To appear in M.J. Kahana & A.D. Wagner (Eds.) The Oxford Handbook of Human Memory. Oxford University Press, New York, NY USA

# Dopamine and Learning

Katherine Duncan[1] & Daphna Shohamy[2]

[1]Department of Psychology, University of Toronto

[2]Department of Psychology, Zuckerman Mind Brain Behavior Institute, & Kavli Institute for Brain Sciences, Columbia University

1. Overview
2. Origins and targets of dopaminergic pathways
3. Dopamine modulates reward and habit learning in the striatum
4. Dopamine modulates prioritization and integration of memories in the hippocampus
5. Conclusions

To appear in M.J. Kahana & A.D. Wagner (Eds.) The Oxford Handbook of Human Memory. Oxford University Press, New York, NY USA

**Abstract**

A central challenge for theories of memory is to understand how the brain prioritizes learning based on motivational relevance. Emerging findings indicate that the neurotransmitter dopamine plays a critical role in this process. Dopaminergic modulation links learning and memory to motivation and reward, thereby ensuring that memories are adaptive for future behavior. Here we review the neural pathways and behavioral and cognitive consequences of this modulation, with a focus on two main dopaminergic targets: the striatum and the hippocampus. We review evidence regarding the neural and computational mechanisms by which dopamine reinforces learning of habits in the striatum, and the role of dopamine in modulating long-term episodic memories in the hippocampus. Understanding the effects of dopamine across multiple learning and memory systems helps resolve a fundamental challenge in memory research: explaining what we learn, and why.

## 1. Overview

If there were a celebrity among the brain's neurotransmitters, dopamine would be it. Dopamine initially garnered attention among scientists and non-scientists alike because of its association with drugs of abuse: most recreational drugs enhance dopamine in the brain, one way or another (Pierce & Kumaresan, 2006). This association between dopamine and addiction led to the idea that dopamine is "*the pleasure drug*", that it is the substrate of hedonic experiences. Indeed, rats have famously been shown to self-stimulate dopamine neuron fibers to release dopamine, even to the point of starvation (Olds & Milner, 1954). This profile fits well with the image of a drug addict who will give up money, food, and health for the sake of a drug that enhances the effect of dopamine in the brain.

In recent years, however, our understanding of what dopamine does and why it is so reinforcing has changed. It is now clear that rather than describing dopamine as the pleasure drug, a more accurate description may be "*the learning drug.*" It is dopamine's role in learning that seems to drive the rich behaviors that dopamine is now known to be involved in: not only the maladaptive compulsions and addictions, but also adaptive habits, such as those used to seek food, social rewards, and even information. Dopamine plays an important role in reinforcing behaviors that are adaptive by signaling actions, decisions, and events that are associated with reward. This puts dopamine right at the nexus between learning and motivation.

In this chapter, we consider the complex and multifaceted functions of dopamine in learning. We explore dopamine's neural pathways and the modulatory effects of dopamine on plasticity in two of its targets which play specialized roles in learning and memory: the striatum and the hippocampus. The striatum and the hippocampus are commonly thought to work in fundamentally distinct and complementary ways, as two separate learning and memory systems (Eichenbaum & Cohen, 2004; Gabrieli, 1998; Poldrack & Packard, 2003; Squire & Dede, 2015; Squire & Zola, 1996). In recent years it has become clear that the striatum and the hippocampus also interact in important ways, a

perspective that is sharpened by recent advances in understanding how dopamine modulates neural and cognitive activity in both structures.

We start the chapter with an overview of the brain's dopamine pathways. We then discuss how dopaminergic projections to the striatum contribute to the learning of reward-related actions underlying both habits and goal-directed behavior. Next, we shift to the hippocampus, discussing how dopamine modulates its plasticity, the prioritization of consequential memories, and the construction of associative models in the service of flexible behavior. Along the way, we consider the time-course of dopaminergic modulation of different regions and their complementary roles in adaptive behavior.

## 2. Origins and targets of dopamine pathways

The human midbrain is estimated to contain 400,000-600,000 dopaminergic neurons (Björklund & Dunnett, 2007; Wolfram Schultz, 2016; Stark & Pakkenberg, 2004). Given the importance of dopamine for brain function, this is a relatively small number; for comparison, consider that dopamine neurons are outnumbered by roughly three orders of magnitude by area V1 neurons (Wandell & Thomas, 1997). In addition, all of the brain's dopamine neurons are concentrated in relatively small and selective nuclei in the midbrain. Nonetheless, the reach of dopamine neurons is broad and profound, shaping neural responses and plasticity in the striatum, prefrontal cortex, and limbic regions.

Before delving into the function of dopamine neurons in learning, we review the neuroanatomy of the dopaminergic system, detailing classic divisions along with more recent revisions to this architecture (**Figure 1A**). In particular, we focus on neurons residing in the ventral mesencephalon within two loosely organized groups– the pars compacta portion of the substantia nigra (SNc; cell group A9) and the ventral tegmental area (VTA; cell group A10). A third group found in the retrorubral area (cell group A8) is small and less well characterized and will not be discussed here.

Traditionally, long-range projections from midbrain dopamine neurons have been split into three distinct pathways (Lindvall et al., 1974, 1977)[1]. The *nigrostriatal pathway* originates in the SNc and terminates in the dorsal striatum. The SNc has a clear anatomical definition owing to the darkly colored neuromelanin produced by residing dopamine neurons (Zucca et al., 2014). These dopamine neurons are densely packed, making up 70-88% of the SNc's neural population (Margolis et al., 2006; Nair-Roberts et al., 2008) and comprising 70% of all dopamine neurons in the human midbrain (Björklund & Dunnett, 2007). The *mesolimbic* and *mesocortical pathways,* by contrast, arise from the smaller and more neurally diverse VTA, which is comprised of only 50-60% dopaminergic neurons (Margolis et al., 2006). Though outnumbered by SNc dopamine neurons, those in the VTA have a broader reach, with the mesolimbic pathways projecting to the nucleus accumbens, amygdala, and hippocampus, while the mesocortical pathway projects to the prefrontal and cingulate cortex, along with sensory and motor cortical regions.

Though likely oversimplified (Björklund & Dunnett, 2007; Oades & Halliday, 1987), the three-pathway taxonomy continues to be a useful heuristic. In particular, individual dopamine neurons appear to project to the striatum in a very selective manner, rarely crossing dorsal/ventral divisions or sending collaterals outside the striatum (Björklund & Dunnett, 2007; Swanson, 1982). This selectivity has now been confirmed by single-cell axon tracing studies (Aransay et al., 2015; Matsuda et al., 2009; Rodríguez-López et al., 2017). Recent technical innovations have also uncovered unexpected projection selectivity along the medial-lateral axis of the rodent striatum (Figure 1A): Distinct VTA dopamine neurons preferentially project to either the core, lateral shell, or medial shell divisions of the nucleus accumbens (Beier et al., 2015; Rodríguez-López et al., 2017; Yang et al., 2018). Analogously, distinct SNc dopamine neurons preferentially project to either dorsolateral or dorsomedial divisions of the striatum (Lerner et al., 2015).

[1] It should be noted that others have argued that dopamine projections from the midbrain are more meaningfully divided into a dorsal and ventral tier, with the dorsal tier innervating neocortex, limbic, and ventral striatal regions, and the ventral tier innervating the dorsal striatum (Björklund & Dunnett, 2007; C. D. Fiorillo & Williams, 1998; Haber et al., 2000; Lewis & Sesack, 1997).

Further underscoring the segregation of these sub-pathways, medial vs. lateral projecting neurons tend to arise from more medial vs. lateral aspects of the dopaminergic midbrain (Beier et al., 2015; Ikemoto Satoshi, 2007; Lerner et al., 2015; Yang et al., 2018). They also differ in their input (Beier et al., 2015; de Jong et al., 2019; Lammel et al., 2012; Lerner et al., 2015; Matsumoto & Hikosaka, 2009; Yang et al., 2018) and receive stronger projections back from the corresponding striatal region (Beier et al., 2015; Lerner et al., 2015). Medial-lateral divisions also appear relevant for the mesolimbic and mesocortical pathways. While dopamine neurons residing in lateral aspects of the VTA predominately project to the lateral shell of the nucleus accumbens, medial neurons project to more diverse sets of regions, including limbic and prefrontal sites (Figure 1b). Notably these medial neurons tend to have 'unconventional' response profiles, making them harder to identify and less studied than more lateral neurons (see Ungless & Grace, 2012 for a review on these issues). Together, this growing body of research reveals functional specializations along medial-lateral divisions with relevance to behavior (Bromberg-Martin et al., 2010) – a possibility that we discuss in more detail in *Section 3*.

Perhaps the most contentious target to dopamine neurons – the hippocampus – is particularly relevant to learning and memory. As we discuss in *Section 4*, dopamine has a well-established influence on hippocampal neural responses and plasticity (Huang & Kandel, 1995; Li et al., 2003; Moncada & Viola, 2007; O'Carroll et al., 2006; Rossato et al., 2009). Further, moderate dopamine concentrations have been reliably observed in the hippocampus (Oades & Halliday, 1987), with levels in humans on par with those found in the prefrontal cortex (PFC; BA 9) and exceeding norepinephrine concentrations (Scatton et al., 1983). There is also evidence that VTA neurons project to the hippocampus, particularly anterior (ventral in rodents) portions (Oades & Halliday, 1987). Similarly, human fMRI research shows reliable functional connectivity between the VTA and an anterior hippocampal region (Kahn & Shohamy, 2013). However, as these neurons tend to arise from the particularly heterogeneous medial VTA, the degree to which these projections contain dopamine neuron input vs. other cell types has been questioned (Swanson, 1982).

Further complicating matters, the hippocampus may receive dopaminergic input from an alternative source – norepinephrine neurons in the locus coeruleus (LC), which have recently been shown to corelease dopamine (Kempadoo et al., 2016; Takeuchi et al., 2016; Wagatsuma et al., 2018). Supporting the importance of midbrain sources, early research demonstrated that lesioning the VTA and (to a lesser degree) SNc markedly reduces hippocampal dopamine levels (Scatton et al., 1980), but lesioning the LC does not (Hamilton & Mackay, 1976). Moreover, retrograde tracers injected in the hippocampus indicated dopaminergic innervation from the VTA/SNc (Broussard et al., 2012; A. Gasbarri et al., 1994; Antonella Gasbarri et al., 1997).

More recently, optogenetic studies have confirmed the sparse innervation of midbrain dopamine neurons in the hippocampus and verified their functional significance (McNamara et al., 2014; Rosen et al., 2015). Other optogenetic studies, however, have found dopamine release from the LC to more powerfully modulate hippocampal function (Kempadoo et al., 2016; Takeuchi et al., 2016; Wagatsuma et al., 2018). Of note, these recent studies target the dorsal hippocampus in rodents (analogous to posterior hippocampus in primates), which is more weakly innervated by midbrain dopamine neurons compared with the ventral portion (analogous to anterior in primates), particularly in humans (Oades & Halliday, 1987).

In summary, midbrain dopamine projections arising from the VTA and SNc densely innervate the striatum and also project to frontal and medial temporal regions. Thus, dopamine is well positioned to shape learning and memory in multiple ways. Importantly, these projections tend to be spatially selective. Distinct populations are thought to innervate different subregions of the striatum, across both well-established ventral and dorsal divisions as well as newly emerging medial and lateral divisions. Other neural populations innervate frontal cortex and medial temporal cortical regions, and these neurons tend to be more ‘unconventional’ and less well studied than those innervating the striatum. Of note, this organization suggest that dopaminergic signals can pinpoint particular divisions of the striatum, but may be simultaneously broadcast across cortical and limbic sites because individual neurons in these pathways innervate many regions

(Aransay et al., 2015). With these notable anatomical distinctions in mind, we next review how dopamine may shape learning and memory in the striatum (*Section 3*) and in the hippocampus (*Section 4*).

## 3. Dopamine modulates reward and habit learning in the striatum

Extensive research implicates dopaminergic neurons and their striatal targets in reward learning and habit formation. Recordings from dopamine neurons in the SNc and the VTA in behaving monkeys have revealed an important reward-related signal. Many of these neurons have a low background firing rate punctuated by brief, phasic excitations and inhibitions. Following reports describing various circumstances under which these phasic firing modulations occur (for an early review, see Schultz, 1992), seminal computational work pointed out that many of these responses could collectively be understood as signalling a *reward prediction error* (Schultz et al., 1997; Montague et al., 1996).

A reward prediction error is the difference between the reward received and the reward that was expected. In other words, a form of feedback that indicates how errant a choice was, given its outcome. Indeed, dopamine neurons show a phasic excitation to reward that is proportional to the prediction error: largest for a completely unpredicted reward, virtually non-existent for a fully predicted reward, and suppressed for rewards that fall short of expectations (Fiorillo et al., 2003; **Figure 2**). The idea that reward prediction errors are central to learning originated long before the discovery of this signal in dopamine neurons. Reward prediction errors had been commonly used to implement reinforcement learning algorithms in machine learning (Rescorla & Wagner, 1972; Sutton & Barto, 1998). In particular, this signal underpins a class of reinforcement learning algorithms – *model-free reinforcement learning* – that use unexpected rewards to "stamp in" preceding choices or actions. The convergence of the neuronal signal and the machine learning algorithm suggested that this form of learning, implemented in dopamine signalling, may underlie the learning of automatic responses or habits. This link between dopamine firing, reward prediction errors, and habit learning, suggests that

one function of midbrain dopamine neurons is to implement a neurobiological substrate for learning to predict rewards and for acting to obtain them.

The relationship between dopamine neurons and reward prediction error signalling has since been replicated extensively in rodent and monkey studies. Convergent findings have also been revealed in humans. Functional magnetic resonance imaging (fMRI) studies of healthy humans engaged in learning tasks reveal that the blood-oxygen-level-dependent (BOLD) signal at dopaminergic targets (principally ventral striatum) is correlated with reward prediction errors during learning (D'Ardenne et al., 2013; McClure et al., 2003; O'Doherty et al., 2003; Pessiglione et al., 2006). The metabolic activity detected by fMRI does not specifically indicate dopamine release, however, pharmacological studies in both healthy individuals and those with dopamine abnormalities (such as individuals with Parkinson's disease) provide a more direct link between dopamine levels and the prediction error related BOLD signal (Pessiglione et al., 2006; Schmidt et al., 2014; Schonberg et al., 2010). Thus, converging evidence supports the idea that the reward prediction error signal is found across species and across methods.

Critically, there is also converging evidence that the reward prediction error signal carried by dopamine neurons also plays an important role in learning. In humans, studies in individuals with Parkinson's disease have revealed that the loss of dopaminergic transmission that characterizes the disease has a detrimental effect on reward-based learning mechanisms (Frank et al., 2004; Maia & Frank, 2011; Schonberg et al., 2010; Shohamy et al., 2004). Such studies typically use tasks involving a series of decisions for possible reward, with participants choosing between two options and the likelihood of reward given each option varying across trials. These tasks are often referred to as *probabilistic learning tasks* (because the likelihood of reward given a choice is probabilistically determined) or as two-armed *"bandit" tasks*, in reference to the gamble that the participant makes on each trial. Studies have found that learning to perform such tasks involves reward prediction error related BOLD activity in the striatum in healthy participants, and that patients with Parkinson's disease show both weaker striatal BOLD responses and less adaptive choices (Frank et al., 2004; Maia & Frank, 2011; Schmidt et

al., 2014; Schonberg et al., 2010; Shohamy et al., 2004; see Foerde & Shohamy, 2011a for review). Dopamine's involvement in reinforcement learning is thus supported by both correlational and causal findings. These findings all suggest that dopamine reinforces the learning of habits, procedures, and actions via its modulation of cortico-striatal plasticity.

The idea that dopamine plays a role in modulating one particular kind of learning – habitual, model-free reinforcement learning – fits well within the broader context of a multiple memory system framework (see Forms of Memory divisions in *Section 2*) – the proposal that distinct kinds of memory are supported by different neural systems. However, the role of dopamine in motivated behavior and learning likely goes beyond the signalling of reward prediction errors. Indeed, as discussed in the pathway section above, there are prominent targets of dopamine projections outside the striatum, raising questions about the extent to which dopamine plays a unitary role across all targets versus a specialized role in each.

For example, consider the lateral PFC, a region which receives dopamine projections from the lateral SNc (Williams & Goldman-Rakic, 1998; Figure 1a) and which has prominent reciprocal connections to the dorsal striatum (Leh et al., 2007; Yeterian & Pandya, 1991). It is possible that dopamine neurons synchronously broadcast reward prediction errors throughout the striatum and interconnected prefrontal regions to coordinate reinforcement learning throughout the circuit (Glimcher, 2011).

However, the story is likely more complicated. For example, the functions of dopamine within the lateral PFC are multifaceted and include enhancing the neural gain for attended information along with persistent neural activity related to working memory maintenance (see Ott & Nieder, 2019 for a recent review). Thus, the role of dopamine in these functions does not fit tidily within the box of rigid and habitual procedural learning. Further complicating matters, the firing of dorsolateral SNc neurons which project to dorsolateral PFC regions may be more tightly related to working memory load than to prediction error (Matsumoto & Takada, 2013), suggesting that ties between dopamine and model-free reinforcement learning may not be maintained across all targets.

Even when considering only striatal dopamine projections, the restrictive interpretation as a reinforcement learning signal has been questioned (e.g., Horvitz, 2000, 2002; Redgrave & Gurney, 2006; Redgrave et al., 1999). While many dopamine neurons appear to signal reward prediction errors, this value-related response takes several hundred milliseconds to emerge and is preceded by a robust early response reflecting stimulus salience and novelty (Schultz, 2016).

Further, when signalling outcomes, dopamine neurons and their striatal targets have been shown to respond to punishment, not just rewards (Matsumoto & Hikosaka, 2009; for parallels in human neuroimaging see Carter et al., 2009; Delgado et al., 2009). Emerging evidence suggests that dopamine neurons signalling unexpected rewards vs. punishments may be spatially organized along the medial vs. lateral aspects of both mesostriatal (de Jong et al., 2019; Lammel et al., 2012) and nigrostriatal pathways (Lerner et al., 2015). In broad strokes, populations of dopamine neurons which code for aversive outcomes tend to reside in dorsal and medial portions of the VTA, others signaling both positive and negative cues disproportionately reside in lateral SNc, while those displaying canonical reward prediction error responses are most prominent in the intermediate midbrain regions (Brischoux et al., 2009; Matsumoto & Hikosaka, 2009; Nomoto et al., 2010; **Figure 1a**). In humans, high-resolution fMRI has provided preliminary support for this organization, with outcome salience signals (absolute prediction error) localized to lateral SN, and reward prediction errors to more medial aspects (D'Ardenne et al., 2013).

Moreover, 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 (Berridge, 2007; Mazzoni et al., 2007; Niv et al., 2007; Robbins & Everitt, 2007; Salamone et al., 2007) and in information seeking (Bromberg-Martin et al., 2010; Bromberg-Martin & Hikosaka, 2009).

Recent work suggests that, rather than being limited to model-free forms of learning, dopamine also plays a role in "model-based" reinforcement learning. Computational models of goal-directed decision making have proposed a family of theories, known as model-based reinforcement learning, which evaluate actions by integrating information from a learned model of the environment (Daw et al., 2005, 2011; Dolan & Dayan, 2013;

Shohamy & Daw, 2015). Critically, model-based reinforcement learning is distinct from the model-free form in that it relies on rich and detailed representations of relations between actions and outcomes, allowing the decision maker to prospect over sequences of actions to strategically achieve goals. Converging research using optogenetics in rodents, and, in humans, fMRI and pharmacological manipulations implicates dopamine and ventral striatal BOLD responses in model-based decision making (Daw et al., 2011; Sharpe et al., 2017; Sharp et al., 2015). This raises the possibility that dopamine may help to construct the world models that enable flexible prospection about potential future rewards, not simply signal past rewards for habitual behavior. Dopamine contributions to this form of reinforcement learning likely also involve dopaminergic targets outside the striatum – a point to which we return in our discussion of dopamine in the hippocampus.

In summary, there are varied perspectives on dopamine's role on striatal mediated learning, ranging from model-free and model-based reinforcement learning to more general signalling of motivation and salience. Integrating across these perspectives, paints a picture in which dopamine neurons provide multiple mechanisms for signaling the occurrence and expectation of events that are of motivational significance. These signals are then transmitted to a selective set of striatal targets to coordinate motivation to learn about, and ultimately obtain, goals.

## 4. Dopamine modulates prioritization and integration of memories in the hippocampus

The convergence of evidence pointing to a role for dopamine neurons in signalling motivational significance raises important questions about the breadth of that signal and its impact on learning and memory, beyond the formation of habits. Indeed, this discovery offers a potential neural mechanism for a longstanding question in memory research: what do we remember, and why?

The hippocampus and surrounding medial temporal lobe (MTL) regions have long been known to play a critical role in long-term memory for the events and episodes in one's life (see chapters 1.4 and 2.1). Yet, despite the presence of dopamine receptors in the hippocampus (Ciliax et al., 2000; Dawson et al., 1986; Jiao et al., 2003; Lewis et al.,

2001), for many years the functional role of dopamine in hippocampal-dependent memory remained elusive. This gap in knowledge was likely related to two distinct obstacles. First, the sparseness of dopamine inputs to the hippocampus (Swanson, 1982) made it technically difficult to study their functions. Second, at the conceptual level, systems neuroscience had been heavily influenced by the idea that the striatum and the hippocampus play fundamentally distinct, and opposing, roles in learning (Eichenbaum & Cohen, 2004; Gabrieli, 1998; Poldrack & Packard, 2003; Squire & Dede, 2015; Squire & Zola, 1996). This perspective likely hindered consideration of the possibility that dopamine – a neurochemical so robustly linked to striatal learning – might also shape the formation of memories by the hippocampus.

All this has changed in the past decade. As we review below, converging findings in humans and animals suggest that dopamine does indeed modulate learning in the hippocampus and nearby MTL cortical regions. Moreover, the function of dopamine within the hippocampal memory system appears to mirror its function in striatal learning. Namely, by signally motivationally relevant events, dopamine serves to enhance both the encoding and consolidation of this information in memory.

## Dopamine and hippocampal memory mechanisms: synaptic plasticity and replay

Early hints that dopamine shapes hippocampal-dependent memories came from demonstrations that it modulates long-term potentiation (LTP), a form of synaptic plasticity thought to underlie memory formation. In rodents, applying dopamine agonists during the induction of LTP in the hippocampus increases the likelihood of weak protocols eliciting protein synthesis and the corresponding structural changes necessary for the late phase of LTP (l-LTP; Lemon & Manahan-Vaughan, 2006; Li et al., 2003). Conversely, dopamine antagonists block l-LTP in these protocols (Bethus et al., 2010; O'Carroll et al., 2006). Complementary results have been found in awake behaving rodents: applying dopamine agonists to the hippocampus during memory formation enhances later expression of these memories. Interestingly, this effect of dopamine is observed only when behaviour is tested at a long (> 1 h) delay (Bethus et al., 2010; O'Carroll et al., 2006), corresponding to l-LTP timing. More recently, optogenetic

manipulations mimicking endogenous dopamine bursts have similarly been shown to enhance the later expression of memories after a long delay (Kempadoo et al., 2016; McNamara et al., 2014; Takeuchi et al., 2016).

Pharmacological manipulations in humans also suggest that dopamine confers mnemonic benefits, and that these benefits emerge over time. For example, a meta-analysis found that dopamine agonists had a much stronger effect on episodic memory performance when memory was tested after at least an hour's delay as compared to less than 30 minutes (Ilieva et al., 2015). In humans, however, agonists led to performance benefits even when memory was tested after short delays. This apparent discrepancy between species may be rooted in the nature of the pharmacological manipulation itself. Agonists used in rodent studies are often selective to dopamine receptors, in particular the D1-like receptor subtypes that are most likely to influence hippocampal plasticity (Shohamy & Adcock, 2010). By contrast, most studies in humans use stimulants (e.g., amphetamine), which have complex modes of action and influence both dopamine and norepinephrine systems (Sulzer et al., 2005). Moreover, administration in humans is also systemic, rather than restricted to the hippocampus. Thus, memory enhancements could reflect a combination of the drugs' effects on the PFC and striatum, which could indirectly strengthen the encoding of episodic memories by enhancing vigilance and working memory, and time-dependent effects on hippocampal plasticity (in line with rodent studies). Indeed, coupling between the BOLD signal in the human VTA and hippocampus during memory formation was shown to correlate with later memory performance only when tested at delays corresponding to l-LTP (K. Duncan et al., 2014). Similar results were obtained in a pharmacological fMRI study in which the effect of L-Dopa on older adults' memory performance after 3 and 6 hour delays was associated with hippocampal BOLD signals (Chowdhury et al., 2012).

Dopaminergic modulation of hippocampal LTP is also notable for the remarkably broad time window on which it acts. This is somewhat surprising, given the high temporal specificity of phasic responses in midbrain dopamine neurons. For example, pharmacological manipulations influence l-LTP when applied even 20-30 minutes before, or after, its induction (Li et al., 2003; Moncada & Viola, 2007; Wang et al., 2010). In

humans, correlated activity between the VTA and the hippocampus is related to later memory performance and, interestingly, this relationship holds for activity recorded several minutes after the to-be-remembered event (Gruber et al., 2016; Tompary et al., 2015). This broad time window contrasts with the effect of dopamine in the striatum, and may be related to functional differences that each structure plays in reinforcement learning across different temporal delays (e.g. Foerde et al., 2013; Foerde & Shohamy, 2011b).

The broad window and retroactive impact of dopamine on memory raises a puzzle – how can dopamine reach back in time to stabilize memory traces formed many minutes earlier? Synaptic tag and capture models (J. Lisman et al., 2011; Redondo & Morris, 2011) provide one solution. Weak LTP induction protocols (which presumably correspond to a relatively mundane experience) elicit the transient early phase of LTP, but are not sufficient to set in motion the cascade of molecular events required to generate the new proteins that physically strengthen the stimulated synapse. Behaviourally, this distinction could relate to the ability to recall mundane details during a conversation, but lose track of them later as time goes by. By contrast, strong activation of a synapse (or actions of dopamine) can trigger the required protein synthesis to support later survival of a memory. These proteins are not generated within activated synapses, but rather must travel within the neuron, such that during transport any concurrently activated synapses – even those that were more weakly activated – can capture the proteins to enhance the persistence of the memories which they underpin. This mechanism enables strengthening of synapses for events that were neutral at the time, but which were followed later by dopaminergic modulation.

In addition to this cellular consolidation mechanism, dopamine also shapes systems-level consolidation through hippocampal replay. Following encoding, hippocampal neurons replay sequences of activity that reflect earlier encoding (Wilson & McNaughton, 1994), a process which is thought to result in physiological strengthening of the hippocampal memory trace (Carr et al., 2011; O'Neill et al., 2010; Roumis & Frank, 2015) while entraining corresponding cortical representations (McClelland et al., 1995). Optogenetic stimulation of VTA dopamine projections to the hippocampus during spatial learning

increased rates of hippocampal replay during subsequent periods of sleep (McNamara et al., 2014). Of note, mice receiving this stimulation also expressed better spatial memory following this period of heightened replay (McNamara et al., 2014). This pattern of results suggests that dopamine signals during learning could tag important experiences for later consolidation (Atherton et al., 2015). Moreover, hippocampal replay following maze navigation in rodents has been shown to occur concurrently with the firing of dopamine neurons in the VTA (Gomperts et al., 2015) and this coordination was stronger during waking than sleeping periods. Awake replay has been speculated to resolve temporal credit assignment problems in reinforcement learning (Foster & Wilson, 2006; Singer & Frank, 2009) and to underly memory-guided decisions (Jadhav et al., 2012; Pfeiffer & Foster, 2013), raising the possibility that post-encoding dopaminergic transmission may shape the adaptive use of recent experience, or perhaps prioritize the consolidation of memories that have proven their utility.

Dopamine and adaptive memory prioritization: which memories are selected?

These mechanisms help explain how some memories are prioritized over others, raising the next critical question: which memories are selected for prioritization? That is, what are the general principles that determine which hippocampal memories benefit from dopaminergic modulation? Broadly speaking, both physiological and behavioural studies indicate an important role for behaviourally significant events – events that are associated with reward, that are novel, or surprising. Indeed, these are the sorts of events that have been shown to elicit dopamine release to begin with (J. E. Lisman & Grace, 2005; Schultz, 2016), suggesting that dopamine may enhance hippocampal dependent-memories formed in varied salient and motivationally-relevant contexts (K. D. Duncan & Schlichting, 2018; J. E. Lisman & Grace, 2005; Shohamy & Adcock, 2010).

In humans, several studies have linked rewards to memory enhancement. Reward-related memory enhancements have been associated with increased BOLD activity in the midbrain, and in greater connectivity between the midbrain and the hippocampus (Adcock et al., 2006; Bunzeck et al., 2012; Cohen et al., 2014; Krebs et al., 2009; Wittmann et al., 2005; Wolosin et al., 2012). Moreover, increases in midbrain activation

and midbrain-hippocampal correlations elicited in *anticipation* of the image have been shown to predict later memory performance (Adcock et al., 2006; Wolosin et al., 2012), even when the reward is information itself (Gruber et al., 2014). These studies show that the anticipation of either extrinsic or intrinsic rewards can enhance episodic memory via coupled activation in dopamine-rich midbrain regions and the hippocampus. Related research suggests that people whose memory is most influenced by incentivization cues, are also more likely to recruit cortical regions associated with deep, elaborative encoding (Cohen et al., 2014). Thus, the motivation incited by imbuing episodic learning with the promise of rewards may promote memory formation through multiple routes.

Importantly, rewards can also retroactively enhance memory for neutral events that preceded them (Braun et al., 2018; Murayama & Kuhbandner, 2011; Patil et al., 2017, see Dunsmoor et al., 2015 for punishments driving similar effects). These behavioral findings are consistent with the notion of reward-based tagging; moreover, paralleling dopaminergic modulation of l-LTP, this retroactive influence on memory performance is most strongly observed after long delays. Alternatively, enhanced hippocampal replay following reward may drive its retroactive benefits. Rodent hippocampal neurons replay recent spatial trajectories at higher rates following the receipt of reward (Ambrose et al., 2016; Singer & Frank, 2009), and rewarded trajectories are disproportionately reflected in hippocampal replay bouts (Michon et al., 2019). Disruption of potential replay opportunities in this study also disrupted the animals' memory for highly rewarded locations, while leaving lower reward locations comparatively intact.

FMRI research in humans also suggests that rewarded events are more strongly represented during consolidation than neutral events that were not rewarded (Gruber et al., 2016). During rest periods, functional connectivity between the dopaminergic midbrain and the hippocampus in one study (Gruber et al., 2016), and higher-order sensory cortices representing highly-rewarded visual categories in another (Murty et al., 2017) were related to enhanced memory for rewarded events. Together, these studies show that dopamine contributes to the prioritized consolidation of episodic memories by

reward – even rewards given after the event – allowing hippocampal memories to be shaped by their motivational significance (**Figure 3**).

Other research has explored how midbrain dopamine neurons mediate in the effects of novelty on hippocampal memories. One model suggests that signals arising from the hippocampus could regulate dopamine release which, in turn, regulates hippocampal memory formation (J. E. Lisman & Grace, 2005). According to this model, the hippocampus detects novel and unexpected events by comparing ongoing experience to retrieved memories, resulting in a novelty signal which then travels through a multi-synaptic pathway to disinhibit dopamine neurons in the VTA (Floresco et al., 2001, 2003; Glangetas et al., 2015; Luo et al., 2011). Consistent with this perspective, novelty is associated with stronger hippocampus-dependent memories both in rodents and in humans. Extensive research in rodents has shown that exploration of a novel open field tens of minutes before learning increases the long-term retention of memories (see Moncada et al., 2015 for a review). This novelty induced "behavioral tagging" phenomenon, and the underlying enhancement of l-LTP, has been shown to depend on D1-type receptor activation in the hippocampus (Li et al., 2003; Takeuchi et al., 2016). Novelty has also been shown to boost learning in humans: material learned tens of minutes following exposure to novel images is better remembered later on (Fenker et al., 2008; Schomaker et al., 2014). The lingering benefits of novelty for learning have even been observed in the classroom (Ballarini et al., 2013). Although these demonstrations have not been directly linked to dopamine, the demonstrated persistent reach of novelty is consistent with the timing of dopamine-dependent behavioural tagging in rodents.

Finally, an important question is the extent to which hippocampal modulation of memories is related specifically to reward prediction errors as in "model-free" reinforcement learning algorithms. Studies that have leveraged reinforcement learning models to target the influence of prediction errors on hippocampal memories have led to mixed results (De Loof et al., 2018; Jang et al., 2019; Rouhani et al., 2018; Wimmer et al., 2014). In one study, trial unique object images were incidentally presented on top of repeating choice options, which were stochastically predictive of monetary rewards (Wimmer et al., 2014), revealing that later object recognition performance was negatively

related to model-estimated reward prediction errors as well as to reward prediction error BOLD responses in the striatum. By contrast, reward prediction errors were positively related to later object recognition in a task in which object images were used to signal the probability of obtaining recently cued outcomes (Jang et al., 2019). Though, it should be noted that neither the reward prediction errors associated with the preceding cue nor those associated with the following outcome predicted later object memory, despite occurring so close in time. Further, the influence of object prediction errors on memory did not depend on an intervening consolidation period, as would be expected if this effect was mediated by dopamine. Thus, while there is strong evidence that rewards modulate hippocampal memory formation, there are mixed findings regarding the effect of reward prediction error signals on episodic memory. As discussed below, this may be related in part to questions about which form of reinforcement-learning models most closely relates to hippocampal memory function.

Dopamine and the integration of episodic memories: building a "world model"

As described in *Section 3,* model-based reinforcement learning involves building a world model that reflects past experiences and the relations between them, information that is not represented in model-free algorithms. (Daw et al., 2005, 2011; Dolan & Dayan, 2013; Shohamy & Daw, 2015). The hippocampus is thought to contribute to the construction of the sort of structured associations that underlie this world model (Davachi, 2006; Dusek & Eichenbaum, 1997; Gershman & Daw, 2017; Konkel & Cohen, 2009; Miller et al., 2017; Shohamy & Adcock, 2010; Wimmer & Shohamy, 2012). It has been suggested that the role of the hippocampus in building a world model may be specifically linked to its broader role in relational and temporal memories for individual events (Gershman et al., 2012).

Recent work suggests that dopamine may play a particularly important role in integrating memories to build such a world model. A task used in both rodents and humans to test model-based behavior is "sensory preconditioning" (Brogden, 1939; Jones et al., 2012; Wimmer & Shohamy, 2012). Sensory preconditioning plays out over three phases. In the first phase, two otherwise unrelated stimuli (*S1* & *S2*) are associated by repeatedly

presenting them in sequence. Then, one stimulus is reinforced, e.g. by pairing *S2* with a reward. In the critical test phase, subjects choose between *S1* and another equally familiar stimulus to determine whether the learned value of *S2* transferred to *S1*. Humans and other animals tend to prefer *S1* despite it never being directly rewarded (**Figure 4**).

In humans, fMRI studies have shown that this sort of behavior involves the hippocampus, as well as correlated activity in midbrain dopamine regions and in the ventral striatum, itself a target of midbrain dopamine projections (Shohamy & Wagner, 2008; Wimmer & Shohamy, 2012). For example, the later transfer of value in a sensory preconditioning task was linked to hippocampal BOLD responses and functional connectivity with the striatum during *S2* reward (Wimmer & Shohamy, 2012). At the same time, value transfer was also related to evidence of the neural reactivation of the *S1* stimulus that was associated with the rewarded *S2* stimulus. The link between neural reactivation and later transfer was also observed in an MEG study using a similar paradigm, in which MEG's greater temporal resolution isolated transfer-related reactivation to a few hundred milliseconds following reward (Kurth-Nelson et al., 2015). These studies in humans highlight the role of the hippocampus in model-based learning. Moreover, the finding that hippocampal contributions were related to its correlation with midbrain dopamine regions and their ventral striatal targets suggests that such transfer may also involve dopamine.

More direct evidence for dopamine in model-based inference comes from a series of sensory preconditioning studies in rodents (Keiflin et al., 2017; Sharpe et al., 2017). Like humans, rodents also show a preference for the *S1* stimulus after undergoing sensory preconditioning. In these studies, optogenetic activation of midbrain dopamine neurons during the first phase of learning had a direct effect on sensory preconditioning in rodents, enhancing the learned association between the *S1-S2* cues. Notably, activation of dopamine neurons did not have a general effect on value learning, *per se*, rather it specifically drove learning of the *S1-S2* association, suggesting a specific role for midbrain dopamine neurons in model-based behaviors.

The specific mechanisms by which dopamine supports model-based learning remain unknown. Specifically, while the rodent optogenetic studies show a direct role for midbrain dopamine neurons, it is as yet unclear which dopaminergic targets are involved. The human fMRI data suggest that the hippocampus is a strong candidate, while parallel lesion work in rodents also implicates the OFC (Jones et al., 2012), which may play a complementary role to that of the hippocampus in supporting model-based learning (Wimmer & Shohamy, 2012; Zhou et al., 2019). Moreover, as reviewed in *Section 3*, open questions remain regarding whether midbrain dopamine neurons and their striatal targets contribute to both model-based learning and model-free learning (Daw et al., 2011), or just one or the other. Resolving this question is challenging in part because apparently habitual behavior demonstrated in many model-free paradigms could also be generated through model-based learning.

In summary, studies highlight a role for interactions between midbrain dopamine regions and the hippocampus in several key functions, including prioritization of memory for reward- and novelty-related events, and integrating associations across memories to build an adaptive world model. These functions ensure that the content of memory is relevant and that it can be deployed flexibly to guide future behavior.

## 5. Conclusions and future directions

Dopamine modulates neural plasticity in several key targets, playing an essential role in learning and memory. Here, we focused on two main regions – the striatum and the hippocampus. These regions each support different aspects of learning, each is modulated by dopaminergic inputs, and in each region dopamine serves to enhance the encoding of motivationally relevant information and to shape adaptive behavior.

Much of the work reviewed here examines the role of dopamine on striatal and hippocampal learning mechanisms separately. In addition to these local effects, dopamine is also likely to influence the interaction between the striatum and the hippocampus. Indeed, while early theories of the organization of memory emphasized the separate and

distinct roles of the striatum and the hippocampus in learning, there is now extensive evidence for functionally relevant interactions between them (e.g. K. Duncan et al., 2018; Foerde & Shohamy, 2011b; Poldrack et al., 2001; Shadlen & Shohamy, 2016; Wimmer & Shohamy, 2012). Moreover, dopaminergic projections to the prefrontal cortex play a critical role in the maintenance and gating of working memory functions (see Chapters 2.9 and 2.10), and these processes also interact with action control and selection processes in the striatum (Chatham et al., 2014; Collins et al., 2017; Collins & Frank, 2012), as well as with long-term episodic memory (Forsberg et al., 2020; Fukuda & Vogel, 2019). Thus, an important goal for future research is to understand how dopamine affects the nature of these interactions at the circuit-level and the implications for learning-guided behavior.

Finally, another important area of ongoing investigation has to do with the timescale of the effects of dopamine on learning. As mentioned earlier, in rodents, studies have shown that dopamine is particularly important for facilitating long-term changes in synaptic plasticity in the hippocampal (Bethus et al., 2010; McNamara et al., 2014; O'Carroll et al., 2006; Takeuchi et al., 2016). Similarly, work in non-human primates has identified an important role for dopamine in learning of value memory representations that can be stable for up to months (Ghazizadeh, Griggs, et al., 2018; Ghazizadeh, Hong, et al., 2018; Kim et al., 2015). These results suggest that dopamine may be particularly important for enhancing the long-term persistence of learning.

However, results in humans have been mixed: while some pharmacological studies show long-term effects of dopamine agonists on memory consolidation, others show short-term effects of dopamine on learning (Chowdhury et al., 2012; Grogan, 2015; Sharp et al., 2015; Shiner et al., 2012). The discrepancies are likely due, in part, to the different kinds of paradigms used across studies, as well is to the differential effects of dopamine on different targets, such as the prefrontal cortex vs. the hippocampus. A better understanding of the timescale of effects of dopamine on different forms of learning is needed. One fruitful approach may be to take into account both the different timescales as well as the different forms of memory that dopamine may modulate. Most existing

studies focussed on a subset of these factors, for example, manipulating either short term or long term effects of dopamine, and measuring their impact on either habit learning, working memory, or long-term episodic memory. Combining manipulations of dopamine at different timescales with behavioral probes that measure different forms of learning will be a useful approach for dissecting the complementary and potentially interactive effects of dopamine on different forms of learning.

Our understanding of dopamine's function has undergone a complex evolution. Dopamine was initially viewed as the physiological manifestation of our hedonistic drives to which we are inextricable and insatiably drawn. The discovery that firing patterns in midbrain dopamine neurons parallels the computation of reward prediction error signals in machine learning led to a vast change in this view, recasting the essential role of dopamine in terms of learning. As we reviewed here, emerging research broadly supports the tight links between dopamine and learning, while continuing to raise questions about its precise role. Recent studies suggest that the role of dopamine in learning is multifaceted, reflecting its actions along distinct pathways, in distinct targets, at a variety of timescales. Together, this more complex view emphasizes the importance of dopamine for *flexible* behaviour. Specifically, by prioritizing motivationally salient events in our memory and facilitating the scaffolding of world models based on these experiences, one of the chief contributions of dopamine in learning may be to foster our ability to use past experience to guide future-oriented choices.

## REFERENCES

Adcock, R. A., Thangavel, A., Whitfield-Gabrieli, S., Knutson, B., & Gabrieli, J. D. E. (2006). Reward-motivated learning: mesolimbic activation precedes memory formation. Neuron, 50(3), 507–517.

Ambrose, R. E., Pfeiffer, B. E., & Foster, D. J. (2016). Reverse replay of hippocampal place cells is uniquely modulated by changing reward. Neuron, 91(5), 1124–1136.

Aransay, A., Rodríguez-López, C., García-Amado, M., Clascá, F., & Prensa, L. (2015). Long-range projection neurons of the mouse ventral tegmental area: A single-cell axon tracing analysis. Frontiers in Neuroanatomy, 9(MAY). https://doi.org/10.3389/fnana.2015.00059

Atherton, L. A., Dupret, D., & Mellor, J. R. (2015). Memory trace replay: the shaping of memory consolidation by neuromodulation. Trends in Neurosciences, 38(9), 560–570.

Ballarini, F., Martínez, M. C., Díaz Perez, M., Moncada, D., & Viola, H. (2013). Memory in Elementary School Children Is Improved by an Unrelated Novel Experience. PloS One, 8(6), e66875.

Beier, K. T., Steinberg, E. E., DeLoach, K. E., Xie, S., Miyamichi, K., Schwarz, L., Gao, X. J., Kremer, E. J., Malenka, R. C., & Luo, L. (2015). Circuit Architecture of VTA Dopamine Neurons Revealed by Systematic Input-Output Mapping. Cell, 162(3), 622–634.

Berridge, K. C. (2007). The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology, 191(3), 391–431.

Bethus, I., Tse, D., & Morris, R. G. M. (2010). Dopamine and memory: modulation of the persistence of memory for novel hippocampal NMDA receptor-dependent paired associates. Journal of Neuroscience, 30(5), 1610–1618.

Björklund, A., & Dunnett, S. B. (2007). Dopamine neuron systems in the brain: an update. In Trends in Neurosciences (Vol. 30, Issue 5, pp. 194–202). https://doi.org/10.1016/j.tins.2007.03.006

Braun, E. K., Wimmer, G. E., & Shohamy, D. (2018). Retroactive and graded

prioritization of memory by reward. Nature Communications, 9(1), 4886.

Brischoux, F., Chakraborty, S., Brierley, D. I., & Ungless, M. A. (2009). Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. Proceedings of the National Academy of Sciences of the United States of America, 106(12), 4894–4899.

Brogden, W. J. (1939). Sensory pre-conditioning. Journal of Experimental Psychology, 25(4), 323.

Bromberg-Martin, E. S., & Hikosaka, O. (2009). Midbrain dopamine neurons signal preference for advance information about upcoming rewards. Neuron, 63(1), 119–126.

Bromberg-Martin, E. S., Matsumoto, M., & Hikosaka, O. (2010). Dopamine in motivational control: rewarding, aversive, and alerting. Neuron, 68(5), 815–834.

Broussard, J. I., Jenson, D., & Dani, J. A. (2012). Dopaminergic influence over hippocampal synaptic plasticity and function. Clinical and Experimental Pharmacology & Physiology, 2(3), e108.

Bunzeck, N., Doeller, C. F., Dolan, R. J., & Duzel, E. (2012). Contextual interaction between novelty and reward processing within the mesolimbic system. Human Brain Mapping, 33(6), 1309–1324.

Carr, M. F., Jadhav, S. P., & Frank, L. M. (2011). Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. Nature Neuroscience, 14(2), 147.

Carter, R. M., MacInnes, J. J., Huettel, S. A., & Adcock, R. A. (2009). Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses. Frontiers in Behavioral Neuroscience, 3, 21.

Chatham, C. H., Frank, M. J., & Badre, D. (2014). Corticostriatal output gating during selection from working memory. Neuron, 81(4), 930–942.

Chowdhury, R., Guitart-Masip, M., Bunzeck, N., Dolan, R. J., & Düzel, E. (2012). Dopamine modulates episodic memory persistence in old age. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 32(41), 14193–14204.

Ciliax, B. J., Nash, N., Heilman, C., Sunahara, R., Hartney, A., Tiberi, M., Rye, D. B.,

Caron, M. G., Niznik, H. B., & Levey, A. I. (2000). Dopamine D(5) receptor immunolocalization in rat and monkey brain. Synapse , 37(2), 125–145.

Cohen, M. S., Rissman, J., Suthana, N. A., Castel, A. D., & Knowlton, B. J. (2014). Value-based modulation of memory encoding involves strategic engagement of fronto-temporal semantic processing regions. Cognitive, Affective & Behavioral Neuroscience, 14(2), 578–592.

Collins, A. G. E., Ciullo, B., Frank, M. J., & Badre, D. (2017). Working Memory Load Strengthens Reward Prediction Errors. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 37(16), 4332–4342.

Collins, A. G. E., & Frank, M. J. (2012). How much of reinforcement learning is working memory, not reinforcement learning? A behavioral, computational, and neurogenetic analysis. The European Journal of Neuroscience, 35(7), 1024–1035.

D'Ardenne, K., Lohrenz, T., Bartley, K. A., & Montague, P. R. (2013). Computational heterogeneity in the human mesencephalic dopamine system. Cognitive, Affective & Behavioral Neuroscience, 13(4), 747–756.

Davachi, L. (2006). Item, context and relational episodic encoding in humans. Current Opinion in Neurobiology, 16(6), 693–700.

Daw, N. D., Gershman, S. J., Seymour, B., Dayan, P., & Dolan, R. J. (2011). Model-based influences on humans' choices and striatal prediction errors. Neuron, 69(6), 1204–1215.

Daw, N. D., Niv, Y., & Dayan, P. (2005). Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. Nature Neuroscience, 8(12), 1704.

Dawson, T. M., Gehlert, D. R., McCabe, R. T., Barnett, A., & Wamsley, J. K. (1986). D-1 dopamine receptors in the rat brain: a quantitative autoradiographic analysis. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 6(8), 2352–2365.

de Jong, J. W., Afjei, S. A., Pollak Dorocic, I., Peck, J. R., Liu, C., Kim, C. K., Tian, L., Deisseroth, K., & Lammel, S. (2019). A Neural Circuit Mechanism for Encoding Aversive Stimuli in the Mesolimbic Dopamine System. Neuron, 101(1), 133–151.e7.

Delgado, M. R., Jou, R. L., LeDoux, J., & Phelps, L. (2009). Avoiding negative outcomes: tracking the mechanisms of avoidance learning in humans during fear conditioning. Frontiers in Behavioral Neuroscience, 3, 33.

De Loof, E., Ergo, K., Naert, L., Janssens, C., Talsma, D., Van Opstal, F., & Verguts, T. (2018). Signed reward prediction errors drive declarative learning. PloS One, 13(1), e0189212.

Dolan, R. J., & Dayan, P. (2013). Goals and habits in the brain. Neuron, 80(2), 312–325.

Duncan, K., Doll, B. B., Daw, N. D., & Shohamy, D. (2018). More Than the Sum of Its Parts: A Role for the Hippocampus in Configural Reinforcement Learning. Neuron, 98(3), 645–657.e6.

Duncan, K. D., & Schlichting, M. L. (2018). Hippocampal representations as a function of time, subregion, and brain state. Neurobiology of Learning and Memory, 153(Pt A), 40–56.

Duncan, K., Tompary, A., & Davachi, L. (2014). Associative encoding and retrieval are predicted by functional connectivity in distinct hippocampal area CA1 pathways. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 34(34), 11188–11198.

Dunsmoor, J. E., Murty, V. P., Davachi, L., & Phelps, E. A. (2015). Emotional learning selectively and retroactively strengthens memories for related events. Nature, 520(7547), 345.

Dusek, J. A., & Eichenbaum, H. (1997). The hippocampus and memory for orderly stimulus relations. Proceedings of the National Academy of Sciences, 94(13), 7109–7114.

Eichenbaum, H., & Cohen, N. J. (2004). From conditioning to conscious recollection: Memory systems of the brain. Oxford University Press on Demand.

Fenker, D. B., Frey, J. U., Schuetze, H., Heipertz, D., Heinze, H.-J., & Duzel, E. (2008). Novel scenes improve recollection and recall of words. Journal of Cognitive Neuroscience, 20(7), 1250–1265.

Fiorillo, C. D., Tobler, P. N., & Schultz, W. (2003). Discrete coding of reward probability and uncertainty by dopamine neurons. Science, 299(5614), 1898–1902.

Fiorillo, C. D., & Williams, J. T. (1998). Glutamate mediates an inhibitory postsynaptic

potential in dopamine neurons. Nature, 394(6688), 78–82.

Floresco, S. B., Todd, C. L., & Grace, A. A. (2001). Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 21(13), 4915–4922.

Floresco, S. B., West, A. R., Ash, B., Moore, H., & Grace, A. A. (2003). Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. Nature Neuroscience, 6(9), 968–973.

Foerde, K., Race, E., Verfaellie, M., & Shohamy, D. (2013). A role for the medial temporal lobe in feedback-driven learning: evidence from amnesia. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 33(13), 5698–5704.

Foerde, K., & Shohamy, D. (2011a). The role of the basal ganglia in learning and memory: insight from Parkinson's disease. Neurobiology of Learning and Memory, 96(4), 624–636.

Foerde, K., & Shohamy, D. (2011b). Feedback timing modulates brain systems for learning in humans. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 31(37), 13157–13167.

Forsberg, A., Guitard, D., & Cowan, N. (2020). Working memory limits severely constrain long-term retention. Psychonomic Bulletin & Review. https://doi.org/10.3758/s13423-020-01847-z

Foster, D. J., & Wilson, M. A. (2006). Reverse replay of behavioural sequences in hippocampal place cells during the awake state. Nature, 440(7084), 680–683.

Frank, M. J., Seeberger, L. C., & O'Reilly, R. C. (2004). By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science, 306(5703), 1940–1943.

Fukuda, K., & Vogel, E. K. (2019). Visual short-term memory capacity predicts the "bandwidth" of visual long-term memory encoding. Memory & Cognition, 47(8), 1481–1497.

Gabrieli, J. D. E. (1998). Cognitive neuroscience of human memory. Annual Review of Psychology, 49(1), 87–115.

Gasbarri, A., Packard, M. G., Campana, E., & Pacitti, C. (1994). Anterograde and

retrograde tracing of projections from the ventral tegmental area to the hippocampal formation in the rat. Brain Research Bulletin, 33(4), 445–452.

Gasbarri, A., Sulli, A., & Packard, M. G. (1997). The dopaminergic mesencephalic projections to the hippocampal formation in the rat. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 21(1), 1–22.

Gershman, S. J., & Daw, N. D. (2017). Reinforcement learning and episodic memory in humans and animals: an integrative framework. Annual Review of Psychology, 68, 101–128.

Gershman, S. J., Moore, C. D., Todd, M. T., Norman, K. A., & Sederberg, P. B. (2012). The successor representation and temporal context. Neural Computation, 24(6), 1553–1568.

Ghazizadeh, A., Griggs, W., Leopold, D. A., & Hikosaka, O. (2018). Temporal–prefrontal cortical network for discrimination of valuable objects in long-term memory. Proceedings of the National Academy of Sciences of the United States of America, 115(9), E2135–E2144.

Ghazizadeh, A., Hong, S., & Hikosaka, O. (2018). Prefrontal Cortex Represents Long-Term Memory of Object Values for Months. Current Biology: CB, 28(14), 2206–2217.e5.

Glangetas, C., Fois, G. R., Jalabert, M., Lecca, S., Valentinova, K., Meye, F. J., Diana, M., Faure, P., Mameli, M., Caille, S., & Georges, F. (2015). Ventral Subiculum Stimulation Promotes Persistent Hyperactivity of Dopamine Neurons and Facilitates Behavioral Effects of Cocaine. Cell Reports, 13(10), 2287–2296.

Glimcher, P. W. (2011). Understanding dopamine and reinforcement learning: the dopamine reward prediction error hypothesis. Proceedings of the National Academy of Sciences of the United States of America, 108 Suppl 3, 15647–15654.

Gomperts, S. N., Kloosterman, F., & Wilson, M. A. (2015). VTA neurons coordinate with the hippocampal reactivation of spatial experience. eLife, 4, e05360.

Grogan, J. P. (2015). Roles of dopamine in human memory. University of Bristol.

Gruber, M. J., Gelman, B. D., & Ranganath, C. (2014). States of curiosity modulate hippocampus-dependent learning via the dopaminergic circuit. Neuron, 84(2), 486–496.

Gruber, M. J., Ritchey, M., Wang, S.-F., Doss, M. K., & Ranganath, C. (2016). Post-learning Hippocampal Dynamics Promote Preferential Retention of Rewarding Events. Neuron, 89(5), 1110–1120.

Haber, S. N., Fudge, J. L., & McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. Journal of Neuroscience, 20(6), 2369–2382.

Hamilton, P. N., & Mackay, A. V. P. (1976). A sensitive gas-liquid chromatographic assay for homovanillic acid (HVA) and 3, 4-dihydroxyphenylacetic acid (DOPAC) applied to twenty areas of the human brain. Brain Research, 118(1), 161–166.

Horvitz, J. C. (2000). Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. Neuroscience, 96(4), 651–656.

Horvitz, J. C. (2002). Dopamine gating of glutamatergic sensorimotor and incentive motivational input signals to the striatum. Behavioural Brain Research, 137(1-2), 65–74.

Huang, Y.-Y., & Kandel, E. R. (1995). D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. Proceedings of the National Academy of Sciences, 92(7), 2446–2450.

Ikemoto Satoshi. (2007). Dopamine reward cicuitry:two projection systems from the ventral midbrian to the nucleus accumbens-olfactory tubercle complex. Brain Research Reviews, 56(1), 27–78.

Ilieva, I. P., Hook, C. J., & Farah, M. J. (2015). Prescription Stimulants' Effects on Healthy Inhibitory Control, Working Memory, and Episodic Memory: A Meta-analysis. Journal of Cognitive Neuroscience, 27(6), 1069–1089.

Jadhav, S. P., Kemere, C., German, P. W., & Frank, L. M. (2012). Awake hippocampal sharp-wave ripples support spatial memory. Science, 336(6087), 1454–1458.

Jang, A. I., Nassar, M. R., Dillon, D. G., & Frank, M. J. (2019). Positive reward prediction errors during decision-making strengthen memory encoding. Nature Human Behaviour, 3(7), 719–732.

Jiao, X., Paré, W. P., & Tejani-Butt, S. (2003). Strain differences in the distribution of dopamine transporter sites in rat brain. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 27(6), 913–919.

Jones, J. L., Esber, G. R., McDannald, M. A., Gruber, A. J., Hernandez, A., Mirenzi, A., & Schoenbaum, G. (2012). Orbitofrontal cortex supports behavior and learning using inferred but not cached values. Science, 338(6109), 953–956.

Kahn, I., & Shohamy, D. (2013). Intrinsic connectivity between the hippocampus, nucleus accumbens, and ventral tegmental area in humans. Hippocampus, 23(3), 187–192.

Keiflin, R., Pribut, H. J., Shah, N. B., & Janak, P. H. (2017). Phasic activation of ventral tegmental, but not substantia nigra, dopamine neurons promotes model-based Pavlovian reward learning. BioRxiv, 232678.

Kempadoo, K. A., Mosharov, E. V., Choi, S. J., Sulzer, D., & Kandel, E. R. (2016). Dopamine release from the locus coeruleus to the dorsal hippocampus promotes spatial learning and memory. Proceedings of the National Academy of Sciences, 113(51), 14835–14840.

Kim, H. F., Ghazizadeh, A., & Hikosaka, O. (2015). Dopamine Neurons Encoding Long-Term Memory of Object Value for Habitual Behavior. Cell, 163(5), 1165–1175.

Konkel, A., & Cohen, N. J. (2009). Relational memory and the hippocampus: representations and methods. Frontiers in Neuroscience, 3, 23.

Krebs, R. M., Schott, B. H., Schütze, H., & Düzel, E. (2009). The novelty exploration bonus and its attentional modulation. Neuropsychologia, 47(11), 2272–2281.

Kurth-Nelson, Z., Barnes, G., Sejdinovic, D., Dolan, R., & Dayan, P. (2015). Temporal structure in associative retrieval. eLife, 4, e04919.

Lammel, S., Lim, B. K., Ran, C., Huang, K. W., Betley, M. J., Tye, K. M., Deisseroth, K., & Malenka, R. C. (2012). Input-specific control of reward and aversion in the ventral tegmental area. Nature, 491(7423), 212–217.

Leh, S. E., Ptito, A., Chakravarty, M. M., & Strafella, A. P. (2007). Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study. Neuroscience Letters, 419(2), 113–118.

Lemon, N., & Manahan-Vaughan, D. (2006). Dopamine D1/D5 receptors gate the acquisition of novel information through hippocampal long-term potentiation and long-term depression. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 26(29), 7723–7729.

Lerner, T. N., Shilyansky, C., Davidson, T. J., Evans, K. E., Beier, K. T., Zalocusky, K. A., Crow, A. K., Malenka, R. C., Luo, L., Tomer, R., & Deisseroth, K. (2015). Intact-Brain Analyses Reveal Distinct Information Carried by SNc Dopamine Subcircuits. Cell, 162(3), 635–647.

Lewis, D. A., Melchitzky, D. S., Sesack, S. R., Whitehead, R. E., Auh, S., & Sampson, A. (2001). Dopamine transporter immunoreactivity in monkey cerebral cortex: regional, laminar, and ultrastructural localization. The Journal of Comparative Neurology, 432(1), 119–136.

Lewis, D. A., & Sesack, S. R. (1997). Dopamine systems in the primate brain. Handbook of chemical neuroanatomy, volume 13: the primate nervous system, part I. Amsterdam: Elsevier.

Lindvall, O., Björklund, A., & Divac, I. (1977). Organization of mesencephalic dopamine neurons projecting to neocortex and septum. Advances in Biochemical Psychopharmacology, 16, 39–46.

Lindvall, O., Björklund, A., Moore, R. Y., & Stenevi, U. (1974). Mesencephalic dopamine neurons projecting to neocortex. Brain Research, 81(2), 325–331.

Li, S., Cullen, W. K., Anwyl, R., & Rowan, M. J. (2003). Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. Nature Neuroscience, 6(5), 526.

Lisman, J. E., & Grace, A. A. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. Neuron, 46(5), 703–713.

Lisman, J., Grace, A. A., & Duzel, E. (2011). A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. Trends in Neurosciences, 34(10), 536–547.

Luo, A. H., Tahsili-Fahadan, P., Wise, R. A., Lupica, C. R., & Aston-Jones, G. (2011). Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. Science, 333(6040), 353–357.

Maia, T. V., & Frank, M. J. (2011). From reinforcement learning models to psychiatric and neurological disorders. Nature Neuroscience, 14(2), 154.

Margolis, E. B., Lock, H., Hjelmstad, G. O., & Fields, H. L. (2006). The ventral tegmental area revisited: Is there an electrophysiological marker for dopaminergic

neurons? The Journal of Physiology, 577(3), 907–924.

Matsuda, W., Furuta, T., Nakamura, K. C., Hioki, H., Fujiyama, F., Arai, R., & Kaneko, T. (2009). Behavioral/Systems/Cognitive Single Nigrostriatal Dopaminergic Neurons Form Widely Spread and Highly Dense Axonal Arborizations in the Neostriatum. https://doi.org/10.1523/JNEUROSCI.4029-08.2009

Matsumoto, M., & Hikosaka, O. (2009). Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature, 459(7248), 837–841.

Matsumoto, M., & Takada, M. (2013). Distinct representations of cognitive and motivational signals in midbrain dopamine neurons. Neuron, 79(5), 1011–1024.

Mazzoni, P., Hristova, A., & Krakauer, J. W. (2007). Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. Journal of Neuroscience, 27(27), 7105–7116.

McClelland, J. L., McNaughton, B. L., & O'Reilly, R. C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychological Review, 102(3), 419–457.

McClure, S. M., Berns, G. S., & Montague, P. R. (2003). Temporal prediction errors in a passive learning task activate human striatum. Neuron, 38(2), 339–346.

McNamara, C. G., Tejero-Cantero, Á., Trouche, S., Campo-Urriza, N., & Dupret, D. (2014). Dopaminergic neurons promote hippocampal reactivation and spatial memory persistence. Nature Neuroscience, 17(12), 1658.

Michon, F., Sun, J.-J., Kim, C. Y., Ciliberti, D., & Kloosterman, F. (2019). Post-learning Hippocampal Replay Selectively Reinforces Spatial Memory for Highly Rewarded Locations. Current Biology: CB, 29(9), 1436–1444.e5.

Miller, K. J., Botvinick, M. M., & Brody, C. D. (2017). Dorsal hippocampus contributes to model-based planning. Nature Neuroscience, 20(9), 1269.

Moncada, D., Ballarini, F., & Viola, H. (2015). Behavioral Tagging: A Translation of the Synaptic Tagging and Capture Hypothesis. Neural Plasticity, 2015, 650780.

Moncada, D., & Viola, H. (2007). Induction of long-term memory by exposure to novelty requires protein synthesis: evidence for a behavioral tagging. Journal of Neuroscience, 27(28), 7476–7481.

Montague, P. R., Dayan, P., & Sejnowski, T. J. (1996). A framework for mesencephalic dopamine systems based on predictive Hebbian learning. Journal of Neuroscience, 16(5), 1936–1947.

Murayama, K., & Kuhbandner, C. (2011). Money enhances memory consolidation–But only for boring material. Cognition, 119(1), 120–124.

Murty, V. P., Tompary, A., Adcock, R. A., & Davachi, L. (2017). Selectivity in Postencoding Connectivity with High-Level Visual Cortex Is Associated with Reward-Motivated Memory. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 37(3), 537–545.

Nair-Roberts, R. G., Chatelain-Badie, S. D., Benson, E., White-Cooper, H., Bolam, J. P., & Ungless, M. A. (2008). Stereological estimates of dopaminergic, GABAergic and glutamatergic neurons in the ventral tegmental area, substantia nigra and retrorubral field in the rat. Neuroscience, 152(4), 1024–1031.

Niv, Y., Daw, N. D., Joel, D., & Dayan, P. (2007). Tonic dopamine: opportunity costs and the control of response vigor. Psychopharmacology, 191(3), 507–520.

Nomoto, K., Schultz, W., Watanabe, T., & Sakagami, M. (2010). Temporally extended dopamine responses to perceptually demanding reward-predictive stimuli. Journal of Neuroscience, 30(32), 10692–10702.

Oades, R. D., & Halliday, G. M. (1987). Ventral tegmental (A10) system: neurobiology. 1. Anatomy and connectivity. In Brain Research Reviews (Vol. 12, Issue 2, pp. 117–165). https://doi.org/10.1016/0165-0173(87)90011-7

O'Carroll, C. M., Martin, S. J., Sandin, J., Frenguelli, B., & Morris, R. G. M. (2006). Dopaminergic modulation of the persistence of one-trial hippocampus-dependent memory. Learning & Memory , 13(6), 760–769.

O'Doherty, J. P., Dayan, P., Friston, K., Critchley, H., & Dolan, R. J. (2003). Temporal difference models and reward-related learning in the human brain. Neuron, 38(2), 329–337.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other brain regions in the rat./. comp. physiol. Psychol. https://doi.org/10.1037/h0058775

O'Neill, J., Pleydell-Bouverie, B., Dupret, D., & Csicsvari, J. (2010). Play it again:

reactivation of waking experience and memory. Trends in Neurosciences, 33(5), 220–229.

Ott, T., & Nieder, A. (2019). Dopamine and Cognitive Control in Prefrontal Cortex. Trends in Cognitive Sciences, 23(3), 213–234.

Patil, A., Murty, V. P., Dunsmoor, J. E., Phelps, E. A., & Davachi, L. (2017). Reward retroactively enhances memory consolidation for related items. Learning & Memory , 24(1), 65–69.

Pessiglione, M., Seymour, B., Flandin, G., Dolan, R. J., & Frith, C. D. (2006). Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature, 442(7106), 1042.

Pfeiffer, B. E., & Foster, D. J. (2013). Hippocampal place-cell sequences depict future paths to remembered goals. Nature, 497(7447), 74–79.

Pierce, R. C., & Kumaresan, V. (2006). The mesolimbic dopamine system: the final common pathway for the reinforcing effect of drugs of abuse? Neuroscience and Biobehavioral Reviews, 30(2), 215–238.

Poldrack, R. A., Clark, J., Paré-Blagoev, E. J., Shohamy, D., Creso Moyano, J., Myers, C., & Gluck, M. A. (2001). Interactive memory systems in the human brain. Nature, 414(6863), 546–550.

Poldrack, R. A., & Packard, M. G. (2003). Competition among multiple memory systems: converging evidence from animal and human brain studies. Neuropsychologia, 41(3), 245–251.

Redgrave, P., & Gurney, K. (2006). The short-latency dopamine signal: a role in discovering novel actions? Nature Reviews. Neuroscience, 7(12), 967–975.

Redgrave, P., Gurney, K., & Reynolds, J. (2008). What is reinforced by phasic dopamine signals? Brain Research Reviews, 58(2), 322–339.

Redgrave, P., Prescott, T. J., & Gurney, K. (1999). Is the short-latency dopamine response too short to signal reward error? Trends in Neurosciences, 22(4), 146–151.

Redondo, R. L., & Morris, R. G. M. (2011). Making memories last: the synaptic tagging and capture hypothesis. Nature Reviews. Neuroscience, 12(1), 17–30.

Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning : Variations in the effectiveness of reinforcement and nonreinforcement. Current Research and

Theory, 64–99.

Robbins, T. W., & Everitt, B. J. (2007). A role for mesencephalic dopamine in activation: commentary on Berridge (2006). Psychopharmacology, 191(3), 433–437.

Rodríguez-López, C., Clascá, F., & Prensa, L. (2017). The mesoaccumbens pathway: A retrograde labeling and single-cell axon tracing analysis in the mouse. Frontiers in Neuroanatomy, 11. https://doi.org/10.3389/FNANA.2017.00025

Rosen, Z. B., Cheung, S., & Siegelbaum, S. A. (2015). Midbrain dopamine neurons bidirectionally regulate CA3-CA1 synaptic drive. Nature Neuroscience, 18(12), 1763.

Rossato, J. I., Bevilaqua, L. R. M., Izquierdo, I., Medina, J. H., & Cammarota, M. (2009). Dopamine controls persistence of long-term memory storage. Science, 325(5943), 1017–1020.

Rouhani, N., Norman, K. A., & Niv, Y. (2018). Dissociable effects of surprising rewards on learning and memory. Journal of Experimental Psychology. Learning, Memory, and Cognition, 44(9), 1430–1443.

Roumis, D. K., & Frank, L. M. (2015). Hippocampal sharp-wave ripples in waking and sleeping states. Current Opinion in Neurobiology, 35, 6–12.

Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. Psychopharmacology, 191(3), 461–482.

Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., & Agid, Y. (1983). Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain Research, 275(2), 321–328.

Scatton, B., Simon, H., Le Moal, M., & Bischoff, S. (1980). Origin of dopaminergic innervation of the rat hippocampal formation. Neuroscience Letters, 18(2), 125–131.

Schmidt, L., Braun, E. K., Wager, T. D., & Shohamy, D. (2014). Mind matters: placebo enhances reward learning in Parkinson's disease. Nature Neuroscience, 17(12), 1793–1797.

Schomaker, J., van Bronkhorst, M. L. V., & Meeter, M. (2014). Exploring a novel environment improves motivation and promotes recall of words. Frontiers in Psychology, 5, 918.

Schonberg, T., O'Doherty, J. P., Joel, D., Inzelberg, R., Segev, Y., & Daw, N. D. (2010). Selective impairment of prediction error signaling in human dorsolateral but not ventral striatum in Parkinson's disease patients: evidence from a model-based fMRI study. NeuroImage, 49(1), 772–781.

Schultz, W. (1992). Activity of dopamine neurons in the behaving primate. Seminars in Neuroscience, 4(2), 129–138.

Schultz, W. (2016). Dopamine reward prediction-error signalling: A two-component response. In Nature Reviews Neuroscience (Vol. 17, Issue 3, pp. 183–195). Nature Publishing Group. https://doi.org/10.1038/nrn.2015.26

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. Science, 275(5306), 1593–1599.

Sesack, S. R., & Grace, A. A. (2010). Cortico-Basal Ganglia reward network: microcircuitry. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 35(1), 27–47.

Shadlen, M. N., & Shohamy, D. (2016). Decision Making and Sequential Sampling from Memory. Neuron, 90(5), 927–939.

Sharpe, M. J., Chang, C. Y., Liu, M. A., Batchelor, H. M., Mueller, L. E., Jones, J. L., Niv, Y., & Schoenbaum, G. (2017). Dopamine transients are sufficient and necessary for acquisition of model-based associations. Nature Neuroscience, 20(5), 735.

Sharp, M. E., Foerde, K., Daw, N. D., & Shohamy, D. (2015). Dopamine selectively remediates "model-based"reward learning: a computational approach. Brain: A Journal of Neurology, 139(2), 355–364.

Shiner, T., Seymour, B., Wunderlich, K., Hill, C., Bhatia, K. P., Dayan, P., & Dolan, R. J. (2012). Dopamine and performance in a reinforcement learning task: evidence from Parkinson's disease. Brain: A Journal of Neurology, 135(Pt 6), 1871–1883.

Shohamy, D., & Adcock, R. A. (2010). Dopamine and adaptive memory. Trends in Cognitive Sciences, 14(10), 464–472.

Shohamy, D., & Daw, N. D. (2015). Integrating memories to guide decisions. Current Opinion in Behavioral Sciences, 5, 85–90.

Shohamy, D., Myers, C. E., Grossman, S., Sage, J., Gluck, M. A., & Poldrack, R. A.

(2004). Cortico-striatal contributions to feedback-based learning: Converging data from neuroimaging and neuropsychology. Brain: A Journal of Neurology, 127(4), 851–859.

Shohamy, D., & Wagner, A. D. (2008). Integrating memories in the human brain: hippocampal-midbrain encoding of overlapping events. Neuron, 60(2), 378–389.

Singer, A. C., & Frank, L. M. (2009). Rewarded outcomes enhance reactivation of experience in the hippocampus. Neuron, 64(6), 910–921.

Squire, L. R., & Dede, A. J. O. (2015). Conscious and unconscious memory systems. Cold Spring Harbor Perspectives in Biology, 7(3), a021667.

Squire, L. R., & Zola, S. M. (1996). Structure and function of declarative and nondeclarative memory systems. Proceedings of the National Academy of Sciences, 93(24), 13515–13522.

Stark, A. K., & Pakkenberg, B. (2004). Histological changes of the dopaminergic nigrostriatal system in aging. In Cell and Tissue Research (Vol. 318, Issue 1, pp. 81–92). https://doi.org/10.1007/s00441-004-0972-9

Sulzer, D., Sonders, M. S., Poulsen, N. W., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: a review. Progress in Neurobiology, 75(6), 406–433.

Sutton, R. S., & Barto, A. G. (1998). Introduction to reinforcement learning (Vol. 2). MIT press Cambridge.

Swanson, L. W. (1982). The projections of the ventral tegmental area and adjacent regions: A combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Research Bulletin, 9(1-6), 321–353.

Takeuchi, T., Duszkiewicz, A. J., Sonneborn, A., Spooner, P. A., Yamasaki, M., Watanabe, M., Smith, C. C., Fernández, G., Deisseroth, K., & Greene, R. W. (2016). Locus coeruleus and dopaminergic consolidation of everyday memory. Nature, 537(7620), 357.

Tompary, A., Duncan, K., & Davachi, L. (2015). Consolidation of Associative and Item Memory Is Related to Post-Encoding Functional Connectivity between the Ventral Tegmental Area and Different Medial Temporal Lobe Subregions during an Unrelated Task. The Journal of Neuroscience: The Official Journal of the Society

for Neuroscience, 35(19), 7326–7331.

Ungless, M. A., & Grace, A. A. (2012). Are you or aren't you? Challenges associated with physiologically identifying dopamine neurons. Trends in Neurosciences, 35(7), 422–430.

Wagatsuma, A., Okuyama, T., Sun, C., Smith, L. M., Abe, K., & Tonegawa, S. (2018). Locus coeruleus input to hippocampal CA3 drives single-trial learning of a novel context. Proceedings of the National Academy of Sciences, 115(2), E310–E316.

Wandell, B., & Thomas, S. (1997). Foundations of vision. Psyccritiques, 42(7).

Wang, S.-H., Redondo, R. L., & Morris, R. G. M. (2010). Relevance of synaptic tagging and capture to the persistence of long-term potentiation and everyday spatial memory. Proceedings of the National Academy of Sciences of the United States of America, 107(45), 19537–19542.

Williams, S. M., & Goldman-Rakic, P. S. (1993). Characterization of the dopaminergic innervation of the primate frontal cortex using a dopamine-specific antibody. Cerebral Cortex , 3(3), 199–222.

Williams, S. M., & Goldman-Rakic, P. S. (1998). Widespread origin of the primate mesofrontal dopamine system. Cerebral Cortex , 8(4), 321–345.

Wilson, M. A., & McNaughton, B. L. (1994). Reactivation of hippocampal ensemble memories during sleep. Science, 265(5172), 676–679.

Wimmer, G. E., Braun, E. K., Daw, N. D., & Shohamy, D. (2014). Episodic memory encoding interferes with reward learning and decreases striatal prediction errors. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 34(45), 14901–14912.

Wimmer, G. E., & Shohamy, D. (2012). Preference by association: how memory mechanisms in the hippocampus bias decisions. Science, 338(6104), 270–273.

Wittmann, B. C., Schott, B. H., Guderian, S., Frey, J. U., Heinze, H.-J., & Düzel, E. (2005). Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. Neuron, 45(3), 459–467.

Wolosin, S. M., Zeithamova, D., & Preston, A. R. (2012). Reward modulation of hippocampal subfield activation during successful associative encoding and

retrieval. Journal of Cognitive Neuroscience, 24(7), 1532–1547.

Yang, H., de Jong, J. W., Tak, Y. E., Peck, J., Bateup, H. S., & Lammel, S. (2018). Nucleus Accumbens Subnuclei Regulate Motivated Behavior via Direct Inhibition and Disinhibition of VTA Dopamine Subpopulations. Neuron, 97(2), 434–449.e4.

Yeterian, E. H., & Pandya, D. N. (1991). Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. The Journal of Comparative Neurology, 312(1), 43–67.

Zhou, J., Montesinos-Cartagena, M., Wikenheiser, A. M., Gardner, M. P. H., Niv, Y., & Schoenbaum, G. (2019). Complementary Task Structure Representations in Hippocampus and Orbitofrontal Cortex during an Odor Sequence Task. Current Biology: CB. https://doi.org/10.1016/j.cub.2019.08.040

Zucca, F. A., Basso, E., Cupaioli, F. A., Ferrari, E., Sulzer, D., Casella, L., & Zecca, L. (2014). Neuromelanin of the human substantia Nigra: An update. In Neurotoxicity Research (Vol. 25, Issue 1, pp. 13–23). https://doi.org/10.1007/s12640-013-9435-y

**FIGURES AND LEGENDS**

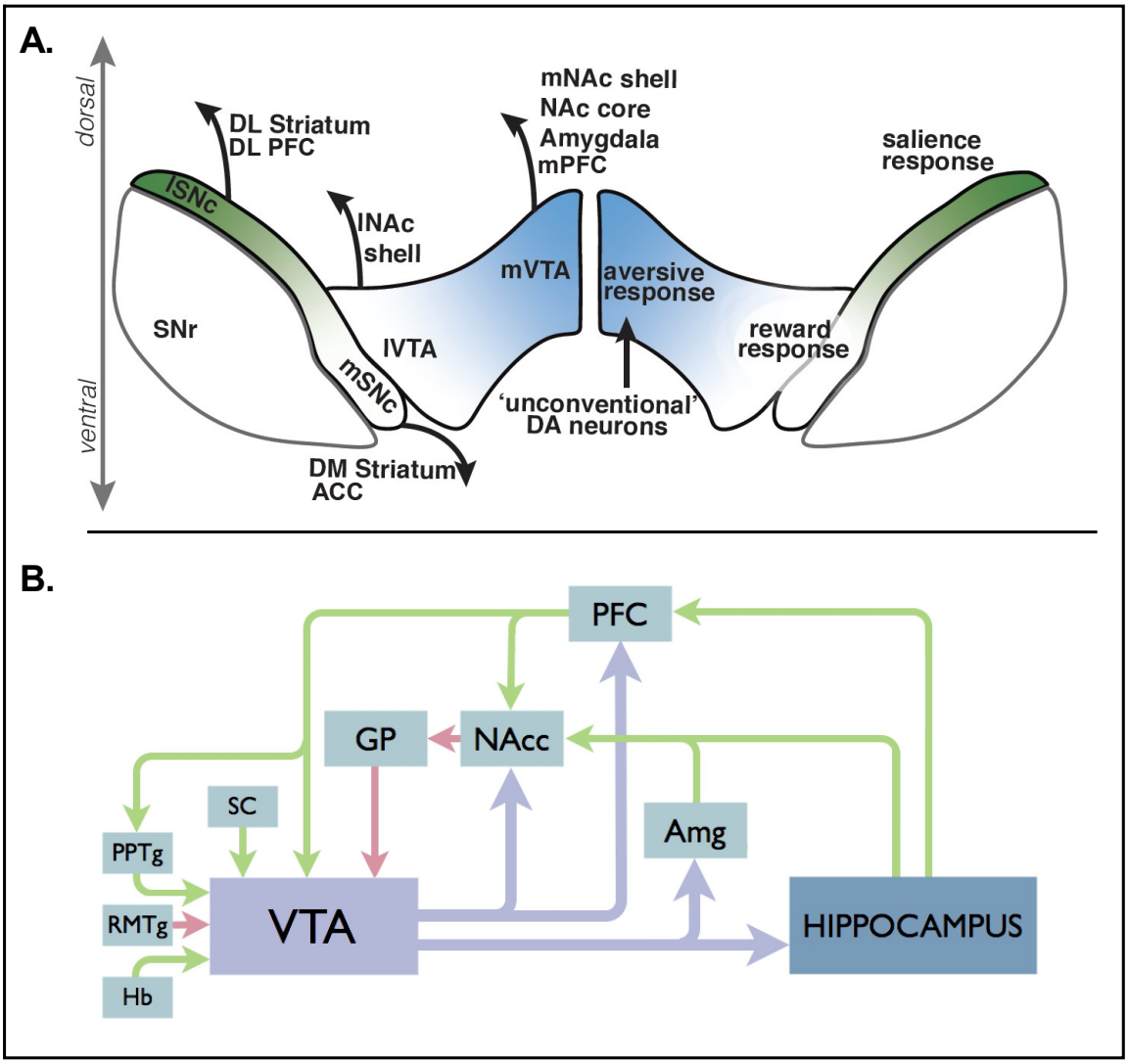


**Figure 1. Dopamine circuits and pathways. (A) Distribution of output pathways and response properties across the dopaminergic midbrain.** The left side of the schematic illustrates regions targeted by dopamine neurons located in the lateral and medial regions of the substantia nigra pars compacta (lSNc and mSNc) as well as lateral and medial regions the VTA (lVTA and mVTA). Labels on the right side, mark emerging evidence for differences in dopamine neurons response preferences across these subregions. Dopamine neurons projecting to the medial NAc (primarily arising form mVTA) have been found to respond to aversive stimuli (de Jong et al., 2019; Lammel et al., 2012), whereas dopamine neurons projecting to lateral NAc and dorsomedial (DM) striatum

respond to rewarding stimuli and the cues that predict them (Lerner et al., 2015). Finally, dopamine neurons projecting to the dorsolateral (DL) striatum (primarily arising from lSNc) have been shown to respond to both aversive and rewarding stimuli (Lerner et al., 2015; Matsumoto & Hikosaka, 2009; Nomoto et al., 2010). The color gradation across the lateral-medial dimension signifies that, while functionally relevant, it is best considered as a continuum rather than separate divisions. **(B) Inputs and outputs of the ventral tegmental area** *(Reproduced from Shohamy and Adcock, 2010).* For clarity, only some of the projections are shown. Dopamine neurons in the VTA project to several key targets, including the striatum (including nucleus accumbens; NAcc), the hippocampus, and the prefrontal cortex (PFC). There are direct projections from VTA to hippocampus, and connections from hippocampus – through nucleus accumbens (NAcc) and globus palidus (GP) – back to VTA (J. E. Lisman & Grace, 2005). Additional opportunities for indirect interaction with the striatum and the hippocampus may take place via relays in the PFC. Midbrain dopamine neurons in the VTA also innervate other select brain regions, all implicated in different forms of memory, including 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 (Oades & Halliday, 1987), sometimes characterized as "convergence zones" (Williams & Goldman-Rakic, 1993). *Inputs to the VTA* modulate dopamine neuronal responses. Excitatory activity (green) in the hippocampus disinhibits dopamine neurons by inhibiting (red arrows) the globus pallidus (GP). Other relevant inputs originate from subcortical sensory areas (e.g. superior colliculus; SC) and prefrontal cortex (PFC; directly and via the pedunculopontine tegmentum, PPTg). Additional nuclei that are the focus of recent research include inhibitory influences that may 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 (J. E. Lisman & Grace, 2005; Redgrave et al., 2008; Sesack & Grace, 2010)

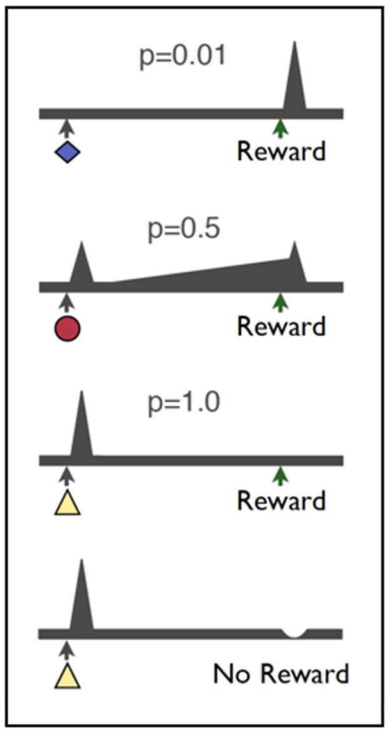


**Figure 2. Schematic representation of responses in midbrain dopamine neurons** (*following Fiorillo et al., 2003)*. Dopamine neurons have two characteristic response modes: they normally fire in a tonic pattern (approx. 5 Hz) and periodically fire with short, phasic bursts (approx. 20 Hz). It has been suggested that these response patterns may relate to different behavioral contexts. Here, dopamine neurons respond to rewards that are probabilistically predicted by visual cues. A phasic dopamine response is elicited when an animal receives an unexpected reward (p=0.01) or a cue that always predicts reward (p=1.0). 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) – that is, when there is uncertainty about the upcoming reward – the dopaminergic phasic response appears to trade-off between the cue and the reward.

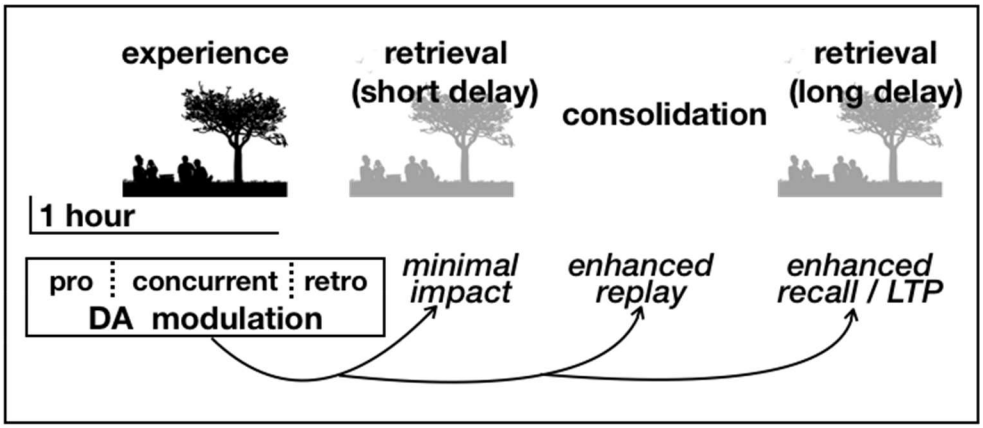


**Figure 3. Schematic illustrating the timescales over which dopamine modulates hippocampus-dependent memories.** Dopamine antagonists and agonists influence memory when applied to the hippocampus before a to-be-remembered experience (proactive), during the experience (concurrent), or following the experience (retroactive). Proactive and retroactive windows extend for roughly 20-30 minutes, in accordance with the synaptic tag and capture model (Redondo & Morris, 2011). The impact of dopaminergic manipulations, however, is not observed at short delays (<20 minutes after experience) (Bethus et al., 2010; O'Carroll et al., 2006). Optogenetic release of dopamine within the hippocampus has be shown to enhance the replay of recently activated hippocampal place cells during offline consolidation (McNamara et al., 2014). Lastly, dopaminergic manipulations applied around the time of encoding enhance both the subsequent retrieval of memories (Bethus et al., 2010; O'Carroll et al., 2006) and the expression of the late phase of LTP (Bethus et al., 2010; Lemon & Manahan-Vaughan, 2006; Li et al., 2003; O'Carroll et al., 2006).

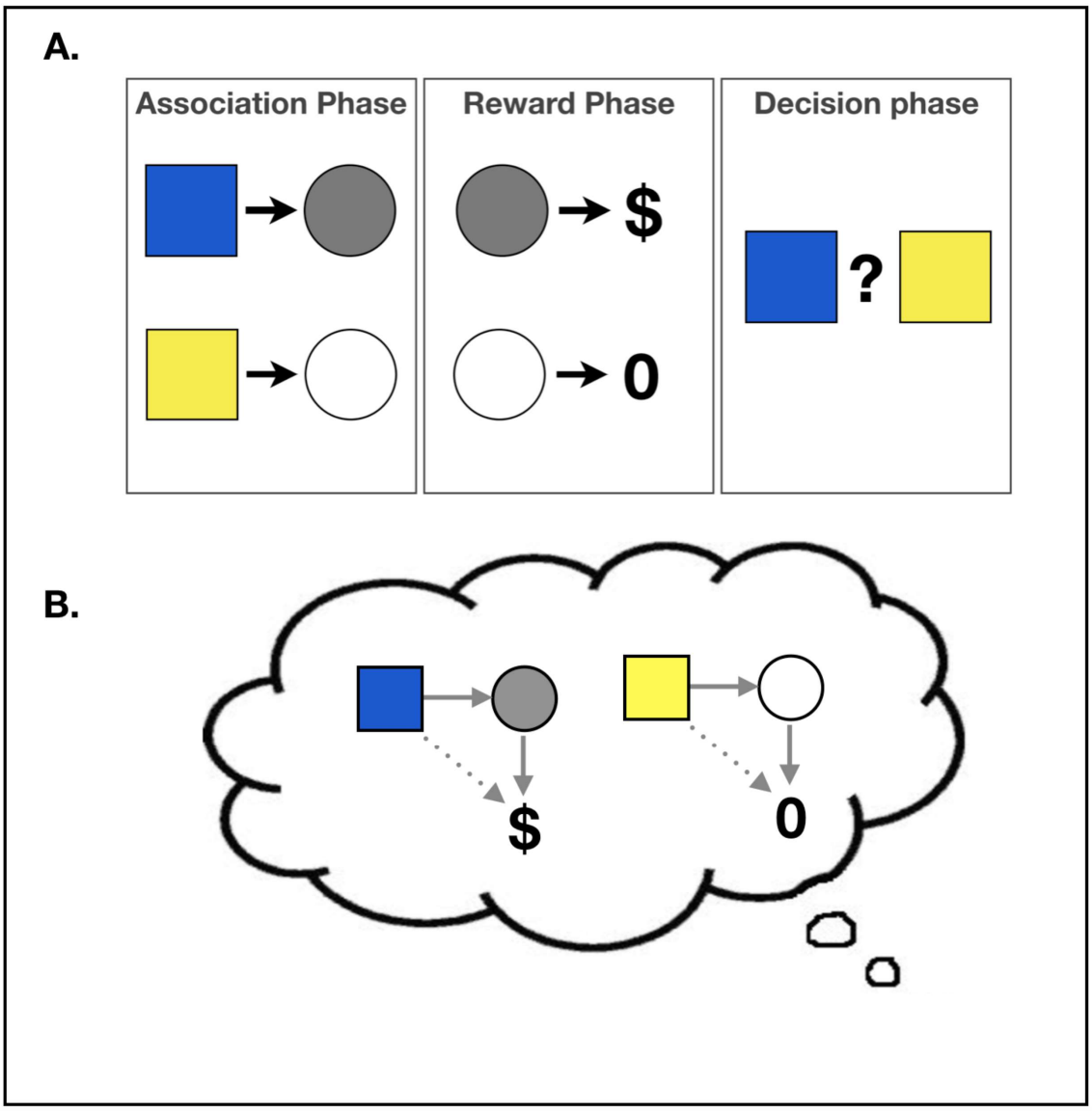


**Figure 4**. **Schematic of the sensory preconditioning task and model-based learning.** Sensory preconditioning has been used across species to measure how model-based associations are modulated by dopamine and used to guide behavior. **(A)** Subjects first learn associations between neutral sensory stimuli (here, colored squares and circles), then learn that one of those stimuli (the grey circle) is paired with reward while the other stimulus (white circle) is never paired with reward. In the final test, subjects are given a choice between the two neutral stimuli, neither of which was directly paired with reward. **(B)** A subject that learned about the broader associations in the task – integrating the first

phase with the second (model-based learning) –will prefer the neutral stimulus that is associated with the stimulus that was later paired with reward. A subject that learned only to associate the grey circle with reward (model-free learning) should have no preference between the two neutral stimuli.