Boecker et al., 2008), which helps reduce the heightened arousal from exercise back to baseline (Saanijoki et al., 2018). While traditionally seen as encoding the pleasure associated with external stimuli (Barbano and Cador, 2007; Boecker et al., 2008; Buchel et al., 2018; Colasanti et al., 2012), opioids may instead function to reduce metabolic costs by downregulating physiology and behavior, with hedonic experiences emerging as a byproduct of metabolic relief.

Taken together, this body of evidence indicates that dopaminergic and opioidergic pathways extensively modulate visceromotor regions within a closed brain–body control loop (Fig. 2). Descending signals adjust peripheral physiology, and the resulting bodily consequences return to the brain via interoceptive pathways to update central estimates of physiological demand and energetic cost, a process termed *Metaboception* (Liu et al., 2025; Picard and Murugan, 2025). The brain occupies a dual role in this energy economics: it is both the central allocator that coordinates organism-wide energy regulation, and a metabolically demanding organ that competes for, and is often prioritized in energy allocation (Curtelin et al., 2018; Jensen et al., 2014; Koepsell, 2020; McBryde et al., 2017; Morgello et al., 1995). Motivation and reward are proposed to emerge from centrally computing the energetic costs of physiological processes, such that adjustments that require increased energy generate motivational drive, whereas adjustments that reduce effort are reinforcing. Such an architecture is adaptive because it enables system-level normalization and prioritization of competing energetic demands across physiological systems (including neural physiology), as well as behavioral (Gao and Horvath, 2008; Gastelum et al., 2021; Schneider et al., 2017) and cognitive (Bo et al., 2025; Mehrhof et al., 2025) demands. This principled mechanism offers a unified and parsimonious explanation for dopamine's and opioids' involvement across multiple levels of their reported functions, spanning physiology, affect, and behavior.

## 3. Disruptions in central dopamine and opioid systems drive systemic metabolic consequences

Disruptions within central dopamine and opioid systems reliably lead to impaired physiological regulation, underscoring their fundamental physiological functions. For example, according to the dopaminergic hypothesis of schizophrenia, positive symptoms involve dopamine hyperactivity in the mesolimbic pathway (Abi-Dargham et al., 2000; Howes and Kapur, 2009). In line with the metabolic framework, schizophrenia patients have overactive physiological responses, including immune hyperregulation (Maes et al., 2019) that can lead to autoimmunity (Eaton et al., 2006), sympathetic hyperactivity (Kuwahara et al., 2009; Montaquila et al., 2015), and increased secretion of stress hormones (Walker et al., 2008). In contrast, Parkinson's disease, characterized by dopamine deficiency (Damier et al., 1999), is associated with reduced physiological activity, including hypotension (Goldstein, 2006), chronic fatigue (Beiske et al., 2010), and reduced metabolic and gastric function (Anandhan et al., 2017; Eberling et al., 1994; Marrinan et al., 2014). Degeneration of dopamine neurons relates to symptoms like reduced appetite (Siervo et al., 2024), lower body weight (Bachmann and Trenkwalder, 2006; Kashihara, 2006), bradykinesia, and impaired motivation (Bergman and Deuschl, 2002; Den Brok et al., 2015; Dujardin et al., 2007; Moustafa et al., 2016). Depression, also linked with impaired dopamine (Kapur and John Mann, 1992; Moraga-Amaro et al., 2014), is associated with suppressed

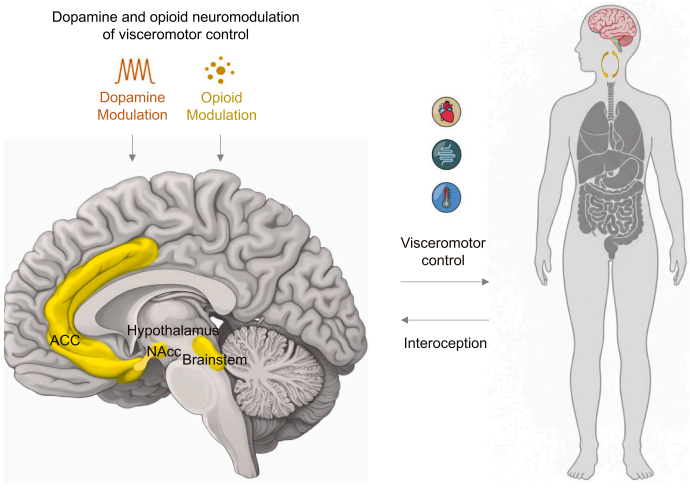



**Fig. 2.** Peripheral physiology is regulated by the brain through distributed visceromotor circuitry, which comprises the canonical central targets of dopamine and opioid signaling. Systemic physiology is not governed by a small set of dedicated nuclei, but by a distributed allostatic–interoceptive system spanning cortical, subcortical, brainstem, and peripheral nodes. This system includes cortical visceromotor regions in the anterior cingulate cortex (ACC) and ventral anterior insula, as well as the hypothalamus, amygdala, ventral striatum, and brainstem nuclei such as the periaqueductal gray, parabrachial nucleus and nucleus tractus solitarius (Barrett and Simmons, 2015b; Kleckner et al., 2017; Theriault et al., 2025; Zhang et al., 2025a, 2025b). These regions continuously monitor the internal milieu via interoceptive representations and modulation of autonomic, endocrine, and metabolic pathways (Zhang et al., 2025a, 2025b). These visceromotor regions overlap with the canonical targets of the reward circuitry and are densely modulated by dopaminergic and opioidergic signaling. Based on this architecture, reward is proposed to be computed from the metabolic consequences of peripheral adjustments, with actions that improve metabolic efficiency preferentially reinforced. Icons depict representative examples of brain-controlled visceromotor targets, including thermoregulation, digestion, and sympathetic output. Visceromotor nodes visible in the midsagittal view are highlighted in yellow.

immunity (Natelson, 1999), slow metabolism (Lamers et al., 2018), flat affect (Loas et al., 1994), deficient motivation (Grahek et al., 2019), and avoidant behavior (Ottenbreit and Dobson, 2004). Addiction further illustrates how dopamine and opioid dysregulation disrupts physiological regulation (Ersche et al., 2017; Evans and Cahill, 2016; Zhang et al., 2025a, 2025b), with substances like cocaine and nicotine, which stimulate dopamine release (Clarke, 1991; Kuhar et al., 1991; Venton et al., 2006), leading to heightened metabolic rates and lower body weight (Billing and Ersche, 2015; Calarco et al., 2017; Cincotta et al., 1997; Perkins et al., 1989). Opioid users experience physiological suppression, including constipation (Ducrotté et al., 2017), respiratory depression (Dahan et al., 2018), fatigue (Lamprecht et al., 2018), and reduced sexual drive (Bawor et al., 2015).

The connection between central dopamine and opioid systems and peripheral physiology is evident not only in psychiatric or neurological disorders but also in metabolic disorders. For example, obesity involves altered expression of the mu-opioid receptor (Karlsson et al., 2015) and dopamine D2 receptor (Wang et al., 2001). Diabetes is linked to D2 impairments (Lopez Vicchi et al., 2016; Tavares et al., 2021), affecting insulin secretion and glucose tolerance (García-Tornadu et al., 2010). Treatments targeting these pathways, such as dopamine agonists and κ-opioid receptor stimulation, show promise in improving metabolic conditions like hyperlipidemia (Liang et al., 1998; Tian et al., 2016).

Together, these findings reveal a bidirectional link: disruptions in central dopamine and opioid systems drive systemic physiological dysfunction, while metabolic pathology, in turn, destabilizes these neuromodulatory systems. This reciprocal relationship underscores the physiological roles of dopamine and opioids and supports the metabolic framework.

## 4. Dopamine and opioids guide learning through metabolic optimization

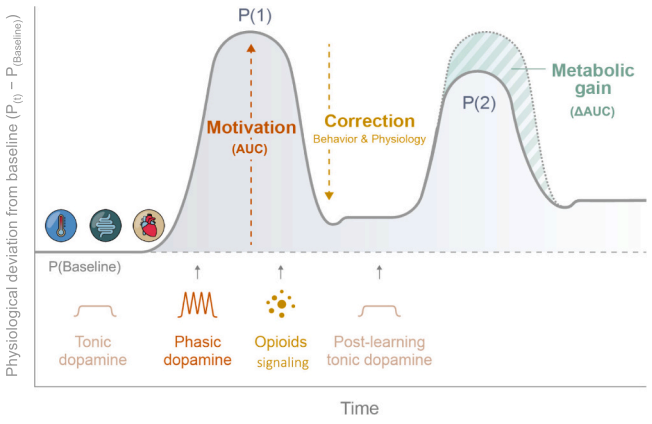
The metabolic framework introduces a novel model of learning and behavioral control by redefining reward not as the evaluation of external outcomes, but as an internal function of metabolic optimization. Behavior and learning are conventionally modeled through subjective constructs, such as *motivation* and *reinforcement*. However, subjective value is difficult to measure directly. The value of external rewards and punishments is typically used as a proxy for internal value, however, this translation varies systematically across individuals and contexts as a function of momentary physiological state and regulatory demands, limiting the reliability of such measures, and, in turn, constraining our understanding of the psychological and neural mechanisms governing behavior and reinforcement. The metabolic framework establishes a fundamental principle for behavior and learning: both are driven by the computational goal of metabolic optimization through two measurable components. The first is *Metabolic Effort*, in which rising physiological demands generate the drive to act, thereby providing a measurable quantification of motivation. The second is *Metabolic Gain*, in which the resolution of physiological demands reinforces adaptive responses, thereby providing a measurable quantification of reinforcement. These measurable signals can directly probe the subjective value to the individual with objective physiological quantities.

This framework applies not only to behavior but also to physiology: Metabolic Gain reflects the benefits of successful adjustments that lower energetic cost, enabling the brain to learn both adaptive behaviors *and adaptive physiological responses*, which can then be reapplied to future challenges. For example, to improve the metabolic efficiency of glucose regulation, the brain may increase chewing (a behavioral adaptation) or secrete insulin in advance of food consumption (a physiological adaptation). This principle is a key feature of allostasis: the brain improves its ability to manage metabolic efficiency by anticipating physiological demands and implementing useful physiological and behavioral adaptations in advance (Barrett and Simmons, 2015a; Schulkin and Sterling, 2019; Sterling, 2012). Expanding on the concept of homeostasis, where systems restore balance by reacting to perturbations after they occur (Cannon, 1929; Ramsay and Woods, 2014), in allostasis, prior knowledge is applied to *predict and prepare* for upcoming demands (Carter et al., 2009; McEWEN, 1998; Quintana and Guastella, 2020; Schulkin, 2003). As such, when a meal is regularly timed, the brain can anticipate the increase in blood glucose, thereby releasing insulin (Storlien, 1985; Vahl et al., 2010) and ghrelin (Drazen et al., 2006) before food consumption to minimize glucose perturbation, thereby reducing metabolic costs. Thus, the brain does not simply react to physiological challenges, instead, it proactively optimizes energy expenditure by learning to implement physiological and behavioral processes in anticipation (Schultz et al., 1997; Sterling, 2012). We refer to this proactive process as *Allostasis-Driven Learning* (Djerassi et al., 2021), in which adaptations that improve physiological efficiency are reinforced because they conserve energy.

The field of Reinforcement Learning provides foundational evidence for the role of dopamine and opioids in learning processes (Deserno et al., 2013; Emanuel and Eldar, 2023; Fields and Margolis, 2015; Koob, 2020; Mikus et al., 2022; Niv, 2009; Schultz et al., 1997; Spanagel and Weiss, 1999; Weber et al., 2025). Dopamine operates in two modes: tonic and phasic (Bergstrom and Garris, 2003; Floresco et al., 2003; Goto and Grace, 2005; Grace, 1991; Weiner and Joel, 2002). Tonic dopamine, characterized by low-frequency firing, is suggested to maintain the baseline levels of motivation (Niv, 2009; Niv et al., 2007) and optimize response vigor over time (Beierholm et al., 2013; Niv, 2007) based on the net reward rate (Niv, 2009; Niv et al., 2005). Phasic dopamine, marked by high-frequency bursts, signals reward prediction errors (i.e., the discrepancy between expected and actual rewards), driving behavioral adjustments to maximize future outcomes (Grace, 2000; Schultz, 1998; Sharpe and Schoenbaum, 2018). In reinforcement learning, phasic dopamine is associated with model-free learning (Nasser et al., 2017), which responds to immediate or unexpected rewards, whereas tonic dopamine is associated with model-based learning, integrating past rewards to optimize future behaviors in a given context (Niv, 2009, 2007; Niv et al., 2005). Opioids are suggested to signal the magnitude of the rewards (Koob, 2020; Navratilova et al., 2015a).

These distinctions map onto the metabolic framework. In the metabolic framework, model-free learning corresponds to homeostasis, whereas model-based learning corresponds to allostasis, with dopamine and opioids functioning in opposing yet complementary ways to optimize energy expenditure. Specifically, homeostasis corrects errors in response to unexpected challenges, whereas allostasis leverages prior knowledge to anticipate and proactively prepare for upcoming demands. Tonic dopamine maintains the physiological baseline, thereby setting the long-term allostatic reactivity potential (Niv, 2009; Niv et al., 2007). When unexpected events arise, phasic dopamine is triggered, mobilizing resources for an immediate adaptive response, while opioids, in contrast, signal the resolution of these responses, downregulating activity and generating metabolic relief. Over time, the brain learns to anticipate and preemptively manage such disturbances through allostasis-driven learning (Djerassi et al., 2021), conserving energy by reducing the intensity and duration of responses (Ingraham et al., 2019; McEWEN, 1998; McEwen and Wingfield, 2003; Peters et al., 2020). Together, these processes ensure that reductions in metabolic costs, captured as Metabolic Gain, reinforce successful adaptations, update tonic dopamine expectations, and drive the refinement of allostatic predictions (Fig. 3).

The metabolic framework extends reinforcement learning by shifting its core signals into metabolic terms, marking three key differences. First, in reinforcement learning, the brain is considered to represent a model of external rewards (or punishments) and their probabilities (Kaelbling et al., 1996; Wiering and Van Otterlo, 2012), while in the metabolic framework, the brain models the internal milieu, and the upcoming metabolic efforts and gains (Barrett and Simmons, 2015a; Djerassi et al., 2021; Weber et al., 2025). Second, the primary adjustment signal in reinforcement learning is reward prediction error (Bayer




$$Motivation = Metabolic\ Effort = AUC = \int_0^T \big(P(t) - P(baseline)\big)dt$$

$$Reinforcement = Metabolic\ Gain = \Delta\text{AUC} = AUC_{P1} - AUCP_2$$

**Fig. 3.** Quantifying motivation and reinforcement through metabolic effort and gain. The energetic costs of a disturbed system accumulate in time (Bobba-Alves et al., 2022; Picard et al., 2014; Pontzer, 2015b) and can be quantified as the cumulative area under the curve (AUC). *Metabolic Effort* is the energy required to resolve a physiological demand, quantifying motivation for adaptation. It is calculated as the integrated physiological response above baseline over time (AUC), providing a physiological measure capturing the magnitude of effort driving adaptive responses. *Metabolic Gain* quantifies reinforcement, calculated as the reduction in pysiological demand in the post-learning response (P2), relative to pre-learning response (P1) (ΔAUC), providing a physiological measure of how beneficial an adaptation was in lowering the overall response cost. Together, Metabolic Effort and Metabolic Gain constitute objective, measurable variables that index both the energetic drive for adaptation and the benefits achieved through successful adaptation. Unlike traditional views that treat reward as an instantaneous signal tied to a single event or neuromodulator, the metabolic framework treats reward as a relational, time-dependent quantity computed as the change in cumulative physiological demand (ΔAUC), arising as a secondary computation downstream of dopaminergic and opioidergic signaling. The value of new information is computed relative to prior physiological states, supporting anticipatory regulation consistent with allostasis.

and Glimcher, 2005; Schultz, 1998), while in the metabolic framework, *Metabolic Effort* acts as the key signal for adjustment. Third, in reinforcement learning, the focus is primarily on learning behaviors. The metabolic framework expands this concept to include not just behaviors but also physiological adaptations. Behavioral and physiological responses are reinforced because they contribute to reducing metabolic costs, emphasizing the importance of energy efficiency in the learning process (Keramati and Gutkin, 2014; Schiller et al., 2021). This account is supported by recent findings demonstrating that reward circuitry regulates autonomic processes not traditionally considered reward-related, such as immune function (Lubianiker et al., 2026). Because immune regulation does not constitute a learned behavior nor carry intrinsic hedonic value, its modulation by reward circuitry is difficult to reconcile with purely behavioral or pleasure-based accounts of reinforcement. Instead, it aligns naturally with a metabolic framework, in which these circuits coordinate energy allocation and efficiency across physiological systems, reinforcing states and responses that reduce overall metabolic cost. Phasic and tonic dopamine play complementary roles in maintaining and updating the brain's internal model of the body's needs. Tonic dopamine supports allostasis-driven learning by maintaining an anticipatory model of the internal milieu that proactively prepares for metabolic efforts and gains. Phasic dopamine, instead, signals an unexpected rise in metabolic effort, driving both immediate adaptations and updates to the internal model of the body.

The metabolic framework of reward enables definitive, biologically based modeling of learning, and the subjective experience of motivation and hedonic feeling: the rise of energetic costs evokes a sense of motivation to address a perturbation. The alleviation of energetic costs is experienced as a hedonic sense of relief, reinforcing adaptive responses. Unlike traditional models that assign a one-to-one mapping of motivation or reinforcement to dopamine or opioid release, the physiological roles of dopamine and opioids suggest that motivation and reinforcement are computed from the metabolic consequences of their opposing functions: dopaminergic activation and opioid-mediated resolution.

### *4.1. The metabolic role of dopamine and opioids in abstract knowledge and complex behaviors*

In addition to their role in low-level physiological processes, dopamine and opioids have also been repeatedly associated with complex, learned, and context-dependent behaviors, such as responses to money (Calabro et al., 2023; Madden et al., 1997; Martucci et al., 2019; Zald et al., 2004), music (Ferreri et al., 2019; Salimpoor et al., 2011; Stefano et al., 2004), and art (Garcia-Ruiz et al., 2019; Spee et al., 2018; Vessel et al., 2022). In the metabolic framework, this involvement is explained by the ability of the brain to learn and apply complex behavioral strategies to improve physiological regulation and metabolic efficiency. Indeed, literature shows that higher-level processes like language (Crane et al., 1970; Ilves and Surakka, 2012; Nikula et al., 1993), music (Bernardi, 2005; Blood and Zatorre, 2001; Koelsch et al., 2008; Yin et al., 2022), emotions (Gross and Levenson, 1993; Lench et al., 2011), money (Fowles et al., 1982; Tranel, 1983), and religion (Gervais and Norenzayan, 2012; Good et al., 2015), can disrupt or stabilize physiological states, thus triggering dopaminergic and opioid responses (Calabro et al., 2023; Kasanova et al., 2017; Koepp et al., 2009; Salimpoor et al., 2011; Zald et al., 2004). In this context, dopamine and opioids could serve as the mechanism that translates the meaning of abstract concepts or complex behaviors into physiological consequences, endowing them with subjective value through metabolic changes. However, because this evidence in humans is based primarily on indirect measures from neuroimaging, further research is needed to establish the underlying causal mechanisms.

One complex behavior that involves dopamine and opioids is social interactions. Human (Atzil et al., 2017) and rodent (Hansen et al., 1993; Lavi-Avnon et al., 2008) mothers release dopamine in response to their offspring, promoting bonding behaviors (Rilling, 2013; Rilling and Young, 2014; Zeevi et al., 2022a). Dopamine is also secreted during sexual interactions (Louilot et al., 1986; Robinson et al., 2002) and aggression (Louilot et al., 1986), emphasizing its role across diverse social contexts. The opioid system is also implicated in social behaviors, particularly in processing social rewards and encoding the hedonic aspects of interactions (Chelnokova et al., 2014; Resendez et al., 2013), thereby promoting social bonding and behavior (Inagaki, 2018; Løseth et al., 2024; Loseth et al., 2014; Machin and Dunbar, 2011; Massaccesi et al., 2022; Nelson and Panksepp, 1998; Panksepp et al., 1980). Dopamine is traditionally viewed as a driver of social motivation. Within the metabolic framework, dopamine is proposed to support context-dependent physiological upregulation that helps meet the energetic demands imposed by social interactions. Because social encounters can strongly perturb physiology, dopamine may respond to social cues by signaling metabolic effort, thereby enhancing motivation for affiliative or aggressive responses, accompanied by physiological adaptations of hormone secretion (Babygirija et al., 2012; Sherman et al., 2017; Simon, 1981; Summers et al., 2005) and autonomic activation (Cohen et al., 2024; Lorber, 2004; Murray-Close et al., 2012; Zeevi et al., 2022b). Opioids complement this by encoding metabolic relief when physiological responses are resolved, reinforcing behaviors that benefit regulation and metabolic efficiency.

Taken together, the subjective value of any stimulus, whether a cultural symbol such as money or art, or a social agent such as a parent, partner, or enemy, can emerge through learning and reflects its predicted metabolic impact (Picard, 2025).

## 5. Discussion

The metabolic framework of dopamine and opioids introduces a novel hypothesis, redefining their roles as key metabolic agents governing physiological regulation. The dopaminergic system upregulates physiological responses, whereas the opioid system subsequently dampens these responses, guiding the body back to a less costly state. This physiological mechanism shapes affective experience and motivates behavior (Critchley and Garfinkel, 2017; Feldman et al., 2024; MacCormack and Lindquist, 2019; Shenhav, 2024), rooted in the drive and hedonic value of minimizing metabolic effort. Reinforced by metabolic gains, the brain learns to incorporate beneficial adjustments proactively to minimize future perturbations and optimize the body's energy budget. While previous research has linked dopamine and opioids to reward, the metabolic framework offers a mechanistic principle by which optimizing metabolic efficiency governs behavior and learning.

The dopamine-opioids mechanism is efficient because it is grounded in two key computational principles of adaptation. First, its *bimodal organization* enables rapid onset and offset of physiological responses, ensuring swift corrections that minimize metabolic costs. This design optimizes selection under metabolic constraints, allowing precise control with minimal energetic expenditure. Second, the mechanism is *domain-general*: dopamine and opioids play analogous roles across multiple physiological systems, each operating at different scales yet requiring coordinated behavioral and physiological adaptations. A critical feature of this generality is scale-invariant responsiveness (Karin and Alon, 2022), in which reactions depend on fold-changes rather than absolute values (Adler and Alon, 2018; Hart et al., 2018, 2013; Shoval et al., 2010), ensuring consistent regulation across different baselines. Indeed, evidence show that dopamine encodes fold changes across various informational inputs and modalities (Bromberg-Martin et al., 2010; Eshel et al., 2016; Gardner et al., 2018; Karin and Alon, 2022; Schultz and Dickinson, 2000). However, domain-generality raises the problem of specificity: when glucose rises, what ensures that dopamine promotes insulin secretion but does not activate the HPA axis? This requires an 'AND-gate' mechanism (Mangan and Alon, 2003), in which localized cues (e.g., plasma glucose) and system-wide signals (dopamine signaling) converge to generate context-appropriate responses only when both conditions are met. Such specificity allows the brain to tailor adaptations to distinct perturbations while maintaining centralized control across competing demands, such as fatigue and hunger. The adaptive value of this domain-general, scale-invariant computation lies in its capacity to prioritize and coordinate multiple physiological processes on a unified scale.

The bimodal function of dopamine and opioids introduces a novel conceptual differentiation between two types of positive affect. The first is relief, a primary form of positive affect that arises from the resolution of physiological perturbations. The second is reinforcement, or Metabolic Gain, a secondary computation that quantifies the energetic benefits of novel adaptations over time. Both rely on the interplay between dopamine and opioids: dopamine drives activation and motivation to respond, while opioids signal resolution and relief. Contrary to prevailing accounts, these neurotransmitters do not themselves encode the value of stimuli. The actual value that drives behavior (motivation) or reinforces adaptations (reinforcement) can only be attained through the metabolic outcome of their mutual function, expressed as Metabolic Effort and Metabolic Gain. Elegant research has elucidated the roles of dopamine and opioids in regulating pain and reward, highlighting their interplay, shared neural mechanisms, and marking relief as a temporal function of the emission of negative valence (Leknes et al., 2011; Leknes and Tracey, 2008). The metabolic model builds on this work and extends it by proposing that relief reflects the resolution of any metabolically effortful physiological response, rather than being specific to pain, thereby situating relief within a general principle of metabolic savings.

A recent account has proposed that motivation and reinforcement are shaped by physiological states and their interoception (Weber et al., 2025). Here, these concepts are formalized as measurable computations grounded in energy regulation. Metabolic Effort quantifies motivation as the energy an organism is willing to expend to resolve a physiological demand, corresponding to the metabolic cost of that demand. Metabolic Gain quantifies reinforcement as the benefit obtained when that cost is reduced, corresponding to the metabolic savings achieved by successful adaptations. Rather than estimating the subjective value of external stimuli, this framework advances a decisive shift by physiologically quantifying the actual costs and benefits of adaptation. Building on, and extending, reward-based models, this account addresses the long-standing challenge of reliably capturing subjective value, offering instead a biologically grounded, quantifiable, and evolutionarily principled account of behavior and learning.

### 5.1. Dopamine-opioid regulation is evolutionary adaptive and conserved

The evolutionary adaptiveness of the dopamine–opioid mechanism is grounded in selection pressures favoring energetic efficiency, a fundamental constraint shaping biological organization. Because energetic resources are finite, adaptations that enhance regulatory efficiency are favored because they reduce metabolic burden and free energy for other fitness-relevant functions, including growth, reproduction, and energetically demanding neural processes (Pontzer, 2015b; Raubenheimer and Simpson, 2016) (for discussion, see (Theriault et al., 2023b)). This places mechanisms that optimize energy allocation under strong selective pressure, particularly in environments characterized by energetic scarcity (Dunsworth et al., 2012; Niven and Laughlin, 2008b; Pontzer, 2015b; Sterling and Laughlin, 2015b). Organisms capable of flexibly updating context-dependent behavioral strategies in response to energetic demands would therefore have been favored by natural selection.

The dopamine-opioid mechanism proposed here confers fitness benefits at both proximal and ultimate timescales. Proximately, coupling motivation and learning to metabolic consequences enables efficient behavioral regulation in real time, supporting adaptive action selection, rapid adjustment to changing physiological and environmental conditions, and reduced energetic waste. Ultimately, such a system is favored because the improved energetic regulation enhances survival and reproductive success, thereby supporting the conservation of dopamine and opioid systems as domain-general regulators of metabolic efficiency.

Indeed, converging evidence suggests that this mechanism may be phylogenetically conserved, as dopamine and opioids signaling regulate physiological processes and metabolically relevant behaviors across a wide range of invertebrate taxa, including *Caenorhabditis elegans*, *Drosophila melanogaster*, *Aplysia californica*, *Helix aspersa*, *Periplaneta americana*, and *planarian flatworms* (Barron et al., 2010). In these phyla, dopamine and opioids modulate immune function (Cattabriga et al., 2023; Esch et al., 2020; Salzet et al., 2000; Tong et al., 2020), feeding (Cheong et al., 2015; Cooper et al., 2010; Hills et al., 2004; Luedtke et al., 2010), energy mobilization (Barros et al., 2014; Plaçais et al., 2017), locomotion, reproduction (Jiang et al., 2022), and nociception (Nieto-Fernandez et al., 2009). This suggests that dopaminergic and opioidergic roles in physiological regulation have an ancient evolutionary origin, predating the emergence of mammalian reward circuitry and its associated behaviors, higher-order cognition, and affective experience.

From an evolutionary perspective, the dopamine–opioid mechanism provides a parsimonious, energy-efficient solution, coordinating physiological regulation and energy mobilization across taxa and systems in both brain and periphery. This makes it well suited for conservation across evolution.

### 5.2. Implications

This work advances a generative theoretical shift by redefining reward as a function of metabolic optimization and recasting dopamine and opioids as physiological modulators rather than reward agents, with broad theoretical, clinical, and applicable implications. First, at the theoretical level, this framework positions metabolism as a fundamental mechanistic constraint that shapes cognition, affect, and behavior. By highlighting the energetic costs that underlie all neural and physiological activity, it links low-level metabolic regulation with high-level psychological phenomena, explaining how the management of bodily energy informs subjective experience and complex behavior (Horvath, 2022; Juster et al., 2016; Picard et al., 2019, 2025). Moreover, it portrays unified roles for dopamine and opioids, explaining their function across levels of organization, from physiology to behavior and cognition, and synthesizing domains that have traditionally been studied in isolation. Second, the metabolic roles of dopamine and opioids have clinical implications, pointing to novel mechanistic routes for neuropathology (Udeh-Momoh et al., 2025) such as schizophrenia, depression, and addiction. From this perspective, illness can be understood as impaired metabolic function and disrupted efficiency in physiological regulation (Bobba-Alves et al., 2023; Huang et al., 2025; Picard, 2025). Targeting these processes, rather than neurotransmitter imbalance alone, could open new strategies for improving neural and psychiatric health (Andreazza et al., 2025; Nord and Garfinkel, 2022). Finally, this framework offers an applicative breakthrough by introducing a novel way to quantify motivation as *Metabolic Effort* and reinforcement as *Metabolic Gain*. This approach advances learning research, supporting the development of causal and cross-species models, and yielding precise predictions that link molecular and circuit mechanisms to behavior. Moreover, grounding learning in metabolic processes highlights distinctions between biological learning and artificial learning models, offering insights to improve both brain science and artificial intelligence.

### 5.3. Limitations

The metabolic framework does not yet account for the contributions of other neurotransmitter systems to metabolism, including additional monoamines (epinephrine, norepinephrine, serotonin or histamine) serving as excitatory transmitters, and inhibitory transmitters like gamma-aminobutyric acid (GABA). Investigating how these neurotransmitters contribute to the allostatic process could extend the framework beyond dopamine and opioids, offering a more comprehensive understanding of how metabolic constraints shape brain function, behavior, and cognition. Moreover, while metabolism may provide a unifying mechanism linking affect, behavior, and learning, it is not proposed as the sole point of convergence among these processes. Higher-order mechanisms are likely to also play a significant role in shaping these psychobiological features.

Importantly, this novel framework does not claim exclusivity in explaining how the brain optimizes metabolism, or how the brain processes affect, behavior, and cognition. Rather, it offers a novel mechanistic account of how reward arises from the physiological functions of dopamine and opioids, clarifying how these neuromodulators translate metabolic regulation into behavioral control and affective experience.

Some findings highlight complexities beyond the scope of our framework. For example, some studies report that opioids can enhance, rather than suppress, motivated behaviors (Barbano and Cador, 2007; Boecker et al., 2008; Buchel et al., 2018; Colasanti et al., 2012), such as food intake (Jenck et al., 1987; Mahler and Berridge, 2012; Morley et al., 1982; Morley and Levine, 1981) and sexual behavior (Mahler and Berridge, 2012). Similarly, dopamine has been reported to suppress, rather than promote, immune function (Ghosh et al., 2003; Mikulak et al., 2014; Zhao et al., 2013), or follow, rather than precede, opioid release (Bontempi and Bonci, 2020; Herz, 1995; Johnson and North, 1992), challenging the temporal sequence proposed here. For example, opioid-induced dopamine release could represent a sequential adaptation: following the removal of a threat, opioids first downregulate the stress response, after which dopamine activity promotes hunger to replenish depleted energy stores. Similarly, an opioid-dependent downregulation of an immune response may trigger a dopaminergic drive to restore energy balance. Such adaptive cascades illustrate how the attenuation of one physiological process can activate another, reflecting compensatory or complementary functions within an integrated metabolic system.

## 6. Conclusions

The metabolic framework of reward posits that dopamine and opioids jointly translate physiological processes into motivational and hedonic functions that guide adaptive behavior. Dopamine mobilizes physiological resources to meet rising metabolic demands, while opioids facilitate recovery by restoring energetic balance. Together, these opposing yet complementary systems compute metabolic gain, or the reduction in energetic cost following successful adaptation, thereby reinforcing behaviors and physiological processes that improve efficiency over time. By reframing reward as a function of metabolic optimization, this framework unites motivation, reinforcement, and physiological regulation within a single biological principle, offering a coherent foundation for understanding how the brain learns to sustain the body's energetic economy.

## Funding Statement

This work was supported by the European Research Council (ERC) [Starting Grant 101116444] awarded to Shir Atzil, with no involvement of the funding source in the conception, writing, or decision to submit the manuscript.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT in order to improve English language editing and manuscript readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article. ChatGPT and Gemini were used in Fig. 2.

## Declaration of Competing Interest

The authors declare no conflict of interest.

## Acknowledgements

The authors thank Yitzchak Yadegari for the graphic illustrations in Figs. 1, 2 and 3. We also thank Yuval Hart and Hagai Bergman for fruitful discussions and critical reading of the manuscript.

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