

Dopamine and adaptive memory

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Memory is essential to adaptive behavior because it allows past experience to guide choices. Emerging findings indicate that the neurotransmitter dopamine, which signals motivationally important events, also modulates the hippocampus, a crucial brain system for long-term memory. Here we review recent evidence that highlights multiple mechanisms whereby dopamine biases memory towards events that are of motivational significance. These effects take place over a variety of timescales, permitting both expectations and outcomes to influence memory. Thus, dopamine ensures that memories are relevant and accessible for future adaptive behavior, a concept we refer to as ‘adaptive memory’. Understanding adaptive memory at biological and psychological levels helps to resolve a fundamental challenge in memory research: explaining what is remembered, and why.

Introduction

Memory is essential to behavior, enabling organisms to draw on past experience to improve choices and actions. Much research has focused on how the hippocampus builds accurate memory for past events. Emerging findings indicate that the neurotransmitter dopamine, known to play a key role in motivated behavior, has a direct impact on memory formation in the hippocampus. Here, we review this emerging literature that demonstrates that interactions between midbrain dopamine regions and the hippocampus promote memory for episodes that are rewarding and novel and build memory representations well-suited to guide later choices. By integrating findings from both human and animal research, we argue for a framework in which dopamine helps create enriched mnemonic representations of the environment to support adaptive behavior.

The hippocampus: Creating building blocks for memory-guided behavior

After decades of research, our understanding of the brain mechanisms that contribute to long-term memory for events or episodes – often referred to as episodic memory – has evolved significantly. Episodic memories are formed rapidly (after even a single experience) and are rich in contextual details. Episodic memories are also thought to be relational: they encode relationships between multiple elements of an event [1,2]. Extensive converging evidence indicates that episodic memory depends crucially on the hippocampus and surrounding medial temporal lobe (MTL) cortices [1,3,4].

In humans, a common framework for understanding the role of the hippocampus in memory formation originated with neuropsychological studies in patients ([5]; for a review see [6]). This research demonstrated that the hippocampus supports a specialized system for creating episodic memories of everyday events, and that this episodic system is distinct and dissociable from brain systems responsible for other kinds of memory (e.g. emotional memory, habit learning, etc. [6]).

A key function of memory, however, is presumably to improve choices and actions. Indeed, research in animals has always necessarily investigated memory in the service of rewards and goal-directed behaviors: prototypical paradigms for testing hippocampal memories in animals are remembering where in a maze or underneath which object a food reward can be found. In such situations, neurons in the hippocampus respond to the received reward, and not only to the location or object that predict it [7]. Further, while rats navigate a maze in search of rewards, anticipatory hippocampal responses occur at key decision points and before goal-directed movements [8].

Recent work in humans has similarly begun to demonstrate relationships between episodic memory and future goal-directed behavior. First, in addition to its role in remembering the past, the MTL also supports the ability to imagine specific episodes in the future [9,10], with direct implications for decision making [11]. Second, because of their relational structure, episodic memories are flexible: they are constructed in a manner that allows relevant elements of a past event to be brought to bear as needed to guide future behavior [1,12].

Together, these findings emphasize a role for the hippocampus that extends beyond memory for objects and locations, to include motivated, goal-directed behavior. Below we describe evidence demonstrating that episodic memories are modulated by the potential relevance of events to later behavior and by the motivational state of the organism, as well as evidence that the neurotransmitter dopamine plays a key role in this process.

Brain systems for learning and motivation

Converging evidence indicates that the release of dopamine signals motivationally important events and behaviors. Key findings come from a series of seminal neurophysiology studies of dopamine-containing midbrain neurons in primates receiving reward (for a review see [13]). In these studies, a monkey receives a reward (e.g. juice), which is predicted by a cue (e.g. a tone). Dopamine neurons respond with a burst of activity – often referred to as a phasic response – when the monkey unexpectedly receives a reward. Crucially, however, the response is

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Box 1. Integrating methods to determine the role of dopamine in memory

fMRI studies linking midbrain or striatal activation and memory in humans have been interpreted as suggesting an important role for dopamine in memory. However, it is important to note that with standard imaging parameters caution is warranted when interpreting BOLD signals from brainstem nuclei [51,66]. Furthermore, fMRI measures changes in BOLD across states and does not directly measure changes in dopamine levels (for review see [67] and [68]). A current challenge among researchers is thus to gain direct information about how changes in dopamine levels affect memory in humans. Several approaches to addressing this question have been developed and applied to other cognitive domains, suggesting their suitability for advancing knowledge regarding the direct role of dopamine in long-term episodic memory. These approaches include:

- **Genetics.** Individual variability in genes affecting dopamine transmission permits correlations between genetically-determined dopamine availability and behavioral and neural processes linked to memory (e.g. [42,69]).
- **Dopamine deficiency in patients.** In populations who are known to have dopamine depletion, such as Parkinson's disease (and to a lesser extent normal aging), studying memory on and off dopaminergic medications reveals robust effects on specific learning processes (e.g. [34,70]).
- **PET imaging.** PET has been used to relate dopamine receptor density to cognitive function [45]. In addition, the displacement of radioactive ligands from dopamine receptors following a manipulation can be used as an index of endogenous dopamine release [71], allowing researchers to validate the use of midbrain BOLD activation as a proxy [37].
- **Pharmacological manipulation.** In healthy individuals and patients, drugs are available that increase dopamine receptor activation or pools of available dopamine, or counter these effects (e.g. [72]).
- **Pharmacological fMRI.** Dopamine agonists and antagonists have also been used to examine changes to BOLD activation during cognitive processes (for review see [68]).

not simply a report of reward: when reward is entirely expected based on prior experience, the neurons respond not to the reward but to the predictive cue instead. Furthermore, when reward is expected but fails to arrive, the neurons are briefly inhibited below their baseline response rates. Thus, the phasic responses of dopamine neurons seem to report the difference between observed and expected reward – a so-called reward prediction error (for a review see [13] and Figure 1). Computational models have emphasized the importance of such reward prediction errors in driving learning, and in the past several years, functional magnetic resonance imaging (fMRI) has revealed similar findings in humans engaged in a variety of reward-related behaviors (for a review see [14]). Together, these studies demonstrate that midbrain dopamine neurons and their striatal targets play a central role both in responding to rewards and in learning to predict them.

The role of dopamine in motivated behavior, however, goes beyond putative prediction errors. Recent evidence indicates that dopamine neurons respond not only to reward and its expectation, but also to novel and surprising events, including punishment ([15]; for parallels in human neuroimaging see [16] and [17]). Further, dopamine has long been known to relate to the amount of effort exerted towards obtaining rewards (also related to 'wanting' and to 'incentive salience') and is implicated broadly in behavioral vigor [18–22]. Notably, it has been suggested that the

neuronal mechanisms underlying these processes could be related to sustained changes in dopamine release – referred to as tonic responses – and not to the temporally-specific phasic bursts [21].

A comprehensive characterization of the role of dopamine in behavior is still the subject of active study. In particular, there is continued debate about whether phasic responses do indeed reflect reward prediction errors [19,23]. What is clear, however, is that dopamine neurons provide multiple mechanisms for signaling the occurrence and expectation of events that are of motivational significance, and for sending these signals to a selective set of target regions to coordinate motivation to learn about, and ultimately obtain, goals. Thus, dopaminergic signals provide a potential mechanism for making the contents of memory motivationally relevant. A key question is whether, and how, this happens.

Dopamine modulates hippocampal memories

Much of the evidence for the role of dopamine in modulating hippocampal function comes from anatomical and electrophysiological studies in animals. Midbrain dopamine neurons project directly to the hippocampus and to the surrounding MTL cortices [24,25] (Figure 2; see Table I in Box 2). Indeed, in animals, dopamine seems to be essential for hippocampal long-term memory. Studies in animals indicate that dopamine acting at hippocampal synapses is a necessary precursor not only for long-term potentiation (LTP), a prime cellular model of learning and memory [26–28], but also for the behavioral persistence of long-term memories [29–31]. Importantly for models of episodic memory, dopamine-dependent facilitation of neural plasticity is evident after even a single event [32]. Finally, dopamine release in the hippocampus is itself modulated by hippocampal activity: outputs from the hippocampus facilitate dopaminergic signaling in the midbrain, which in turn can enhance hippocampal plasticity via dopamine release (for a review see [33]).

These findings raise questions about the behavioral contexts in which dopamine would modulate memory formation in the hippocampus, and the implications for episodic memory in humans. Until recently, the role of dopamine in episodic memory in humans has been relatively understudied. If anything, studies with humans with specific impairments of dopamine transmission, such as in Parkinson's disease, indicate that episodic memory is intact and that only incremental, feedback-driven, learning is impaired ([34,35]; for a review see [36]). However, Parkinson's disease involves relatively selective depletion of dopamine in the dorsal striatum and thus does not provide a good model for understanding dopamine in the hippocampus.

As reviewed below, the accumulation of new evidence from human research indicates that midbrain dopamine regions do modulate episodic memory, that this happens via interactions with the hippocampus, and that this modulation occurs under specific behavioral contexts. Much of this evidence comes from fMRI, demonstrating blood-oxygenation-level-dependent (BOLD) activation in midbrain regions that contain dopamine neurons. Importantly, this indirect evidence from neuroimaging is complemented by

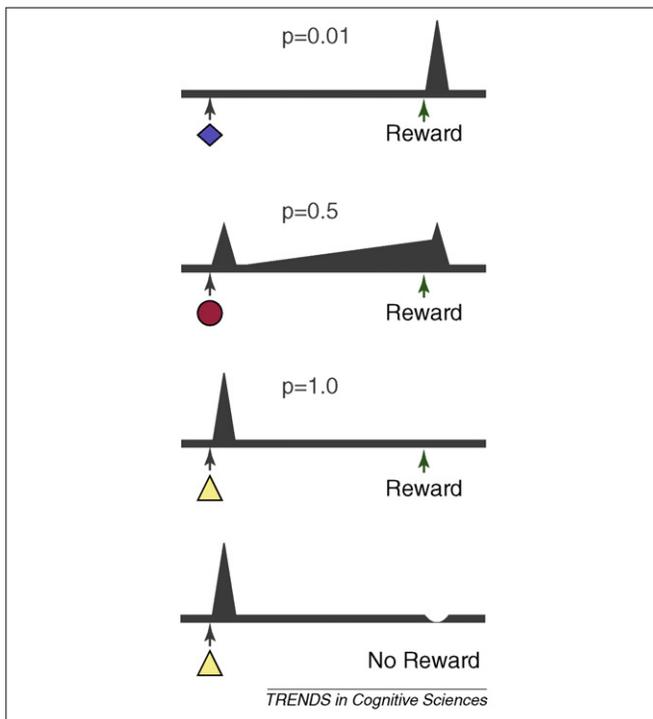


Figure 1. Schematic representation of responses in midbrain dopamine neurons. Dopamine neurons have two characteristic response modes: They normally fire in a tonic pattern (approx. 5 Hz) and periodically fire with short, phasic bursts (approx. 20 Hz). It has been suggested that these response patterns could relate to different behavioral contexts. Here, dopamine neurons respond to rewards that are probabilistically predicted by visual cues (based on [95]). A phasic dopamine response is elicited when an animal receives an unexpected reward ($P=0.01$, after the diamond cue) or a cue that always predicts reward ($P=1.0$, after the triangle cue). When a predicted reward fails to appear, the dopamine neuronal response is briefly inhibited below baseline. When a reward is predicted by a cue part of the time ($P=0.5$, after the circle cue) – that is, when there is uncertainty about the upcoming reward – the dopaminergic phasic response seems to trade-off between the cue and the reward. Importantly, there is also a slow and sustained ramping up of activity. This signal is well-suited to provide sustained modulation of target regions and could reflect tonic dopamine. Indeed, other evidence has led to the suggestion that tonic dopamine responses provide candidate signals of expectancy or motivation [21].

other methods that provide more direct evidence about dopamine *per se* (Box 1). In particular, one key finding demonstrates that BOLD responses in the midbrain during reward anticipation correlate with dopamine release in the striatum, ([37]; Box 1).

Recent findings suggest the following general principles:

Novelty engages midbrain modulation of the hippocampus

It has long been recognized that novelty modulates episodic memory. fMRI studies demonstrate greater hippocampal activation during encoding of novel relative to familiar stimuli (e.g. [38,39]), and activation in midbrain dopamine regions is also greater in response to novel events than to familiar ones [40]. A recent study used intracranial EEG recordings from the hippocampus and the nucleus accumbens (a primary target of midbrain dopamine neurons) in humans to provide more direct evidence of the role of novelty in eliciting neural responses [41]. The presentation of novel pictures, but not familiar ones, led to enhanced EEG responses in both the hippocampus and the nucleus accumbens. Finally, genetic imaging demonstrates that

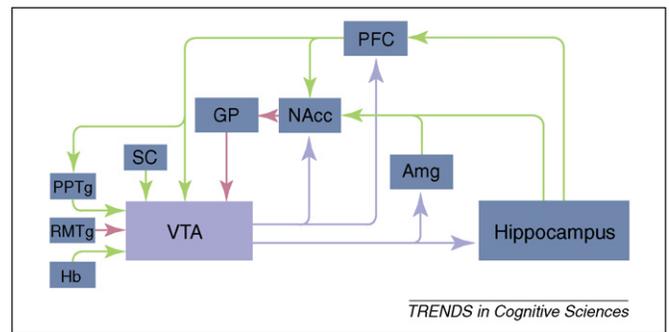


Figure 2. Inputs and outputs of the midbrain ventral tegmental area (VTA) and the hippocampus. For clarity, only some of the projections are shown. A loop between the hippocampus and VTA consists of direct projections from VTA to the hippocampus, and connections from hippocampus – through nucleus accumbens (NAcc) and globus pallidus (GP) – back to VTA [33]. At least one additional route is possible, via relays in the prefrontal cortex (PFC). Midbrain dopamine neurons in the VTA also innervate other select brain regions, all implicated in different forms of memory, including PFC, NAcc and the amygdala (Amg). This selective topography is notable: dopamine neurons, unlike those in other neuromodulatory systems such as acetylcholine or norepinephrine, innervate a select set of brain regions [96], sometimes characterized as ‘convergence zones’ [97]. Inputs to the VTA modulate dopamine neuronal responses. Excitatory activity (green) in the hippocampus disinhibits dopamine neurons by inhibiting (red) GP. Other relevant inputs originate from subcortical sensory areas (e.g. superior colliculus; SC) and PFC (directly and via the pedunculopontine tegmentum, PPTg). Additional nuclei that are the focus of recent research include inhibitory influences that might signal aversive stimuli (e.g., the rostromedial tegmental nucleus (RMTg), mediator of inhibitory inputs from lateral habenula (Hb). Putative contributions of these afferents to tonic and phasic dopamine are reviewed in [23,33,98].

polymorphisms in the dopamine transporter (DAT1) gene affect BOLD activity in the midbrain during episodic encoding of novel stimuli [42]. These results in humans are consistent with models that suggest a key role for a network between the hippocampus and the ventral tegmental area (VTA) in enhancing long-term memory for novel events [33].

Interestingly, work in animals and humans indicates that, in addition to enhanced memory for novel items, novelty can also lead to prolonged effects by enhancing memory for items that take place in a novel context, an effect mediated by midbrain dopamine regions [43,44]. In humans, there is evidence to indicate that dopamine is related to novelty-seeking behaviors and that individual variability in dopamine receptor density in the midbrain is related to novelty-seeking traits [45].

Reward anticipation drives interactions between midbrain dopamine regions and the hippocampus

Much recent evidence supports the view that processing of novelty and reward are tightly interrelated [33,46–49]. The role of reward in driving responses in midbrain dopamine regions has been widely documented across species (e.g. [13,50,51]), indicating that reward might also modulate interactions between midbrain dopamine regions and the hippocampus.

Indeed, recent fMRI studies in humans demonstrate that reward modulates activation in the hippocampus and the midbrain in multiple ways [52–54]. First, activation in the midbrain following reward cues has been related to episodic memory for those cues (Figure 3a, [52,53]). These fMRI studies importantly demonstrate a link between

Box 2. Convergent systems for the modulation of memory

Midbrain dopamine neurons innervate a relatively select topography of brain regions implicated in different forms of memory (see Figure 1 in main text). This indicates that beyond the direct effects of dopamine on the hippocampus, interactions among a wider network of brain regions provide additional mechanisms by which motivation can affect learning and memory.

Dopaminergic projections to the striatum and to the amygdala have been strongly implicated in learning and both have been demonstrated to interact with the hippocampus either competitively or cooperatively [41,73–78]. Prefrontal cortex has long been known to be modulated by dopamine [79–81] and could support goal representation during reward-motivated learning [54,82].

The effects of dopamine release on multiple targets indicate that as dopamine flows into the hippocampus, it also modulates other specialized systems to render goal-related and behaviorally relevant events in memory. In addition, dopaminergic neuromodulation of the hippocampus undoubtedly co-occurs and interacts with modulation by norepinephrine and acetylcholine, each of which have been proposed to signal salient events or uncertainty [83], and to influence long-term plasticity in the hippocampus [84,85]. The consequences of interactions between these neuromodulatory systems on memory are largely unknown and are an important question for future research.

An additional important question is how the effects of dopamine in the hippocampus compare with its effects on other regions. One way to begin addressing this question is by comparing the distribution of dopamine receptors across these regions.

Similarities between prefrontal and hippocampal dopamine innervation and ultrastructural receptor distributions indicate some func-

tional parallels between them. As shown in Table I, levels of binding for terminals (dopamine transporter; DAT below) and receptors (D5, D1-like and D2-like) in the hippocampus seem to be more similar to prefrontal cortex than to striatum. Beyond these parallels, it is unknown whether dopamine ‘tunes’ active representations in the hippocampus in a manner analogous to its enhancement of prefrontal working-memory representations.

Notably, in the hippocampus, D5 is the main dopamine receptor type. As in frontal cortex, D5 receptors in the hippocampus are located primarily on dendritic shafts and are mainly extrasynaptic. By contrast, D5 receptors in the striatum are mainly localized to spines and therefore more likely to be synaptic [86]. Phasic responses have been argued to affect synaptic but not extrasynaptic dopamine levels, whereas increases in tonic dopamine preferentially elevate extrasynaptic levels [87]. In prefrontal cortex, D5 receptors are in fact closely associated with well-defined extrasynaptic microdomains specialized for volume transmission [88].

In the hippocampus, comparison of dopamine receptor distribution across species highlights several important points. First, the pattern of receptor distributions across the hippocampus varies dramatically across species. These qualitative interspecies differences dictate caution in drawing parallels between findings in rodents and humans. Second, particularly in primates, the localization of terminals within the hippocampus is remote from the densest receptor distributions. This mismatch in distribution, similar to the extrasynaptic localization of D5 receptors mentioned above, indicates that hippocampal function – especially in primates – relies heavily on tonic dopamine.

Table I. Regional distribution of dopamine terminals and receptors across species.

Species	Labeled Structure	Brain Region						References
		Hippocampus			Striatum		Frontal Cortex Layers I-III	
		CA1/2	CA3	DG	CPu	NAcc		
Human	DAT (nCi/mg)	+ ^a	+	++	+++++	+++++	NR	[89]
	D5 (anti-D5 Ab)	*	*	*	*	*	*	[90]
	D1-like (fmol/mg)	+++	+	+	+++++	+++++	+++	[91]
	D2-like (fmol/mg)	++	+	+	++++	++++		[91]
Monkey	DAT (anti-DAT Ab)	-	-	+++		NR	++++	[92]
	D5 (anti-D5 Ab)	++	++	+++		++	++	[86,93]
	D1-like (fmol/mg)	++	+		+++++	+++++	++++	[91]
	D2-like (fmol/mg)		+	+	+++++	+++++		[91]
Rat	DAT (fmol/mg)	+	+	++	+++	+++	NR	[94]
	D5 (anti-D5 Ab)	++	+++	+		++	++	[90,93]
	D1-like (fmol/mg)	+	+	+++	+++++	+++++	++	[91]
	D2-like (fmol/mg)	+	+	++	+++++	++++	+	[91]

^aSymbols indicate relative density across regions: + significant labeling; | minimal labeling; * present (unquantified); NR = not reported. Differences across regions (DG, dentate gyrus; CPu, caudate/putamen; NAcc, nucleus accumbens) indicate that hippocampal dopamine receptor densities are more similar to prefrontal than striatal levels. The distributions also indicate that dopamine terminals (shaded boxes) are remote from the densest receptor distributions, which could have important implications for understanding mechanism, particularly in primates (see text). Methodological differences preclude direct comparison of quantitative data (D5 and DAT via immunocytochemistry; D1-like and D2-like and DAT via autoradiography). Quantitative D5 antibody data are unavailable for humans; quantitative mRNA labeling indicates that the D1-like receptors in hippocampus are mainly D5.

reward, midbrain activation and episodic memory performance.

Second, midbrain responses are not limited to reward cues only, but have also been demonstrated when potential reward is used to motivate memory encoding ([54]; Figure 3b). This fMRI study revealed that reward-related motivation was associated with coupled activation in the midbrain and in the hippocampus, that this activation was elicited before the presentation of items, and that this anticipatory activation predicted later episodic memory. Because no rewards occurred during learning in this study, these findings indicate a broad conceptualization of the effects of reward on learning to include motivation to obtain rewards to be gained in the future. Interestingly, a recent study using a similar manipulation of reward-

motivated encoding found that information about reward value might be directly embedded in episodic memories [55].

Thus, both reward cues in the present and motivation to obtain rewards in the future enhance activation in the midbrain and episodic memory. Together, these findings indicate that episodic memory is not an arbitrary record of events, but could be biased to preserve reward-related information.

Midbrain-hippocampal interactions support the integration of memory across experiences

The findings reviewed above have important implications not only for which memories are preserved, but also for how these memories are represented. Memories modulated by

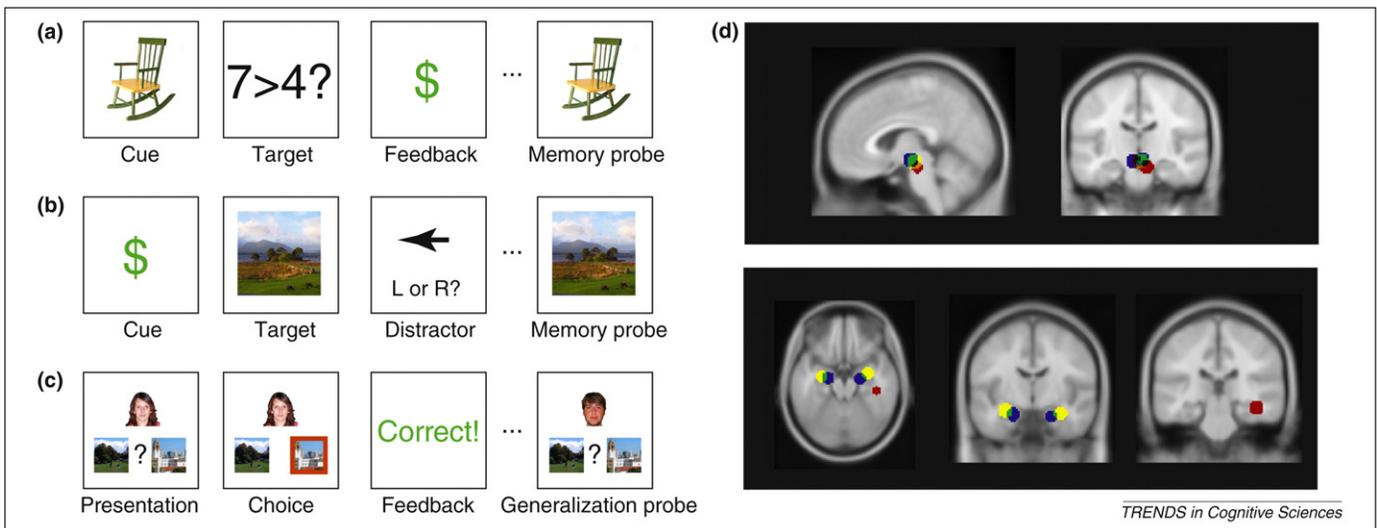


Figure 3. Behavioral paradigms that involve reward and novelty elicit activation in the midbrain and the hippocampus that relates to memory function in humans. **(a) Reward-related encoding** (based on [52]): To examine whether an experience that elicited dopamine release was better remembered, this fMRI study used pictures of objects whose category (living or non-living) indicated reward for successful performance on the next trial of a number judgment task. Based on an expected reward outcome, items in the category that indicated a reward trial would be expected to elicit both phasic and tonic dopamine responses. (Note that every item was novel, and thus might also elicit some increase in tonic dopamine according to [33].) Findings revealed that both midbrain and the MTL were activated following the presentation of items from the reward-predicting category relative to the neutral category. Furthermore, reward-predicting items were better remembered and better associated with their encoding context in source memory. **(b) Motivated memory** (based on [54]): To test the effects of reward anticipation on memory, this fMRI study presented participants with a series of novel pictures to be memorized for a test the next day. Crucially, a few seconds before each picture, participants saw an alerting cue telling them that remembering the picture later would earn them a large monetary reward versus a negligible one. This design allowed the researchers to determine whether anticipatory brain activity putatively related to motivation – that is before the to-be-learned item was even presented – modulates later memories. Findings revealed that the cues for large rewards elicited greater activation of both the midbrain and the hippocampus, increased their correlation, and predicted better memory on the test. **(c) Integrative encoding** (based on [12]): In this learning and generalization paradigm people use feedback to learn a series of associations between faces and scenes. Associations are learned individually but have overlap between them. For example people learn that Bethany prefers cityscapes to fields, and deserts to beaches. They also learn that Walter prefers deserts to beaches. At a later probe phase, people are able to generalize this knowledge to answer a new question: Does Walter prefer cityscapes or fields? Findings from this study revealed that activation in the hippocampus and in the midbrain – during the initial learning phase – correlated with later generalization. **(d) Overlay of midbrain and hippocampal activations** related to adaptive memory in studies illustrated in (a) (red) (b) (blue) and (c) (yellow). These common patterns of activation raise questions about the common processes and putative mechanisms elicited in these studies. Across studies, joint midbrain and hippocampal activation is related to the construction of memories that are well-suited to adaptively guide later behavior. In addition, learning in all of these paradigms requires the integration of information across elements that do not co-occur. This alludes to the need for mechanisms that allow dopamine to help integrate information across different time points, as discussed in detail in the main text.

reward and novelty have all the hallmark features of episodic memory: they are rich in contextual details (such as the source of the memory [52] and the potential value of the item [55]) and are experienced with high confidence [54].

Another key feature of episodic memory that seems to be modulated by interactions between midbrain and hippocampus is representational flexibility [12]. This type of flexibility is essential for generalization of knowledge, and has long been known to depend on the hippocampus (e.g. [56,57]). Recent evidence from humans indicates that hippocampal-midbrain interactions might facilitate generalization of knowledge by promoting integration of discrete episodes [12]. In this fMRI study, participants engaged in feedback-driven associative learning while being scanned (Figure 3c). Those who showed robust activation of the midbrain together with the hippocampus during learning were more likely to later generalize that knowledge to correctly – and rapidly – solve a never-before-seen problem. Thus, when individuals encounter new information that evokes old associations, this associative novelty can promote not only preferential encoding but also the organization of memory to facilitate its later use – processes that could be catalyzed by dopamine [29,31,58]. This ‘integrative encoding’ could thus enable online formation of links between discrete memories, facilitating the use of memories to guide behavior in new situations.

Whether and how dopamine would facilitate integrative encoding is unknown. Evidence from animals indicates that dopamine responses to novel elements in familiar settings might aid the incorporation of new experience into associative networks of information, resulting in generalizable knowledge or ‘schemas’ [12,31,55]. One possibility is that partial overlap across experiences generates predictions and the hippocampus signals violation of these predictions. These ‘mismatch’ signals could elicit midbrain dopamine responses, similar to the responses to novelty and reward cues reviewed earlier.

In summary, recent studies highlight a role for interactions between midbrain dopamine regions and the hippocampus in several key functions, including detecting and recording novel and behaviorally relevant events, enhancing representation of events experienced during reward anticipation, and integrating associations across memories. These functions should ensure that the content of memory is relevant and that it can be deployed flexibly to guide future behavior.

Dopamine modulates hippocampal memories over a range of timescales

Interestingly, the role of dopamine in supporting the formation of memories extends over a range of timescales: before, during, and after an event. As discussed in the next section, this broad range of timescales implies a similarly

broad range of neurobiological mechanisms by which mid-brain dopamine neurons can exert an effect on memory formation in the hippocampus.

Initial evidence highlighted the time period before an event as a window during which the presence of dopamine is crucial. Dopamine enhancement of LTP in the hippocampus was obtained *in vitro* when dopamine was already available at the synapse when neurons were stimulated, implying that dopamine release before an event would enhance memory for that event [27,59]. Exploration of a novel environment before electrical stimulation has also been shown to enhance LTP and this effect depends on dopamine [43]. In humans, cues indicating potential later reward for remembering an upcoming event enhance mid-brain-hippocampal interactions before the event occurs [54]. Similarly, exposure to novel images can proactively enhance memory formation for familiar images presented later [44].

There is also evidence for ‘retroactive’ effects of midbrain dopamine regions on memory. In humans, the presentation of behaviorally relevant stimuli (novel or rewarding) elicits activation in midbrain dopamine regions, with better long-term memory for those events [40,52]. Importantly, in these studies, midbrain activation was presumably stimulated by the events themselves, rather than by events preceding them.

Finally, dopamine can have effects on hippocampal plasticity and memory on a longer timescale after events are experienced, during a phase often referred to as consolidation. Recent findings in animals demonstrate that dopamine supports the persistence of associative memory over timescales as long as 24 hours [31]. Investigations of candidate mechanisms of active consolidation – for example, hippocampal ‘replay’ during rest after learning – also show modulation by reward [60,61]. Finally, a recent study of dopaminergic effects on avoidance learning indicates a second crucial window for dopamine availability that occurs 12 hours after learning and implies not only protracted effects of an earlier release, but also a role for the presence of dopamine during future reactivation and active consolidation [30].

Collectively, then, evidence suggests that the range of timescales over which dopamine is important to durable memory formation by the hippocampus is broad, as illustrated in Figure 4: it begins before experience and continues into a temporal window of hours or days. Importantly, the richness of these relationships indicates that although dopamine could indeed be a biological teaching signal, to be delivered at the ‘biologically right moment’ (Nobel Laureate Konrad Lorenz, in [62]), the right time for teaching signals in the hippocampal memory system seems broadly drawn.

Putative neurobiological mechanisms: Tonic vs. phasic dopamine

The precise mechanisms whereby dopamine modulates memory formation in the hippocampus are not yet known. Nevertheless, existing findings point to a potentially important role for tonic responses in dopamine neurons. In particular, animal research indicates that hippocampal activity originating in the subiculum disinhibits midbrain

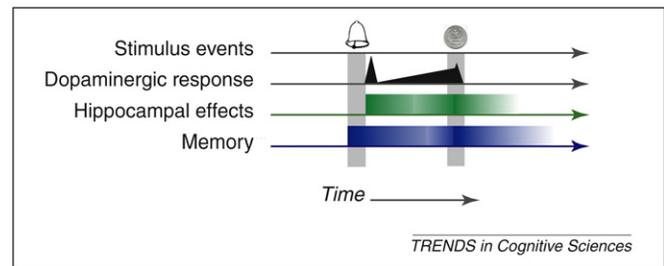


Figure 4. Hypothesized temporal characteristics of memory modulation by dopamine. Midbrain dopamine neurons change their activity both in response to salient transient events such as novelty and reward and during sustained contexts such as anticipation, motivation or expectancy. Both modes are hypothesized to promote memory formation, but might involve different mechanisms. For dopamine to facilitate memory for an event that elicited – and thus preceded – a dopamine response (for example the sound of a bell, analogous to [52]) a mechanism is required that is retroactive in time. One proposed mechanism targets recently active synapses [99]. Enhanced memory for events that occur during sustained dopamine activation, hypothesized to correspond to motivation or expectancy (analogous to [12,54]), is consistent with a generalized decrease in thresholds for lasting plasticity. Such a generalized mechanism could also occur following phasic dopamine responses to salient events; however, phasic dopamine responses could be more spatially restricted to synapses and therefore show more selectivity. An additional window of dopamine contribution to memory longevity, not shown here, has been described hours after the encoded events [30].

dopamine neurons, thus increasing the number of tonically active cells, but does not produce phasic responses in individual neurons [63]. As detailed below, this key finding could form the basis of two putative mechanisms.

One possibility is that tonic responses increase hippocampal dopamine indirectly via facilitation of phasic bursts

It has been proposed that enhanced tonic dopamine reflects an increased number of neurons that are disinhibited by hippocampal activity. Disinhibition increases spontaneous activity but also makes it easier for an individual neuron to burst [63]. Enhanced phasic responses in the midbrain could then impact dopamine release and memory encoding in the hippocampus [33,47]. This mechanism is clearly consistent with observed effects of dopamine on encoding of individual cues. It could also possibly explain observed anticipatory and sustained effects of dopamine on encoding: sustained contexts (such as exploration of novel environments or reward anticipation), by increasing tonic responses, would increase the likelihood that dopamine neurons would burst in response to a specific event within that context.

With the emphasis on a functional role for phasic bursts, this view makes several predictions. First, it predicts that memory encoding should be enhanced specifically for individual time-constrained events (e.g. the appearance of a single stimulus) rather than for the sustained episodes or contexts within which they occur. Second, it predicts that selective disruption of either phasic responding or tonic responding should abolish the facilitatory effects of dopamine on hippocampal encoding. Notably, however, this prediction is somewhat inconsistent with results from a recent study in rodents [64]. This study used a novel method to selectively disable phasic responses, while having no impact on tonic responses. Disabling phasic responses led to marked and selective disruption of reward learning and instrumental conditioning, whereas long-term spatial mem-

ory – a hallmark of hippocampal function – remained intact (as did motivation and working memory).

Another possibility is that tonic dopamine directly modulates hippocampal encoding

An increase in tonic dopamine activity from increased hippocampal input to VTA could, in and of itself, lead directly to changes in tonic dopamine release in the hippocampus. This mechanism would provide a parsimonious account of the observed effects of anticipatory and sustained dopamine on encoding. This mechanism could also possibly explain observed effects of dopamine on encoding of individual cues: enhanced tonic dopamine could facilitate encoding of the context, the events that take place within that context, and the relation between them.

In support of the idea that tonic dopamine could play an important role in the hippocampus, there is substantial anatomical and ultrastructural evidence indicating a prominent role for extrasynaptic (i.e. tonic) dopamine in the hippocampus, similar to patterns seen in prefrontal cortex, and unlike those in striatum (Box 3). Additionally, evidence of dopamine release in the hippocampus has been obtained only via microdialysis, argued to preferentially reflect tonic dopamine levels [65].

In fact, evidence that phasic responses in midbrain dopamine neurons modulate the hippocampus is lacking: disrupted phasic activity does not impact long-term spatial memory (as noted above [64]). Further, there is no evidence from animals or from human fMRI that the hippocampus is transiently activated in situations known to elicit phasic responses in midbrain dopamine neurons. This indicates that temporally-specific prediction error signals might be an inappropriate model for this system. Although this view is consistent with extant evidence, the predicted enhancement not only of specific salient events, but also the contexts in which they occur, remains to be tested.

It is important to note that these two mechanisms are not mutually exclusive. It is possible that midbrain dopamine modulates hippocampal function via both tonic and phasic responses. Indeed, the range of behavioral contexts and timescales across which dopamine has been implicated in episodic memory formation seem unlikely to be

accounted for by a single mechanism (Figure 4). Further, multiple other brain systems and neurotransmitters are probably involved (Box 2).

A final important question to be resolved is how dopamine released at or around the time of encoding affects the life of the memory trace long after it has been laid down. Generalized enhancement of memory for events encountered following tonic (and perhaps phasic) dopaminergic activation could be explained via volumetric effects of dopamine release that lower thresholds for LTP in all active synapses [26–28,43]. Explaining how dopamine could enhance the encoding of items that elicit phasic release, however, requires a retroactive mechanism (Figure 4). One proposed mechanism is that of ‘synaptic tagging’: a process whereby excitation in the hippocampus can leave a ‘tag’ on a specific synapse to facilitate enhancement of later, overlapping inputs exciting the same synapse, even if they are weaker. Synaptic tagging could potentially provide a powerful mechanism for dopamine-enhanced encoding of individual items or related experiences and could be especially important for understanding how the hippocampus facilitates encoding over temporal delays to integrate information across multiple experiences (e.g. in integrative encoding). Such mechanisms could also mark synapses for slow structural changes on the order of minutes or hours [28,29,31,58] that underlie lasting memories [31] or potentiate changes during later exposure to dopamine [30], for example in reactivation [60,61]. These protracted effects predict that dopamine might be particularly well-suited to enhancing memories after long delays. Pharmacological studies in animals support this idea [31]. However, this remains an important open question for future research in humans.

An important goal for future animal research will be to determine how tonic and phasic responses in midbrain dopamine neurons affect synaptic and extrasynaptic dopamine concentrations in the hippocampus to produce changes in neural activity and plasticity, and in turn, influence memory formation. At present, all the evidence for cellular mechanisms comes from rodents. Although there are likely to be many commonalities across species, there are also important differences (see Table I in Box 2) that raise the need for future research that can bridge these gaps.

Box 3. Questions for future research

- Do tonic and phasic dopamine have dissociable effects on the hippocampus and long-term memory?
- Under what circumstances could these neurobiological mechanisms produce maladaptive behavior?
- Does learning under appetitive motivation differ in quantity or quality from learning under threat?
- Norepinephrine and acetylcholine also signal salience and uncertainty and also affect hippocampal memory. What are the common and distinct mnemonic effects of these neurotransmitters?
- How do other specialized memory systems based in the striatum and amygdala, also innervated by dopamine, contribute to adaptive memory?
- How is adaptive memory impacted by changes in dopamine with healthy aging or in diseases such as schizophrenia? Does dopaminergic medication impact adaptive memory?
- What are the implications of the adaptive memory construct for learning in educational settings and in everyday life?

Concluding remarks

To summarize, extensive evidence indicates that dopamine release before, during, and after an event supports hippocampal plasticity and episodic memory formation. Dopamine thus seems to influence which episodic memories are formed and how they are represented, enabling memory for past experience to support future adaptive behavior. We use the term ‘adaptive memory’ as a construct for this process to highlight the selectivity of memory and to consider whether this selectivity, which can seem quixotic or random, could be at least partially explained as a phenomenon that emerges from influences of motivational systems. We propose that consideration of this construct will enrich understanding of the intrinsic relations between memory, motivation and decision making, at both the neural and cognitive levels.

The framework we propose on the basis of the 'adaptive memory' construct is also consistent with findings from the rich tradition of behavioral studies on memory, and could help resolve questions that have persisted in that literature for decades without resolution. 'Wanting to remember' has been an intuitively compelling but experimentally elusive phenomenon. A framework incorporating dopamine as a signal for learning, released in response not only to salient events but also to expectations, provides a mechanistic neurobiological account of how motivation influences memory beyond descriptors of internal states. Thus, the adaptive memory construct proposed here could provide insights into understanding not only what we remember, but why.

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