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Motivation as Neural Context for Adaptive Learning and Memory Formation

Jia-Hou Poh[1,2,3] and R. Alison Adcock[2,3,4,5]

[1]Centre for Sleep & Cognition, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

[2]Center for Cognitive Neuroscience, Duke University, Durham, North Carolina, USA; email: alison.adcock@duke.edu

[3]Department of Psychiatry & Behavioral Sciences, Duke University, Durham, North Carolina, USA

[4]Department of Psychology & Neuroscience, Duke University, Durham, North Carolina, USA

[5]Department of Neurobiology, Duke University, Durham, North Carolina, USA

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Keywords

motivation, memory, hippocampus, dopamine, noradrenaline, neuromodulation

Abstract

Our memories shape our perception of the world and guide adaptive behavior. Rather than being a veridical record of experiences, memory is selective. An accumulating body of work suggests that motivational states, emerging from the interplay between internal and external demands, play a critical role in determining what information is encoded in memory and how. Central to the regulation of motivational states are dopaminergic and noradrenergic neuromodulatory systems that can coordinate brain activity to determine how information is propagated, shaping memory outcomes. In this review, we propose that motivational states supported by the dopaminergic ventral tegmental area would facilitate the formation of flexible associative memory, while the noradrenergic locus coeruleus would facilitate unitized goal-relevant memory. By considering how neuromodulatory systems can support different neural contexts, we aim to explain how motivation enables an adaptive memory system, and in bridging motivation and memory, we aim to offer a framework for insights applicable to education and clinical practice.

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INTRODUCTION

Our memories define the lens through which we experience the world around us. By drawing on past experiences, we are able to develop an understanding of our environment and to flexibly adapt our behaviors to changing demands or to novel situations. Memories, however, are not simply a veridical record of all our lived experiences. While some experiences can be brought to mind as scenes with vivid details, some others may appear more conceptual, sparse, or gist-like. This ability to both prioritize specific detailed relationships and abstract meaning from past experiences is essential for the effective use of our memories to inform future behaviors and decisions; but how does the brain determine what information should be remembered and what details should be preserved?

A central determinant of what gets transformed into lasting memories is the interplay between our memory systems and motivational circuits in the brain. Much like how tinted lenses can color our perception of the world, motivational states overlaid on our experiences are crucial in shaping how we navigate, perceive, and remember the events we encounter. Motivation can be seen as a process manifesting from a confluence of internal states and external stimuli and driving an organism toward the attainment of specific goals. For example, when opening the refrigerator while feeling dehydrated (internal state), the can of soda sitting in the corner (external stimulus) may immediately catch your attention, motivating a desire for immediate consumption. In contrast, when you are feeling hungry, the same can of soda might not even be noticed, and it is unlikely to elicit the same behavior. By integrating the demands from internal states and external affordances, motivation can thus act as a filter that guides our interaction with the environment.

While early studies of motivation primarily centered around understanding physical behaviors, there is increasing recognition that motivation can also influence cognitive processes, including how information is processed, encoded, and consolidated. Here, we consider motivation not only as a mechanism for the adaptive allocation of limited physical and cognitive resources but also as an expression of brain states that determine how information is processed and remembered.

In this review we highlight developments in the study of motivated memory and discuss how neuromodulatory systems in the brain constitute a key mechanism that binds motivation and memory. Building on recent findings from cognitive neuroscience and neurobiology, we propose a neural context perspective of motivation, whereby motivational states are defined based on the specific patterns of interaction between different brain regions (i.e., the neural contexts). Specifically, we propose that engagement of the dopaminergic and noradrenergic neuromodulatory systems can instantiate distinct neural contexts that facilitate divergent information processing modes to produce qualitatively different memory outcomes.

By characterizing how neuromodulatory influences can support different brain states/neural contexts, we aim to provide a framework for understanding how different motivational states can enable an adaptive memory system and to highlight the relevance of regulating motivational states for effective learning in the classrooms and the clinics. To begin, we first discuss what motivation actually means.

WHAT IS MOTIVATION?

Everyone knows what attention is.

—James (1890)

No one knows what attention is.

—Hommel et al. (2019)

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To understand how motivation can adaptively allocate physical and cognitive resources, it is necessary to first consider what constitutes motivation and how it can arise. Much like attention, motivation is a construct that is deeply integrated within our everyday language and is seemingly well understood by everyone. We infer motivation from behaviors that we observe (e.g., he works hard because he is motivated to get into his dream college), and we often ascribe motivation as a primary causal factor (e.g., he gets good grades because he is motivated). However, despite how easily we infer and assign motivation to observable behaviors, motivation is not directly quantifiable, and operationalizations of motivation can be highly variable, especially when motivational concepts are used to explain complex behaviors or abstract goals.

Broadly, motivation can be defined as a state that energizes and sustains goal-directed behavior, and this can be applied to simple behaviors like lever pressing or even to the attainment of long-term life ambitions (for a discussion on the definition of high-level motivation construct, refer to Murayama & Jach 2024). It is generally well accepted that motivation includes both an activation and a direction component (Salamone & Correa 2012) that guide the amount of resources to be allocated (activation) and where resources should be allocated (direction). The activation component refers to the invigoration of action, and it is often quantified based on measures like response time, intensity, or response rates. The directional component refers to the guiding of behavior toward a specific goal and can be operationalized based on the expression of choice behaviors, such as the decision to approach or to avoid. By operationalizing these behavioral components, studies are able to measure and quantify levels of motivation that arise in response to a stimulus or to changes in internal states. This use of behavioral outputs to quantify motivation has propelled many advances in our understanding of motivated behavior and decision-making. However, like the motion of a flag that shows us what wind does rather than what wind is, quantifying motor outputs stimulated by incentives leaves aside the fundamental interesting question of what—or how many things—motivation is.

Advances in cognitive neuroscience methods now allow researchers to characterize complex brain states and relate them not only to behavioral outputs but also to physiology, cognition, and subjective experience. As a result, we are now positioned to go beyond the study of what motivation does and are beginning to understand what it is, how motivations shape brain function, and what that feels like. Recent research in our group and others distinguishes motivations from each other—including their behavioral effects—as defined less by objective incentives than by prevailing neuromodulatory tone and network. These approaches shed light on how motivation emerges and the neural mechanisms of its influence on brain function, subjective experience, cognition, and adaptive behavior. More broadly, it suggests the need for a richer vocabulary of motivations to reflect the full range of affective states people feel about things that might happen in the future.

Below, we briefly consider historical perspectives on how motivation emerges, discuss evidence about how motivations are supported by neuromodulatory systems, and propose an expansion of neuroscience terminology to include motivational mood.

Motivation as a Mechanism of Drive Reduction

The adoption of motivational concepts in behavioral neuroscience stemmed from the need to understand the latent psychological processes guiding goal-directed behavior (Hull 1943). One early theory of motivation is homeostatic drive reduction, which suggests that motivation arises from the need to correct imbalances in our body related to basic physiological needs, like hunger and thirst (Berridge 2004). For example, when we are thirsty, we are motivated to drink water to restore balance. Experimental testing of this framework often induces a physiological deficit state through the use of food or water deprivation, and motivation can be quantified based on approach

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and consumption behaviors (e.g., speed of approach, choice, or amount of consumption). In these studies, motivational states are primarily defined based on the specific physiologic deficit; in other words, hunger and thirst can be defined as distinct motivational states.

The reduction of homeostatic drive has been particularly useful in accounting for motivation related to appetitive or consumption behaviors, but its generalizability was constrained by the narrow focus on physiological setpoints. Expanding beyond physiological homeostasis, subsequent theories of drive reductions have included consideration of affective (Solomon & Corbit 1974) and cognitive (Harlow et al. 1950) states as fundamental drivers of motivation. From this perspective, the motivation for learning arises when one experiences a state of information deprivation, and the desire for learning functions to alleviate this state of information deficit.

However, a fundamental implication of drive reduction accounts is the expectation that the value of the reward lies in its ability to alleviate deficits. If so, motivated behaviors should only arise in response to deficit states (e.g., reaching for water only when you are thirsty). Contrasting with this prediction, motivated behaviors can often be elicited before a deficit occurs (e.g., drinking water before you experience thirst), and, conversely, motivated behaviors are known to persist after the satiation of deficits (Berridge 2004). This dissociation is perhaps most prominently demonstrated in animal studies showing that intravenous satiation of nutritional demands did not lead to a reduction in consumption behavior (Morales 2022), suggesting that the motivation to eat was not reduced by the alleviation of physiological deficits. With the gradual displacement of a pure drive reduction account, there was growing support for value learning accounts of motivation.

Motivation from Value Learning

The value learning perspective builds on work in associative learning, whereby neutral cues can acquire incentive value through Pavlovian or instrumental conditioning, and motivation is proposed to arise based on the value of a predicted outcome (Bolles 1972). As a neutral cue is reliably associated with an outcome, it acquires its own incentive value, based on expectation of that outcome. The incentive value of the cue arising from its expected outcome means that motivation can arise from the cue independent of the actual outcome. (For a discussion on the neurobiology associated with liking and wanting, refer to Berridge & Kringelbach 2015.)

Through conceptualizing motivation as a value-driven process, both the activation and direction component of motivation can be explained by the singular goal of value maximization. By this account action vigor (activation) would scale with overall value, while action choices (direction) would orient toward the highest expected value. While the value learning perspective does not consider drive reduction as necessary for motivation, it is sufficiently flexible to accommodate drive reduction. Rather than being the direct cause of motivation, deficit states can be considered as a modulator of value. From this perspective, a state of information deprivation does not directly produce the motivation to learn. It does so indirectly by increasing the expected value of information.

Investigations of the neural substrates of motivation have also supported a value-driven perspective. Across studies in humans and animals, it has been consistently shown that neuromodulatory systems that are critical for value signaling, particularly the dopaminergic (Bromberg-Martin et al. 2010) and noradrenergic (España et al. 2016) systems, are also essential for the expression of motivated behaviors. By assigning motivational significance to stimuli, these neuromodulatory systems have also been proposed as key mediators of motivated memory, a role further discussed below.

By underscoring the role of predicted outcomes in motivation, the value learning perspective can be generalized to include complex decision-making and abstract goals; such complex

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representations are crucial for understanding human motivation. While there are key assumptions of value learning that continue to be challenged (e.g., Shenhav 2024), the value-based approach has been central to computational modeling of motivation and to our progress in understanding motivated memory. Understanding that incentive cues signal the value of their predicted outcomes and elicit anticipatory affective states was an essential starting point for demonstrating that motivation *per se* could influence memory formation, independent of outcomes, prediction errors, or reinforcement of associations (Adcock et al. 2006).

THE INFLUENCE OF DISTINCT MOTIVATIONS ON LEARNING AND MEMORY FORMATION

The interplay between motivation and memory is fundamental in supporting our ability to prioritize salient experiences, ensuring that goal-relevant information is available for future decisions and behavior. However, the influence of motivation on memory is not homogeneous, and studies have shown that the specifics of these effects may depend on precisely characterizing specific motivational states.

Across the different disciplines, there have been numerous attempts at generating taxonomies for classifying the different types of motivation. Here, we focus on three different classifications that have been the subject of experimental studies investigating motivational influence on learning and memory.

Locus: Extrinsic Versus Intrinsic Motivations

The categorization of a motivational state by its locus of origin has been highly influential in applied research on motivation. The self-determination theory (SDT; Ryan & Deci 2000a) is a prominent framework that has guided the adoption of motivational constructs in education research, and it proposes that motivation can be classified as extrinsic or intrinsic. While extrinsic motivation is thought to drive volitional behavior in pursuit of a desired outcome that is distinct from the activity itself, intrinsic motivation is thought to drive volitional behavior because the activity is inherently rewarding.

In education research, intrinsic motivation is often considered as a stronger motivation for learning, and meta-analyses have shown that higher intrinsic motivation is associated with greater student engagement (Froiland & Worrell 2016) and also higher academic performance (Taylor et al. 2014). Intrinsic motivation has also been proposed to enhance learning and memory by promoting a greater depth of encoding (Cordova & Lepper 1996, Vansteenkiste et al. 2004), supporting the integration of information with prior knowledge. Conversely, the reliance on extrinsic rewards/punishments has been suggested to produce pervasive negative effects, including by undermining intrinsic motivations (Murayama et al. 2010, Ryan & Deci 2000b). However, in recent updates of the SDT framework, there has been greater consideration for the different types of extrinsic motivation, and it has been suggested that when extrinsic motivation is internalized, it can be just as beneficial for learning as intrinsic motivation (Ryan & Deci 2020).

While experimental studies in neuroscience have predominantly relied on exogenous reinforcers (hence on extrinsic motivation), there is growing interest toward understanding how intrinsic motivations like curiosity can influence learning and memory. Recent studies in humans have sought to examine the influence of intrinsic motivation by evoking curiosity using a wide range of stimuli like trivia questions (Gruber et al. 2014, Kang et al. 2009, Poh et al. 2022), perceptually ambiguous images (Cohanpour et al. 2024, Jepma et al. 2012), gambles (Rodriguez Cabrero et al. 2019), and evolving line drawings (Hsiung et al. 2023). Similar to that seen with the use of extrinsic rewards, these studies have shown that memory performance was better for information

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that evoked high curiosity (Gruber et al. 2014, Kang et al. 2009, Poh et al. 2022). Interestingly, a state of high curiosity also enhanced memory for irrelevant stimuli presented in close temporal proximity (Gruber et al. 2014, Murphy et al. 2021), suggesting that the memory benefits of high motivation may extend beyond the subject of curiosity.

While a neuroimaging study in humans has observed differences in neural engagement associated with intrinsic and extrinsic motivations (Duan et al. 2020), several other studies have shown that intrinsically motivated memory enhancement was associated with the engagement of reward circuitries similar to that observed during the anticipation of extrinsic rewards (Gruber et al. 2014, Kang et al. 2009, Poh et al. 2022). These findings suggest that the influence of intrinsic and extrinsic motivations on memory may be largely dependent on overlapping mechanisms.

Valence: Approach Versus Avoidance Motivations

The approach/avoidance distinction is perhaps one of the oldest classifications of motivational states (Elliot 1999). It was believed by early philosophers of hedonism that the inherent guiding principle of human motivation is the pursuit of pleasure and the avoidance of pain. Extending into the field of psychology, work by William James continued to highlight a role for pleasure and pain in motivating actions (e.g., James 1890). In general, approach motivation can be defined as the energization of behavior toward a desired outcome (promotion), while avoidance motivation pertains to the avoidance of undesired outcomes (prevention) (Eder & Hommel 2013).

The application of approach/avoidance motivation is prominent in educational psychology. Numerous studies have compared learning outcomes related to rewards or punishments (Luria et al. 2021), and attempts have been made to integrate approach/avoidance motivation within broader theoretical frameworks in education research, such as the achievement goal theory (refer to Elliot 1999 for a detailed discussion). In general, research in education suggests that avoidance motivation is linked with poorer learning outcomes, and meta-analysis has shown that avoidance motivation is negatively associated with grades and positively associated with negative affect (Baranik et al. 2010).

In animal and human neuroscience, approach and avoidance motivation are often operationalized with experimental contexts where rewards are used to incentivize good performance (approach), or penalties are imposed for errors (avoidance). It has been shown that approach and avoidance motivation are generally associated with distinct behavioral and physiological signatures (Guitart-Masip et al. 2012, Harmon-Jones 2011). While approach motivation has been associated with behavioral activation, exploratory information processing, and positive affect (Gable & Dreisbach 2021), avoidance motivation has been associated with behavioral inhibition, narrow attentional focus, and negative affect (Roskes et al. 2013). Consistent with these distinct behavioral expressions, approach and avoidance motivation have also been shown to produce qualitatively different memory outcomes (Murty et al. 2011). In particular, while expectations of reward have been shown to enhance associative memory dependent on the hippocampus (Murty & Adcock 2014, Wolosin et al. 2012), the expectation of a punishment has been shown to bias memory toward a selective encoding of the most salient features (Clewett et al. 2018, Murty et al. 2016).

These patterns of findings may at first appear to suggest that the differences between the memory effects of approach versus avoidance motivation depend on the specific behavioral measures, and that approach is superior to avoidance motivation for enhancing hippocampus-dependent memory. Yet approach motivation does not always have a positive effect on memory performance.

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In a study using a video game to simulate a Morris water maze task, which requires participants to locate a platform hidden under water using environmental cues, it was shown that while reward expectation enhanced memory performance in most participants, the memory benefit of the incentive was negated or even reversed in participants who exhibited a high level of arousal (Murty et al. 2011). The impairment by reward incentives in those with high physiological arousal was similar to the impairments seen in those working to avoid static shocks. This finding, which calls to mind observations of choking when perceived reward stakes are high (Mobbs et al. 2009), suggests that while anticipated rewards can elicit approach motivation and enhance memory, this enhancement can also be disrupted.

Mood: Imperative versus Interrogative Motivational States

The exceptions to the predicted motivational valence effects observed in our studies of memory formation (Murty et al. 2011, 2012, 2016) prompted our group to propose expanding the vocabulary for classifying motivations to incorporate affect related to the state of knowledge about events (and their value) unfolding over time, together with the attitude or intention to take action based on that state of knowledge. Interestingly, this conjunction of ontology and affect is already recognized in linguistics and grammar as the mood of a verb. In English, verb moods include imperative (commanding), interrogative (querying), and indicative (certain). Considering the mood of motivational states, we can contrast motivations that are imperative or interrogative: Each mood is associated with distinct informational and goal states, information processing modes, and, as our group discovered, memory outcomes. In imperative states, information processing is directed toward urgent resolution of a single compelling goal. In interrogative states, information processing is focused on the building of schematic knowledge, with flexible integration to represent more complex value relationships enabling adaptation to achieve more and longer-term goals (Chiew & Adcock 2019, Murty & Adcock 2017, Murty & Dickerson 2016, Poh & Adcock 2025). Based on this premise, we predicted and showed that directly manipulating motivational mood biased behavior in choice paradigms and memory outcomes: Imperative motivation favored exploitation, and interrogative motivation favored directed exploration to resolve uncertainty and enhanced declarative memory formation (Sinclair et al. 2023).

The proposal to classify motivations as imperative or interrogative states has been largely built upon experimental studies manipulating incentive valence to compare reward- and threat-elicited motivations. Because threat-related motivations may be more likely to elicit an imperative state, while reward-related motivations are more likely to elicit an interrogative state, the aforementioned classification of approach/avoidance can account for many patterns of findings. However, several informative exceptions to the predicted valence effects revealed evidence of brain states that varied independently of valence and reliably predicted behavior and memory. The information-based classification emerges from considering neurobiological evidence from these paradigms in which activation of neuromodulatory systems was associated with distinct memory outcomes. These memory differences can be explained by differences in neural engagement within the medial temporal lobe (MTL) during memory formation. While the parahippocampal and perirhinal cortices in the neocortical MTL are theorized to support representations of contexts or items, respectively, the hippocampus proper is theorized to support the representations of relational structures and the binding of discrete events into integrated representations (Brown & Aggleton 2001, Davachi et al. 2003, Eichenbaum 2000, Ranganath & Ritchey 2012).

Based on experimental evidence showing dissociable neuromodulatory engagement during threat- and reward-motivated encoding (Adcock et al. 2006; Murty et al. 2012, 2016), it is

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proposed that an imperative state would be associated with noradrenergic modulation and recruitment of the neocortical MTL with the amygdala, whereas an interrogative state would be associated with dopaminergic modulation of the hippocampus by the ventral tegmental area (VTA). This difference in the engagement of the neocortical MTL and the hippocampus proper is thus proposed as the primary mechanism giving rise to diverging memory outcomes.

Expanding on this framework, in the following section we examine how neuromodulatory systems implicated in the genesis of motivation can modulate local functions with the MTL and also coordinate functional interactions between the MTL and other regions across the brain, including sensory cortices and regions in the prefrontal cortex, to influence memory functions.

NEUROMODULATORY SYSTEMS AS THE NEXUS BETWEEN MOTIVATION AND MEMORY

As highlighted above, the dopaminergic and noradrenergic systems play a pivotal role in bridging motivation and memory, but up until now, we have only described how these neuromodulatory systems may support motivation through the signaling of value. How, then, are low-dimensional value signals translated into complex motivational states that support diverging behaviors and information processing? To understand how distinct motivational states can arise from value signals, it is necessary to consider the functional properties of neuromodulatory nuclei, and here we focus our discussion on the VTA and the locus coeruleus (LC).

The VTA and LC are the primary brain sources of the dopaminergic and noradrenergic systems, respectively. These neuromodulatory nuclei innervate and project widely across different brain regions, yet their sparsity allows for the integration and reduction of diverse inputs into simple value signals, which can then be diffusely projected for coordinated brain-wide signaling. This property makes neuromodulatory systems integral to the rapid instantiation of neural contexts that underlies complex motivational states.

The concept of a neural context was explicated in earlier work aimed at understanding how cognitive functions are represented by network interactions across the brain (McIntosh 2004). This formulation posits that the response characteristics of any brain region are determined by its patterns of interaction with anatomically connected regions, so that the functional significance of localized neural activity can only be understood based on its broader network interactions at any given time.

It is well documented that patterns of functional connectivity across the brain can vary spontaneously even in the absence of changes in external demands (Hutchison et al. 2013, Pezzulo et al. 2021), and such background dynamics have been associated with intrinsic variations in information processing (McCormick et al. 2020). Recent work has shown that dynamic changes in neural context can arise from intrinsic fluctuations in neuromodulatory activity (Munn et al. 2021, Shine et al. 2019b). The augmentation of neuromodulatory tone with pharmaceuticals and optogenetic stimulation has similarly produced diverse patterns of network interaction (Grimm et al. 2024, Shine et al. 2019a, Taylor et al. 2024). These findings provide evidence that neuromodulatory activity can broadly regulate the interaction of functional brain circuitries to effect changes on cognition and behavior.

Building on recent developments in cognitive neuroscience and neurobiology, we propose that modulation by the VTA and the LC is associated with the expression of distinct motivational states represented by distinct neural contexts that facilitate diverging memory outcomes. Specifically, we posit that VTA modulation preferentially engages functional circuitries involving the hippocampus proper and the prefrontal cortex (PFC) to support the formation of flexible relational memory, whereas LC modulation preferentially engages sensory cortices,

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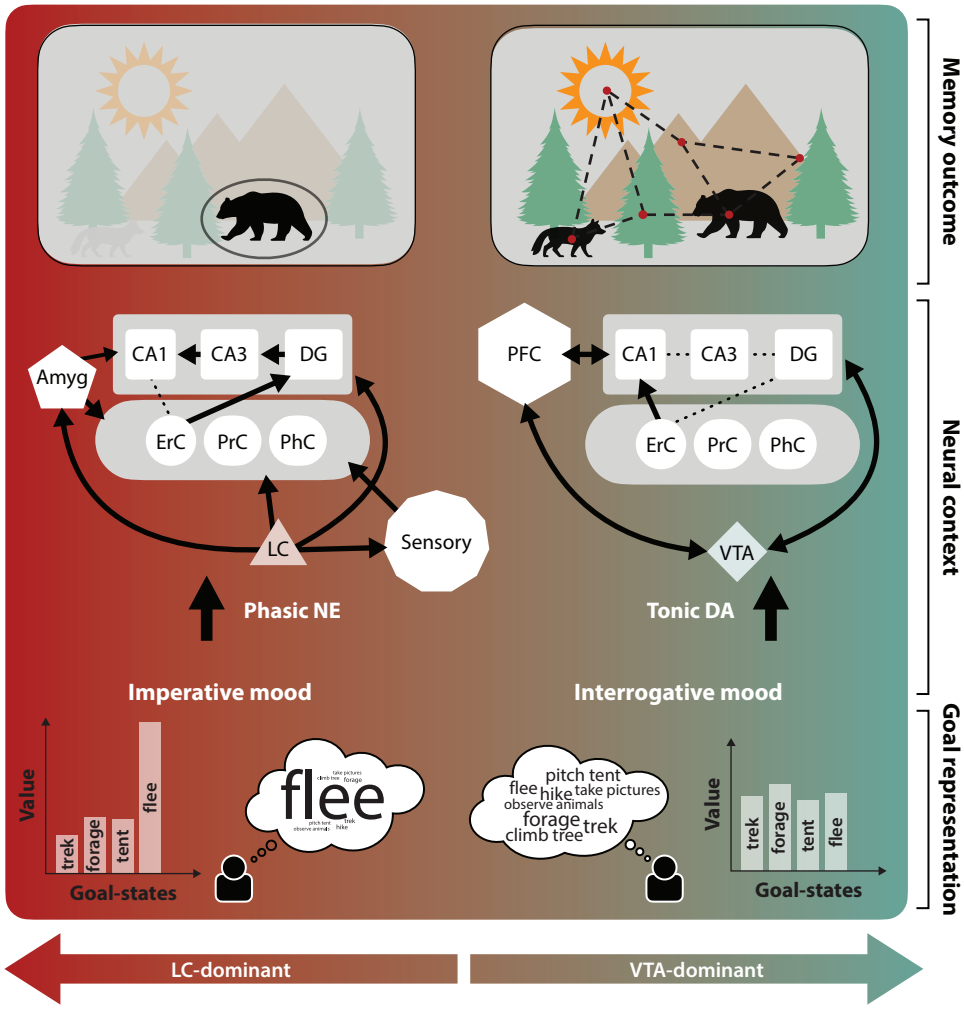


Figure 1

Schematic depiction of how distinct motivational states can drive different modes of information processing and memory formation. Under the imperative mood, in which motivation is driven by a single highly salient goal-state (e.g., fleeing from a bear), phasic NE from the LC promotes a neural context involving the LC, amygdala, neocortical medial temporal lobe (ErC, PrC, and PhC), and sensory cortices, and it forms a unitized memory for the salient goal-relevant item (e.g., the bear). In contrast, under the interrogative mood, motivation is supported by multiple goal-states (e.g., hiking, foraging, trekking), and tonic DA from the VTA promotes a neural context involving the VTA, PFC, and hippocampus (CA1, CA3, DG) to form context-rich relational memories. Abbreviations: Amyg, amygdala; CA1, cornu ammonis area 1; CA3, cornu ammonis area 3; DA, dopamine; DG, dentate gyrus; ErC, entorhinal cortex; LC, locus coeruleus; NE, noradrenaline; PFC, prefrontal cortex; PhC, parahippocampal cortex; PrC, perirhinal cortex; VTA, ventral tegmental area.

the amygdala, and regions in the MTL cortex to support the formation of goal-focused memories (see **Figure 1**).

In the following section, we examine how VTA and LC activity can drive distinct information processing modes through the local modulation of hippocampal functions and also through the coordination of network activities across different brain regions.

MOTIVATION TO ADAPT: VENTRAL TEGMENTAL AREA NEUROMODULATION SUPPORTS INTERROGATION OF VALUE DISTRIBUTIONS AND CONNECTIONS IN ORDER TO SUPPORT FUTURE FLEXIBILITY

Dopaminergic projections from the VTA are predominantly organized along two major pathways: the mesolimbic and the mesocortical pathway. The mesolimbic pathway connects the VTA to the striatum and the hippocampus, while the mesocortical pathway connects the VTA to regions in the PFC. Here, we briefly examine the role of dopamine in the regulation of motivation before discussing how the expression of motivational state supported by VTA neuromodulation can facilitate the formation of associative memory and relational structures.

Motivation Is Regulated by Phasic and Tonic Dopaminergic Modulation

Projections from the mesolimbic circuits play a pivotal role in supporting value learning and the expression of motivated behaviors. Although dopamine is often labeled as the pleasure molecule in popular media, there is a substantial body of work showing that dopamine is not a key contributor to the hedonic experience of reward consumption but is instead crucial for motivating behavior toward the pursuit of goals (Berridge & Robinson 1998, Salamone & Correa 2012). Studies using pharmacology and lesions have demonstrated a clear dissociation between liking, corresponding to the hedonic experience, and wanting, corresponding to the motivational drive (Berridge & Robinson 2016). In rodents, the suppression of dopamine was found to reduce effort in reward seeking but did not disrupt the hedonic reactions during reward consumption (Salamone et al. 2007). Conversely, when dopamine was upregulated, animals exhibited increased reward pursuit without corresponding changes in consumption behavior (Wyvell & Berridge 2000).

Following a reward learning perspective, it has been proposed that dopamine can act as a learning signal for the regulation of reward learning and the reinforcement of actions leading to reward (Bromberg-Martin et al. 2010, Schultz 2007). This account stemmed from studies of associative learning, where the firing of dopamine neurons shifts as cue–reward associations are acquired. Initially, dopamine neurons in the VTA exhibit a transient burst following reward receipt, but as the reward becomes predictable, these neurons cease to respond to the reward and instead fire in response to the reward predictive cue. This shift in phasic firing from outcome to cue is thought to reflect a reinforcement learning mechanism that strengthens the behaviors leading to rewarding outcomes (Schultz et al. 1997). Consistent with this account, greater phasic dopamine activity increased the motivational value of a cue and was also associated with faster, more vigorous responses. Further demonstrating a causal influence, optogenetic stimulation of dopamine neurons, without any actual reward, was sufficient for increasing the motivational value of a cue (Saunders et al. 2018, Sharpe et al. 2017) and for increasing the propensity for repeating a prior behavior (Steinberg et al. 2013, Tsai et al. 2009).

Beyond these fast changes in phasic dopamine activity, increases in tonic dopamine over an extended timescale have also been associated with motivation. It has been suggested that greater availability of rewards in the environment should lead to cumulative increase in residual dopamine, producing higher levels of tonic dopamine. Tonic dopamine has most often been considered as a function of cumulative phasic events (Niv et al. 2005, 2007) or of changes in the baseline levels of spontaneous VTA firing related to the release of inhibition (Floresco et al. 2001, 2003; Lodge & Grace 2006). However, there is also evidence of sustained VTA ramping (Totah et al. 2013) and striatal dopamine release in anticipation of rewards, signaling proximity or progress toward goals (Howe et al. 2013), which may be actively maintained by prefrontal inputs (Ballard et al.

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2011, Lodge 2011, Takahashi et al. 2011; for further discussion, refer to Murty & Adcock 2017, Poh & Adcock 2025). The increase in background levels of tonic dopamine has been proposed to signal the value of effort, increasing motivation when reward availability is high (Niv et al. 2005, 2007). In line with this account, the increase in tonic dopamine has been associated with a greater willingness to exert effort for rewards (Cagniard et al. 2006, Hamid et al. 2016, Westbrook et al. 2020), and, conversely, the depletion of dopamine is associated with greater latencies during reward seeking and a reduced willingness to engage in effortful behaviors (Hosking et al. 2015, Salamone et al. 1994).

Ventral Tegmental Area Dopaminergic Modulation Facilitates Integrative Processing in the Hippocampus

In addition to the role dopamine plays in motivation, evidence from humans and animals also supports a role for dopamine as a critical modulator of long-term memory and neural plasticity in the hippocampus (Edelmann & Lessmann 2018, Frey & Morris 1998, Jay 2003, Lisman & Grace 2005, Lisman et al. 2011, Shohamy & Adcock 2010).

Dopaminergic projections from the VTA to the hippocampus have been well documented in both animals and humans. Anatomical tracing in rodents has shown that dopaminergic neurons from the VTA project directly to the hippocampus (Gasbarri et al. 1994a,b; Samson et al. 1990), and human studies using structural (Elliott et al. 2023) and functional magnetic resonance imaging (MRI) (Kahn & Shohamy 2012) have also identified connections between the VTA and the hippocampus. VTA projections to the hippocampus are not uniformly distributed, and it has been shown that VTA projections to the hippocampus are predominantly in the ventral hippocampus (akin to the anterior hippocampus in humans) (Oades & Halliday 1987). The ventral hippocampus has been suggested to represent more abstract context information than the dorsal hippocampus, and, similarly, the anterior hippocampus in humans has also been shown to integrate information over a longer timescale (Brunec et al. 2018, Kjelstrup et al. 2008, Poppenk et al. 2013, Strange et al. 2014). While the VTA innervates the hippocampus sparsely relative to the dense projections in the ventral striatum, the ablation of VTA has been shown to reduce dopamine levels in the hippocampus (Scatton et al. 1980), and, conversely, stimulation of the VTA has been shown to increase dopamine levels (Rosen et al. 2015). This sparsity, however, suggests that dopaminergic modulation of hippocampus from the VTA may rely predominantly on slower-timescale (tonic) signaling rather than on a temporally precise phasic signal (Murty & Adcock 2017, Poh & Adcock 2025, Shohamy & Adcock 2010). This conjunction of findings suggests the sparse projections from the VTA to the ventral/anterior hippocampus may preferentially enhance the spatial and temporal integration of information over extended timescales.

In addition, these differences in modulatory dynamics can also influence memory outcomes by biasing communication pathways within the hippocampus. The major source of inputs to the hippocampus is the entorhinal cortex (ErC), and this primarily occurs via a direct monosynaptic (ErC → CA1) or an indirect trisynaptic (ErC → dentate gyrus → CA3 → CA1) pathway (Basu & Siegelbaum 2015). Recent computational models have suggested that the two pathways may facilitate distinct modes of information processing, with the monosynaptic pathway facilitating the integration of information and the trisynaptic pathway benefiting the formation of distinct, pattern-separated representations (Schapiro et al. 2017, Sherman et al. 2024).

Early work has shown that the application of dopamine to a bath solution surrounding the hippocampal brain slices can suppress the monosynaptic pathway (thus increasing the influence from the trisynaptic pathway) (Otmakhova & Lisman 1999). This finding is consistent with behavioral

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evidence showing that activation of dopamine neurons can enhance pattern separation during fear conditioning (Zweifel et al. 2011). However, recent work using optogenetics to simulate physiological VTA responses has revealed greater complexity: While tonic activity inhibits the trisynaptic pathway, which should promote integration, higher levels of stimulation simulating phasic firing enhance the trisynaptic pathway, which should promote pattern separation (Rosen et al. 2015). It should be noted that optogenetic stimulation does not establish the transmission of temporally precise phasic VTA signals to the hippocampus, but these findings do suggest that the time courses and response profiles of dopaminergic neuromodulation in the hippocampus can produce distinct processing outcomes, with phasic activity supporting pattern separation and discrimination between representations and tonic activity supporting the formation of associative integrated representations.

Apart from processes that happen during encoding, dopaminergic modulation can also regulate postlearning consolidation processes (Frey & Morris 1998, Redondo & Morris 2011, Rogerson et al. 2014). Consolidation refers to the stabilization of memory representations following learning and can encompass cellular- and systems-level processes (Frankland & Bontempi 2005, McClelland et al. 1995, Wang & Morris 2010), both of which have been shown to be influenced by dopamine. At the cellular level, dopaminergic influence on memory is well characterized by the synaptic tag and capture account (Frey & Morris 1997). In this model, a strong stimulation that results in dopamine release can increase the likelihood of long-term potentiation (LTP) for weak stimulations that occurred in close temporal proximity, resulting in persistent memory trace for both the strong and weak stimulation. This has been suggested as a mechanism for understanding how motivationally salient experiences can enhance memory of other neutral events, and the behavioral predictions of this account are also well supported by evidence from behavioral tagging studies showing both retroactive and proactive memory enhancement for neutral events that surround a motivationally salient event (refer to Dunsmoor et al. 2022 for detailed discussions). These findings suggest that dopaminergic modulation of the hippocampus can have temporally extended effects on memory formation that go beyond the initial encoding event.

Functional Interactions Between the Ventral Tegmental Area and Hippocampus Support Memory Formation

Beyond local modulation of hippocampal functions at the cellular level, the influence of VTA activation on hippocampal-dependent memory has also been demonstrated at a macroscale that is observable with fMRI.

Studies in humans examining motivational influence on memory have primarily focused on the influence of reward motivation. One of the commonly used experimental procedures in the study of reward motivation is the monetary incentivized encoding (MIE) task (Adcock et al. 2006). In the MIE, participants are shown a reward cue indicating the value of an upcoming neutral image and are instructed that they will earn that reward if they successfully remember the image later. Using fMRI, it was shown that following high-reward cues and prior to stimulus onset, greater VTA activation predicted better memory for the upcoming stimulus. Better memory was also associated with increased functional connectivity between the VTA and the hippocampus in this anticipatory interval (Adcock et al. 2006).

Apart from extrinsic motivations (e.g., monetary rewards), recent studies have also begun investigations into the mnemonic influence of intrinsic motivations such as curiosity. Studies using a trivia quiz task have shown that questions eliciting high curiosity were associated with better memory for their associated answers (Kang et al. 2009). In addition, high curiosity also triggered

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greater activation in the VTA and increased functional connectivity between the VTA and hippocampus, similar to that seen during the anticipation of monetary rewards (Gruber et al. 2014, Poh et al. 2022). This increase in VTA–hippocampus connectivity during curiosity was not only associated with improved memory for the trivia answer but also associated with memory for unrelated information that was presented at the same time (Gruber et al. 2014), suggestive of a VTA-modulated learning-state. Recent work using multivariate pattern analysis during a trivia question-and-answer paradigm has shown that VTA activation following the question was associated with the instantiation of a hippocampal state that enhanced binding of the trivia question and its associated answer in memory, completing the cascade from VTA activation to hippocampal memory enhancement (Poh et al. 2022).

Ventral Tegmental Area Activation Supports the Formation of Integrated Representations

The ability to form associations between individual experiences is fundamental for the assimilation of new knowledge and for the abstraction of commonalities between experiences. This ability to abstract common relational structures is thought to be the basis for schema formation, enabling representational flexibility for generalization and inference (Gilboa & Marlatte 2017, Schlichting & Preston 2015, Whittington et al. 2020).

In studies of associative learning, it has been shown that coactivation of the VTA together with the hippocampus is related to subsequent ability to generalize the learned relational structures to newly encountered information (Shohamy & Wagner 2008), and this ability to infer relational structures has been shown to be dependent on the formation of abstract representations in both the hippocampus and the PFC (Bernardi et al. 2020, Morton et al. 2020). While the precise mechanisms of such relational learning remain to be investigated, we posit that, beyond dopaminergic effects in the hippocampus, VTA regulation of hippocampal networks may play a role.

First, dopaminergic modulation of the hippocampus and the PFC has been shown to increase neural excitability and the stability of neural representations (Durstewitz et al. 1999, Kempadoo et al. 2016). This increase in excitability and stability can potentially increase the overlap between neural ensembles that are recruited during the encoding of different events. This increase in overlap suggests that the activation of one memory would increase the likelihood of an overlapping memory to also be reactivated, facilitating the integration of these distinct events (Cai et al. 2016, Chowdhury et al. 2022, Mau et al. 2020).

Second, dopamine may also facilitate integration and abstraction through the modulation of offline consolidation. Periods of sleep have been shown to enhance generalization across memories, and this is thought to be supported by the replay of memories during memory consolidation (Diekelmann & Born 2010, Lewis & Durrant 2011, Marr 1971, Wilson & McNaughton 1994). In rodents, offline hippocampal replay has been shown to happen in conjunction with the firing of VTA dopamine neurons (Gomperts et al. 2015, Valdés et al. 2015), and a study using optogenetics has shown that the stimulation of VTA neurons during learning was sufficient to increase the rate of hippocampal replay (McNamara et al. 2014). In this manner, the VTA may function by tagging information for replay and facilitating its integration during offline consolidation (Murty et al. 2017b).

To summarize, the evidence reviewed above supports the notion of a motivational state, supported by functional circuitry involving the VTA, hippocampus, and PFC, that can promote the formation of relational memory and schematic knowledge. VTA modulation of memory occurs across multiple timescales, supported by processes involving both cellular- and systems-level mechanisms. Next, we turn our attention to the LC.

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MOTIVATION TO ACT: LOCUS COERULEUS–AMYGDALA NEUROMODULATION SUPPORTS GOAL-DIRECTED INFORMATION PROCESSING AND CREATION OF IMPERATIVES

The noradrenergic system, centered around the LC, is known to have diffuse projection across the brain supporting the global signaling of arousal (Berridge & Waterhouse 2003, Sara & Bouret 2012) and the facilitation of brain state transitions (Bouret & Sara 2005, Shine et al. 2018, Wainstein et al. 2022). These properties enable rapid brain state transitions in response to motivationally salient stimuli in the environment. Phasic activation of the LC, in particular, has been proposed to facilitate information processing in favor of optimizing task performance (Aston-Jones & Cohen 2005).

As studies examining noradrenergic modulation of memory have largely focused on the amygdala, a major target of LC projections (Fallon et al. 1978, Foote et al. 1983), the following discussion includes studies on the modulatory role of the amygdala.

Noradrenergic Modulation of Threat Motivation

While the noradrenergic system has been primarily implicated in the regulation of arousal, research is paying increasing attention to its role in driving motivation (Hofmeister & Sterpenich 2015, Jahn et al. 2018, Sara & Bouret 2012). Similar to the anticipatory firing of dopamine neurons in response to motivational cues, noradrenergic neurons in the LC have been observed to exhibit phasic firing in relation to reward cues, and this firing is correlated with the magnitude of the expected reward (Bouret & Richmond 2009). In addition, the activity of LC neurons has been shown to increase in response to the amount of anticipated effort (Varazzani et al. 2015), and pharmacological suppression of noradrenaline was found to reduce effort exertion (Jahn et al. 2018).

Noradrenergic modulation of the amygdala has also been shown to be necessary for the expression of avoidance behavior (Davis 1992) and in punishment-/threat-motivated learning (Falls & Davis 1995, LeDoux et al. 1988, Xue et al. 2012). Studies of threat-motivated learning have mostly used fear conditioning, where a neutral cue is contingently paired with an aversive stimulus. Following multiple pairings, an association would form between the neutral cue and the aversive stimulus, and the cue would then be sufficient to elicit avoidance behavior. Lesion studies have shown that the amygdala is necessary for such fear learning, and animals with amygdala lesions fail to express threat-motivated behaviors (e.g., freezing) in response to cues that predict an upcoming aversive stimulus (Fanselow & LeDoux 1999, LeDoux 2003). Specifically demonstrating a role of LC noradrenergic projections to the amygdala in threat-motivated learning, it was shown that activation and inhibition of LC terminals in the central amygdala increased and reduced freezing behaviors, respectively, and this modulation was dependent on noradrenergic receptor availability (Gu et al. 2020).

The amygdala has also been shown to regulate appetitive motivation. Stimulation of the central amygdala has been shown to narrow the focus of motivation toward a specific reward target at the expense of all other available incentives (Robinson et al. 2014). When excitation of the central amygdala is paired with a specific target, rodents exhibit compulsive motivation and are willing to endure foot shocks for the target, even when other reward options are available (Tom et al. 2019). In other words, the stimulation of the central amygdala creates an imperative. This evidence has been proposed to suggest a more generalized role of the central amygdala in the attribution of incentive salience (Warlow & Berridge 2021). As the regulation of incentive salience has also been shown to be dependent on dopaminergic inputs from the VTA to the amygdala, it has been suggested that the central amygdala may integrate multiple sources of inputs to direct the focus of motivation to specific targets (Warlow & Berridge 2021). In conjunction, these findings

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demonstrate a role for noradrenergic modulation of motivation, particularly in the expression of threat-related motivations.

Locus Coeruleus Noradrenergic Modulation Facilitates Sparse Representations in the Medial Temporal Lobe

Noradrenaline is also a key modulator of synaptic plasticity in the hippocampus (Palacios-Filardo & Mellor 2019, Sara 2009, Tully & Bolshakov 2010). Similar to dopamine, noradrenaline has been shown to modulate neural excitability (Stanton & Sarvey 1985), modifying the threshold for LTP (Katsuki et al. 1997) and also supporting the maintenance of LTP (Maity et al. 2015).

Anatomical tracing in rodents has shown that noradrenergic neurons from the LC project diffusely across the hippocampus (Haring & Davis 1985). Contrasting with the VTA innervation, which is biased toward the ventral hippocampus, the LC has been shown to exhibit denser innervation of the dorsal hippocampus (Hansen 2017, Takeuchi et al. 2016). This has also been demonstrated with chemogenetic stimulation, whereby LC stimulation increases functional connectivity with the dorsal hippocampus in rodents (akin to the posterior hippocampus in humans) (Oyarzabal et al. 2022). In rodents, place fields in the dorsal hippocampus are known to be smaller and exhibit greater stability; in humans, the posterior hippocampus has been shown to exhibit greater sensitivity to sensory information (Strange et al. 2014). These findings collectively suggest that the posterior hippocampus may represent spatial and sensory information with greater fidelity and precision.

LC projections to the hippocampus have been shown to vary across hippocampal subfields, however. The dentate gyrus, a region implicated in the formation of sparse, pattern-separated representations, is densely innervated by the LC (Blackstad 1956, Zhang et al. 2025), and studies have consistently demonstrated noradrenergic influence on LTP within the dentate gyrus (Harley 1998). Depletion of noradrenaline has been shown to reduce spiking activity in the dentate gyrus, while phasic activation of the LC produced a prolonged potentiation of dentate gyrus response (Harley & Sara 1992). Consistent with the role of the dentate gyrus in pattern separation, it has been shown that a salivary marker of noradrenaline was positively associated with behavioral pattern separation performance (Segal et al. 2012), and a recent fMRI study showed that activation in the LC was associated with impaired temporal order memory, suggestive of greater temporal pattern separation (Clewett et al. 2025).

While these findings are broadly consistent with our proposal that LC modulation supports the formation of discrete unitized memory representations, recent work has shown that chemogenetics and optogenetics stimulation that increase tonic LC activity can also result in greater contextual generalization, suggesting that tonic LC, like tonic VTA, activity modulates memory representations (Seo et al. 2021), as we have described in the previous section. Thus, it is possible that distinct memory outcomes may be dependent on the specific neuromodulatory dynamics, whereby tonic activity may promote integration while phasic activity may promote separation. As such, it may be necessary to consider the conditions in which tonic or phasic activity is evoked (Aston-Jones & Cohen 2005).

In further support of the possibility that distinct neuromodulatory dynamics may bias different processing modes in the hippocampus, recent work has shown that LC can also release dopamine in the hippocampus, and this corelease of dopamine is a critical modulator of memory formation over multiple timescales. LC innervation is also very dense compared to VTA innervation in the hippocampus overall.

Across a series of studies, it was shown that burst optogenetic stimulation of the LC enhanced spatial learning (Kempadoo et al. 2016), facilitated the stability of spatial representation (Wagatsuma et al. 2018), and also enhanced memory retention of precise spatial locations

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(Takeuchi et al. 2016). Critically, these effects were sensitive to the blockade of dopamine receptors but were unaffected by the blockade of adrenoreceptors (Takeuchi et al. 2016, Tse et al. 2023).

For these reasons, we propose that, while it has been natural to attribute phasic dopamine release in the hippocampus to the VTA, where phasic signals are a prominent physiological signature, the primary source of temporally precise dopamine signaling of prediction errors to the hippocampus may be the LC, not the VTA (see also Poh & Adcock 2025). In contrast, we posit that the primary mode of VTA dopamine signaling to the hippocampus occurs on a slower timescale, promoting stability of representations and memory integration to encode an elaborated landscape of value distribution.

Locus Coeruleus Noradrenergic Modulation Enhances Task-Relevant Sensory Processing

Noradrenaline is known to influence signal-to-noise ratio in cortical regions (Aston-Jones & Cohen 2005), and the release of noradrenaline has been shown to enhance sensory inputs via multiple mechanisms, including by increasing sensitivity of cortical neurons, suppression of spontaneous noise, and the sensory gating of irrelevant stimuli (McBurney-Lin et al. 2019).

Studies in rodents have shown that reward motivation can enhance the discrimination of perceptually similar odors, and this reward-related enhancement in sensory discrimination is dependent on noradrenergic modulation (Doucette et al. 2007, Escanilla et al. 2012). Further supporting a causal role, LC stimulation has been shown to enhance target detection during perceptual learning (Martins & Froemke 2015), particularly when the target and distractors are perceptually similar (Rodenkirch et al. 2019), suggestive of higher-fidelity stimulus representations.

Interestingly, the modulation of sensory representations by LC activity also appears to be dependent on neuromodulatory dynamics. Using optogenetic stimulation, it was shown that sensory-evoked cortical responses were enhanced by phasic LC activation but were unaffected by tonic LC activation (Vazey et al. 2018). Optogenetic phasic LC activation also replicated the neural response observed following activation by salient sensory stimuli (Vazey et al. 2018), suggesting that motivationally salient stimuli may enhance task-relevant sensory processing through phasic LC activation.

Locus Coeruleus Activation Facilitates Encoding in the Cortical Medial Temporal Lobe

While fMRI studies examining dopaminergic influence on motivated learning have primarily relied on reward motivation, studies on noradrenergic modulation have typically focused on negatively valenced conditions eliciting high arousal, such as during threat motivation (Clewett et al. 2018). Using a variant of the MIE task where participants could avoid monetary losses by successfully remembering a scene image that was superimposed with distractor objects, it was shown that LC activation was greater when participants experienced greater threat motivation, and greater LC activation was also associated with greater memory selectivity (i.e., remembering the scene but not the distractor object) and greater activation in the parahippocampal cortex (Clewett et al. 2018).

In several other studies, high arousal elicited by stimuli such as emotional faces (Jacobs et al. 2020) and sounds (Gallant et al. 2022) was also associated with greater activation in the LC, and while these studies have also observed parallel memory benefits for the high-arousal conditions, they did not observe a direct association between LC activity and memory performance. While

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this may be due to the lower signal-to-noise ratio in the LC, it is also possible that the LC influence on memory may be mediated by its influence on other brain regions, such as the amygdala.

Amygdala Modulates Item Encoding in the Hippocampus and Cortical Medial Temporal Lobe

The amygdala is a major projection target of the LC (Fallon et al. 1978, Li et al. 2013, Uematsu et al. 2015) and has direct projections to the hippocampus and its surrounding neocortical MTL regions (Kemppainen et al. 2002, Pikkarainen et al. 1999). While the amygdala is known to modulate memory processing in the hippocampus (McGaugh 2004), there is some evidence that modulatory influence from the amygdala may preferentially support memory processing by the neocortical MTL (Paz et al. 2006) while impeding memory processing in the hippocampus (Kim et al. 2001, Roozendaal et al. 2003). In rodents, it has been shown that amygdala lesions selectively impaired familiarity judgment supported by the perirhinal cortex, but they did not impair recollection judgment, which is supported by the hippocampus (Farovik et al. 2011). In addition, stress-induced impairment of hippocampal-dependent memory has also been shown to be alleviated following amygdala lesions (Kim et al. 2001).

Studies in humans have also shown a preferential engagement of memory processing by the neocortical MTL with amygdala activity. During high-arousal encoding events, it has been shown that memory for individual items is enhanced (Cahill & McGaugh 1998), while relational memory is impaired (Bauch et al. 2014, Mather 2007, Murray & Kensinger 2013, Murty et al. 2011). This enhancement of item memory at the expense of relational memory is thought to be modulated by the concurrent increase in amygdala activity alongside reduced hippocampal engagement (Bisby & Burgess 2017). Using a threat-motivated variant of the MIE task in which participants were able to avoid a static shock with successful encoding, it was shown that punishment motivation enhanced memory via a distinct neural circuitry than the one observed during reward-motivated encoding (Murty et al. 2012). While reward motivation was associated with the engagement of a VTA–hippocampus circuitry (Adcock et al. 2006), threat-motivated encoding was associated with the engagement of amygdala–cortical MTL circuitry (Murty et al. 2012). When reward- and threat-related motivation were directly compared in an incidental encoding task, it was shown that reward facilitated activation to surprising events in the hippocampus, while threat facilitated activation in the neocortical MTL (Murty et al. 2016).

In summary, we discussed above how a motivational state supported by functional circuitry involving the LC, amygdala, MTL cortex, and sensory regions can promote the formation of sparse item memory representations. The selective enhancement of item-based memory may be supported by gain-tuning during sensory perception and also through the biased engagement of neocortical MTL.

WHAT DRIVES DIFFERENT NEUROMODULATORY ENGAGEMENT?

We have discussed how neuromodulatory engagement by the VTA and the LC can support distinct motivational states to influence memory formation. However, we have yet to consider what are the contextual factors that would determine the engagement of the VTA or of the LC. In this section, we consider two possible ways that neuromodulatory activity from the VTA and the LC might be regulated.

Dissociable Influence of Value and Arousal

As described in the previous sections, the VTA has been primarily associated with signaling of value, while the LC has been associated with the signaling of arousal. This raises the possibility

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that neuromodulatory engagement is driven by two distinct dimensions. The VTA, through its dopaminergic projections to regions such as the nucleus accumbens and the PFC, plays a central role in guiding behavior toward stimuli with high expected value (Berridge & Robinson 1998, Schultz 2016). In contrast, the LC, as the primary source of norepinephrine, modulates arousal and attention in response to the salience of stimuli regardless of their valence (Aston-Jones & Cohen 2005, Sara 2009). This functional dissociation suggests that the VTA may prioritize the motivational significance of stimuli based on their value, while the LC regulates the level of arousal elicited by the stimuli.

While this distinction would be consistent with the established role of the VTA and the LC, the two systems are more likely to operate interactively in ecological settings. Cues that are indicative of high value are also more likely to elicit high arousal, concurrently engaging both the VTA and the LC. However, it has also been suggested that the influence of arousal on cognition might follow a nonmonotonic function wherein performance peaks with moderate levels of arousal and declines with further increases in arousal (Berridge 2008, Yerkes & Dodson 1908). It is currently unclear how this translates to the activity of neuromodulators and how the involvement of adrenal stress hormones would further impact downstream processing. Future investigations would also need to further clarify how reciprocal interactions between the VTA and the LC function across different levels of activity and whether these interactions are coordinated by distinct temporal dynamics (i.e., tonic versus phasic).

Distinct Neuromodulatory Dynamics Represent Distribution of Goal-State Values

In our consideration of VTA and LC neuromodulatory activity as value signals that give rise to motivation, we have primarily based our consideration on value estimation from a single goal-state. While this may be true within a constrained experimental setting, it is unlikely in natural environments, where we not only have to direct our energy toward a specific goal but also have to decide which goal should be pursued. For example, when sitting in front of your computer, you may decide to binge on your favorite Netflix series, scroll through the endless threads on Reddit, start working on that paper you have been procrastinating on, or you might just decide to step away from the computer and head out for a run. To determine which of these goals should be prioritized, the value of these different goal-states must be concurrently represented, allowing for comparison and selection among the available options. Here, we speculate that the representation of value distributions may determine the specific neuromodulatory engagement and thus the predominant tone of modulation in MTL.

Representation of a goal landscape is required in order for the brain to compare the value of different goals and decide which one to pursue. For example, if you are deciding between studying for an exam and watching TV, the brain weighs the value of each option, and the goal with the highest relative value becomes the most salient. This salience determines the selection of goals and biases how physical or cognitive effort is allocated to attain these goal-states.

When the mean value of active goal-states is high, and the distribution is relatively uniform (i.e., no salient goals), high tonic VTA activity would promote interrogative motivational mood, supporting broad integrative processing that enables flexible adaptation to the different goal-states. In contrast, when a high mean value is driven by a sharp peak in the value distribution, either across goals or over time, as seen in phasic bursts signaling prediction errors, arousal-related phasic LC activity would promote imperative motivational mood, that is, focused information that is directed toward resolution of the salient goal (**Figure 1**). However, these neuromodulatory systems should also dynamically interact, adapting to changes in information-processing demands—for example,

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when a perceived threat is determined to be harmless (e.g., realizing that the ambiguous shape by your window is a vine and not a snake) or when the set of active goals changes (e.g., realizing that the paper is due tomorrow).

The biological plausibility of such distributional coding is supported by recent findings showing that VTA dopamine neurons exhibit heterogeneity in their coding of reward prediction errors, providing a mechanism for the simultaneous encoding of multiple future outcomes (Dabney et al. 2020). In addition, there is also increasing evidence that VTA dopamine neurons exhibit a wide range of sensitivities to different environmental variables (Engelhard et al. 2019, Keiflin & Janak 2017, Lee et al. 2024), and these functional clusters can be anatomically organized (Engel et al. 2024, Engelhard et al. 2019). Thus, downstream targets may receive different sources of information from VTA dopamine neurons that enable flexible coding of multiple goal-states.

In addition, the average value of active goal-states may be represented by tonic dopamine activity (both spontaneous, related to disinhibition, and actively sustained as in anticipatory ramping; see Hamid et al. 2016; Howe et al. 2013; Mohebi et al. 2019; Niv et al. 2005, 2007; Totah et al. 2013), while the saliency of goals may be signaled by phasic firing of VTA and LC neurons. It has been shown that reciprocal connections between the LC and the VTA are differentially modulated by tonic and phasic activity (Isingrini et al. 2016, Mejias-Aponte 2016). This interconnection may give rise to dynamics that perpetuate a constant transition between the different processing modes.

By focusing on the coding of a value distribution rather than a singular goal, we emphasize the importance of context in determining the specific influence of motivation on learning and memory formation. While such distributional coding is biologically plausible, it remains speculative and would thus require further investigations.

Interacting Influence of the Ventral Tegmental Area and Locus Coeruleus on Hippocampal Functions: Cooperation or Competition?

Amid ongoing discussions attempting to dissociate the influence of LC and VTA on hippocampal functions, there is accumulating evidence suggestive of mutual regulation between the LC and VTA via reciprocal anatomical connections (Park et al. 2017, Parker et al. 2024, Ratna et al. 2023). Functionally, recent work has shown that glutamatergic projections from the VTA increased the responsivity of LC noradrenergic neurons to aversive stimuli (Parker et al. 2024). The activation of LC noradrenergic neurons, on the other hand, led to increased excitability in VTA dopamine neurons during exposure to novelty (Fois et al. 2022), suggesting mutual potentiation.

In a recent study that directly examines the influence of VTA and LC on hippocampal synaptic plasticity, it was shown that stimulation of the VTA and the LC differentially promoted LTP and long-term depression (LTD), respectively (Hagena & Manahan-Vaughan 2025). While this appears to suggest a competitive relationship between VTA and LC modulation, it should be noted that the observed effect was frequency dependent, with phasic VTA stimulation facilitating LTP and tonic LC stimulation facilitating LTD (Hagena & Manahan-Vaughan 2025).

These findings highlight the importance of considering the temporal dynamics of neuromodulatory activity, in addition to considering anatomical projections. While such dynamics are not easily observed with the noninvasive methods that are used in human studies, such as fMRI, we have demonstrated distinct temporal components of midbrain VTA BOLD signal by modeling the signal transforms in specific afferent systems (Murty et al. 2017a). Using this approach, we modeled PFC activation by goals transmitted via monosynaptic excitation and hippocampal activation by novel items transmitted via multisynaptic disinhibition; we found they distinctly predicted transient and sustained components, respectively, of VTA activation (Murty et al. 2017a). However,

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it is unclear if tonic and phasic activity would elicit distinct brain-wide neural signatures that are observable as differences in BOLD signal. One possibility would be to generate theoretical predictions that are observable at a macro scale (Poh et al. 2022) or to use computational models to extrapolate how such differences in neuromodulatory activity would translate to variations that are observable with BOLD (Zhang et al. 2024)—for example, differential network effects.

In summary, these findings suggest that an ecological understanding of neuromodulatory functions will require further consideration of their interactions, including understanding how distinct temporal dynamics can produce dissociable memory outcomes.

BEYOND THE LABORATORY: IMPLICATIONS FOR THE CLASSROOM AND THE CLINIC

Here, we highlighted that motivational states supported by distinct neural contexts can promote different learning outcomes. Specifically, we posited that the engagement of the VTA would promote associative memory and the formation of relational structures, while the engagement of the LC would promote unitized goal-relevant memory representations.

Engineering Learning Contexts for Different Memory Outcomes

In considering the application of our framework to education, it is essential to understand that we do not consider either motivational state as being generally superior for learning. Rather, we believe that effective learning requires the combination of different motivational states across the different stages of learning. For example, when learning about a new topic, there might be a greater demand for memorization of specific facts and details, which would be facilitated by a LC-driven imperative motivational state. As one acquires the necessary foundations, however, there will be a greater need for an understanding of the connections between different pieces of information and for the ability to make flexible inferences based on existing knowledge. This would then be better supported by a VTA-driven interrogative motivation and learning process.

A central question, then, is how we can create and shape learning contexts that support the appropriate motivational states. In our proposal, we highlight the importance of goal saliency and distributed value as determinants of specific neuromodulatory engagement. In formal education, the use of testing is an important feedback mechanism that enables evaluation of learning outcomes, but it can also be a highly salient goal, especially in the case of high-stakes examinations. In this manner, learning contexts that surround a high-stakes examination may facilitate the memorization of isolated details or gist while compromising the ability for integration and abstraction. In contrast, while the absence of a salient goal might facilitate initial exploratory learning, its perpetuation could result in a breadth of knowledge devoid of depth. One potential way to structure the learning context, then, is through the embedding of intermittent low-stakes goals (e.g., classroom quizzes) that are salient but still leave room for the channeling of resources toward exploration of other goals.

Narrative framing of learning goals may also be a simple and effective way to evoke different motivational states. Recent work by our group has shown that instructed motivational states can bias information-seeking behaviors and influence learning. By using different cover stories for the same reinforcement learning task (i.e., pretending to be a thief either executing or planning a heist), it was shown that the narrative framings induced different motivational states and led to decisions that prioritized either the immediate reward or the reduction of uncertainty (Sinclair et al. 2023). This suggests that the framing of learning goals can bias motivational states to influence learning outcomes (e.g., "You need to learn this because it will be tested" versus "You need to

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learn this because you will need to do it again" or "because it will be helpful for your life goals"), which may be an effective tool that can be integrated within classroom instructions.

However, as demonstrated by the exceptions to the valence effects cited above, distributions of value in goal landscapes are in the eye of the beholder. In addition to engineering the environment to match motivational states to learning goals, we also propose developing skills for self-regulation of motivational states, to empower both students and patients in therapeutic settings with tools for enhancing their own cognition and learning.

Motivating Learning in the Clinic

By focusing on how distinct motivational contexts can promote different learning outcomes, this work provides a framework for the design of targeted therapies to support adaptive learning. In addition to the extrinsic aids described above, we should consider how to convey to learners in both academic and clinical settings the belief that motivation can be regulated and the skills to do so. Our group has demonstrated that adults given neurofeedback about VTA activation using fMRI can learn to sustain activation of VTA via mental simulation (MacInnes et al. 2016), and former participants to the study report using these techniques in daily life. Less heroically, we can teach students and patients the ability to manipulate internalized value distribution landscapes as strategic tools, shifting flexibly from LC-driven imperative motivation to VTA-driven interrogative motivation in response to the current learning demands.

CONCLUSIONS

Motivation is critical in shaping how we perceive and encode information in the world, enabling adaptive behavior in response to changing environmental demands. By highlighting how engagement of the VTA and the LC can instantiate distinct neural contexts underlying motivational states, we provide a framework for understanding divergent memory outcomes that arise from different motivational states despite objectively identical incentives. The VTA, through its interactions with the hippocampus and regions in the PFC, facilitates flexible associative learning that supports relational memory and abstraction. In contrast, the LC, through its interactions with the amygdala, the MTL, and sensory cortices, enhances sensory perception and the encoding of goal-relevant information.

The proposed framework aims to advance our understanding of the neural mechanisms underlying motivated memory and also to inform practices in education and clinical settings. By tailoring the learning context to evoke specific motivational states, educators can optimize memory formation to adapt to different learning goals. By offering students and patients skills and knowledge to shift between motivational states, we can put the power to tune their brains for learning into their own hands.

By characterizing the potential mechanisms that bridge the gap between motivation and memory, this review highlights the importance of neuromodulatory systems in shaping adaptive cognition and behavior, offering a foundation for the translation of basic science to real-world applications.

SUMMARY POINTS

1. Motivations can act as a filter that determines what information is processed and preferentially remembered, and how.

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2. Neuromodulatory systems underlying motivation can create distinct neural contexts that shape memory outcomes by coordinating brain-wide interactions to instantiate different motivational states.
3. We propose that motivational states can be classified by their motivational mood as interrogative (exploratory, uncertainty resolving) or imperative (urgent, goal focused).
4. These motivational moods are characterized by differential engagement of neuromodulatory systems that support different modes of information processing and produce distinct memory outcomes.
5. Tonic increases in dopaminergic activity in the ventral tegmental area (VTA) facilitate the formation of flexible relational memory through interactions with the hippocampus and regions in the prefrontal cortex (interrogative mood).
6. Phasic increases in noradrenergic activity in locus coeruleus (LC) facilitate the formation of unitized item memories through interactions with the amygdala, the neocortical medial temporal lobe, and sensory cortices (imperative mood).
7. To date, all evidence for VTA modulation of the hippocampus implicates tonic, rather than temporally precise phasic, dopamine signaling.
8. Understanding how different neuromodulatory systems are preferentially engaged can help shape both learning contexts and learning skills to optimize pedagogy and clinical interventions.

FUTURE ISSUES

1. How do tonic and phasic modes of neuromodulation interact to shape memory formation over different timescales, and what are the specific neural mechanisms that govern the transitions between these modes?
2. Neuromodulatory regulation has been shown to influence information-seeking decisions; how do VTA and LC activity influence the balance between exploration and exploitation during information seeking, and how does this translate to differences in downstream decision-making?
3. There is increasing evidence that the decline of neuromodulatory functioning with age is associated with the development of age-related memory and cognitive impairments; how do these age-related changes in neuromodulatory systems impact the interaction between motivation and memory in older adults?
4. Deficits in motivation and memory are prevalent across different neuropsychiatric and neurodegenerative disorders; can noninvasive regulation of neuromodulatory systems (e.g., with neurofeedback/biofeedback) remediate impairments in motivation and memory?
5. With the growing adoption of artificial intelligence in educational technologies, can we develop personalized learning that harnesses different motivational states to optimize learning at different stages and to facilitate learning across the lifespan?

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6. A major challenge in public health initiatives is identifying appropriate messaging that is memorable and actionable; can we harness motivational framing to develop more effective lifestyle interventions and education campaigns?

DISCLOSURE STATEMENT

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