Reward-Related Learning via Multiple Memory Systems

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The application of a neuroeconomic approach to the study of reward-related processes has provided significant insights in our understanding of human learning and decision making. Much of this research has focused primarily on the contributions of the corticostriatal circuitry, involved in trial-and-error reward learning. As a result, less consideration has been allotted to the potential influence of different neural mechanisms such as the hippocampus or to more common ways in human society in which information is acquired and utilized to reach a decision, such as through explicit instruction rather than trial-and-error learning. This review examines the individual contributions of multiple learning and memory neural systems and their interactions during human decision making in both normal and neuropsychiatric populations. Specifically, the anatomical and functional connectivity across multiple memory systems are highlighted to suggest that probing the role of the hippocampus and its interactions with the corticostriatal circuitry via the application of model-based neuroeconomic approaches may provide novel insights into neuropsychiatric populations that suffer from damage to one of these structures and as a consequence have deficits in learning, memory, or decision making.

Key Words: Dopamine, hippocampus, memory systems, prediction error, reinforcement learning, striatum

There is an emerging literature investigating the neural basis of decision making that encompasses the field of neuroeconomics (1). Across a variety of techniques and interdisciplinary efforts, neuroeconomics research has emphasized two key points: 1) choice behavior is influenced by learning systems involved in trial-and-error learning (such as instrumental conditioning), and 2) corticostriatal neural systems are involved in the computation of basic principles of conditioning and reinforcement learning that underlie simple decision making. This cross-species account of decision making represents a significant contribution to the field, and informs various influential models of decision making (2–4), but it does not fully reflect the complexity of learning in humans, in whom the existence of multiple memory systems has been well documented (5,6). Given the intricacy of the environment, it would be peculiar if one neural system was primarily responsible for learning signals that contribute to decision making. In fact, choices made in everyday human society are not driven solely by experience through trial-and-error learning; we also learn and allow our decisions to be influenced by communication (e.g., talking to others), knowledge of rules (e.g., when to cross the street), and facts (e.g., this person is untrustworthy). Thus, neuroeconomic models and their potential clinical applications can be informed by consideration of how distinct neural circuits underlying multiple learning and memory systems interact.

In this review, we focus on the distinct and common contributions of the basal ganglia (BG; involved in learning through trial and error), and the medial temporal lobes (MTL), particularly the hippocampus (involved in declarative learning of rules and facts) during learning and how they translate to decision making in both healthy and clinical populations. We first discuss the concept for and evidence supporting multiple memory systems, followed by subsections describing relevant learning and decision-making research involving the BG and MTL, along with potential interactions between these structures. Finally, we evaluate how neuroeconomics research may be expanded on in the context of multiple memory systems and synthesized to help inform neuropsychiatric disorders that involve compromised BG and MTL structures.

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Multiple Memory Systems

The values we assign to different stimuli and prior experiences tend to influence how we make decisions. For instance, an individual may choose to shop at the local family-owned grocery store versus a new larger grocery store in town because of prior positive experiences at the local establishment (Figure 1). Within this example, one explanation of how the choice is made is based on a greater value assigned to the local shop because of reinforcement learning. An impressive collection of studies has highlighted the role of corticostriatal circuits along with modulation of dopamine neurons as integral for this type of learning (7–9). Not surprisingly, individuals with pathologies that involve BG dysfunction, such as Parkinson's disease (PD), have difficulties learning by trial-and-error and updating learned contingencies (10–15), which may manifest as perseverative choices in some contexts (16). Defined by a loss of the majority of dopaminergic neurons in the midbrain, PD consists of several motor impairments (e.g., akinesia) as well as cognitive deficits (17,18). Importantly, patients afflicted with PD can learn through different neural mechanisms, such as MTL structures involved in declarative learning, highlighting PD as a candidate disorder for investigating learning via multiple memory systems (19).

Over the past few decades, an increasingly supported theory suggests that memory is not a unitary process but rather consists of multiple processes that engage distinct neural substrates (5,6,20). A major dissociation is between declarative and nondeclarative memory. Declarative memory consists of knowledge of facts and events; this type of memory may be rapidly formed and later readily recalled, is flexible in nature, and relies on the integrity of the MTL (21). In contrast, nondeclarative memory encompasses several types of learning including habit learning, procedural, conditioning, and priming (20). Such learning is thought to involve regions of the BG, along with cortical structures and the amygdala and is characterized by a slower time course of acquisition and less flexibility with respect to updating, as in the case of habits (21,22).

Support for this theory comes from a vast array of research ranging from nonhuman animal investigations to studies with clinical populations (19). In a classic paradigm, a rodent is trained to navigate a maze to retrieve a food reward (23,24). A clear dissociation between multiple memory systems is apparent by poor performance in a spatial learning version of a radial maze (the "win-shift"

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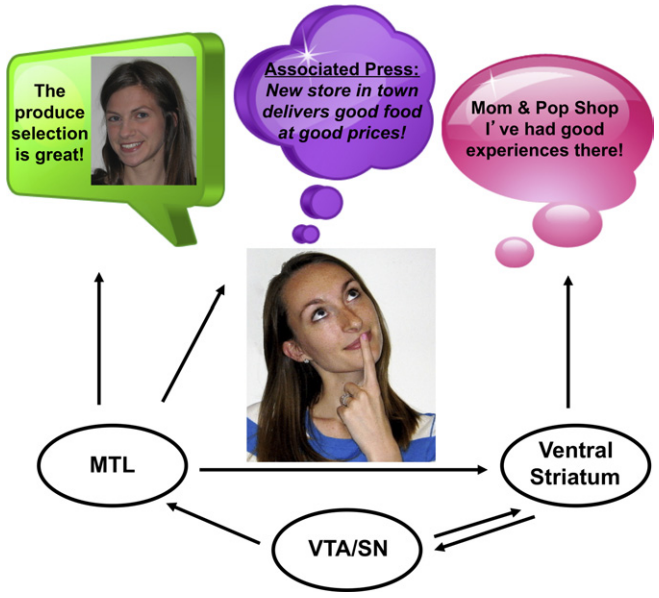

Figure 1. Multiple memory systems during human decision making. In everyday life, humans are required to make hundreds of decisions, ranging from the complex (e.g., what career path to follow) to the simple (e.g., where to buy groceries). One may rely on past experiences (positive or negative) to make future decisions, as illustrated in the figure by positive past experiences at the local "mom & pop shop" grocery store. Repeated good experiences at one store may lead to continually shopping at the establishment, a form of learning and decision making thought to involve the basal ganglia (BG), particularly the input unit of the BG, the striatum. However, decisions can be influenced by distinct neural systems underlying multiple learning and memory systems in addition to the striatum, including the hippocampus, part of the medial temporal lobe (MTL), which may store declarative information about one's environment. For example, speaking with a friend about a new, larger grocery store in town or reading a favorable review in the newspaper may lead one to make the decision to try out the new store. In this manner, multiple memory systems may interact in everyday decision making, via either direct connections between these regions (MTL to striatum in BG) or via midbrain dopaminergic influences stemming from the ventral tegmental area and substantia nigra (VTA/SN), hypothesized to facilitate learning and memory processes in the MTL and BG.

task) in rats with lesions to the fimbria-fornix—the output of the MTL—whereas rats with lesions in the BG are unimpaired at remembering the previously rewarded locations. In contrast, MTL-lesioned rats show intact performance in a stimulus-response version of the maze (the "win-stay" task) in which approach behavior is dictated by a conditioned cue and is impaired in rats with lesions in the dorsal striatum, an input structure in the BG (23–25). This dissociation between the MTL and BG with respect to declarative and nondeclarative-like learning tasks respectively is mirrored across different discrimination-related paradigms, such as delayed nonmatching to sample (26) or concurrent discrimination (27), which suggests that lesions to the MTL adversely affect a monkey's ability to complete discrimination tasks successfully (27, 28) but does not affect skill learning (28). Additionally, patients suffering from MTL amnesia have extremely compromised declarative memory, whereas nondeclarative types of learning (e.g., skill learning) remain intact (29–31). Likewise, patients afflicted with PD have difficulty with some forms of trial-and-error learning, whereas declarative knowledge persists (30,32).

There are several examples in which this dissociation is challenged, however, primarily based on disagreements on what constitutes declarative versus nondeclarative memory (33), in part due to conflicting results in patient populations (34–39). For instance, successful probabilistic trial-and-error learning has been observed in patients with PD (39), leading to the argument that deficits observed may be more nuanced than originally hypothesized, dependent on the type of task (e.g., skill learning vs. perceptual) and the locus of impairment (e.g., corticostriatal circuits vs. distributed neocortical association regions) (35,38). The emergence of neuroeconomics research promises to shed light on this debate by introducing new paradigms and quantitative model-based approaches. A popular method budding from cognitive and computational neuroscience research (40,41) that is rooted in classical learning theories (42) is the application and characterization of model-based learning signals (9). Widely used in the interdisciplinary study of neuroeconomics, these model-derived signals can be used to quantify how a cognitive process is implemented in a specific brain region and can be expanded across different memory systems to explore how such systems interact in the context of goal-directed behaviors.

The Basal Ganglia and Reward Learning

Learning what choice provides the best outcome can be an arduous process, often accomplished by trial and error. In an experimental setting, an animal will learn to predict positive outcomes after repeated successful pairings of a reward with a conditioned stimulus, such as a light or a lever, leading to increased approach behavior toward the stimulus. Early in the decision-making process, therefore, the animal learns to integrate the action–outcome association (e.g., lever-pressing leads to liquid reward) with the value attributed to such outcome (e.g., high value for liquids when thirsty) in a manner that allows constant updating of action–contingencies (e.g., when lever does not yield predicted outcome, a prediction error is coded, leading to updating of current contingencies). These types of studies illustrate how basic learning principles of conditioning can shape current decision making and future behavior. Across species and through different methodologies, research has converged on the role of the corticostriatal circuitry in the computation of basic learning principles of conditioning and reinforcement underlying simple decision making (9,43–46).

The BG complex comprises multiple corticostriatal loops that exert distinct functions (8). The striatum, in particular, has been linked to various types of learning involving procedural skills (47), habits (30,48,49), and reward learning (43,44,50). Functional dissociations between subdivisions of the striatum have also been proposed, with the dorsomedial striatum involved in processing action-contingency (43,51), goal-directed learning (52), and instrumental conditioning (46) and the dorsolateral striatum linked with habit and motor learning (49). Activity in the ventral striatum has been primarily associated with reward-related processing, demonstrating sensitivity to changes in subjective value (9,53) and prediction-based learning (46). Not surprisingly, these striatum subdivisions are also distinguished with respect to cortical connectivity, with the dorsomedial striatum connected to an associative network with the prefrontal and parietal association cortices, the dorsolateral striatum connected to sensorimotor regions, and the ventral striatum connected with ventral portions of the prefrontal cortex (e.g., orbitofrontal cortex) (44,49).

One of the most thought-provoking findings with respect to BG circuitry and affective learning concerns the role of midbrain dopaminergic neurons in coding prediction error signals (54). It was observed that dopaminergic neurons in nonhuman primates respond to unexpected rewards (e.g., drop of juice) but no longer respond to the juice once its delivery becomes predictable. Instead, the neurons fire to the earliest predictor of a reward (e.g., tone

predicting juice). When a predicted reward fails to occur, dopamine neurons show a depression in neuronal firing, thought to be a prediction error signal used to update contingencies during affective learning. Using functional magnetic resonance imaging (fMRI), prediction error learning signals have correlated with blood oxygen level dependent (BOLD) responses in the human midbrain (55) but primarily in dopaminergic targets such as the striatum using a variety of rewards (e.g., juice, money) and paradigms (e.g., classical and instrumental conditioning) in which predictions and contingencies are typically acquired and updated through trial and error (46,56,57).

The human striatum has been shown to be involved in various facets of reward-related processing that encompass affective learning and inform future decision making (9,44)—from anticipating or predicting a potential reward (58) to coding the differential response between positive and negative outcomes (59), particularly when a contingency between an action and an outcome is perceived (51). Thus, it is not surprising that BOLD responses in the human striatum correlate with prediction error learning signals during conditioning paradigms (46,60), with stronger correlations suggesting greater learning rates (61) and exploitative, rather than explorative, decision making (62). More recently, such model-based approaches have begun to be applied to clinical populations with BG dysfunction—namely, PD patients. Consistent with the pathology of the disorder, prediction error signals have been found to be preserved in more ventral regions of the striatum but impaired in dorsolateral regions relative to healthy control subjects (13), suggesting a potential explanation for why PD patients are impaired in probabilistic trial-and-error paradigms (30,32,39,63).

The medication status of PD patients during scientific studies (e.g., on or off dopaminergic medicine) has also become a formidable way of investigating the potential role of a dopaminergic learning signal and its influences on decision making. The mere enhancement or reduction of dopaminergic function by pharmacologic treatment (L-DOPA or haloperidol, respectively) in healthy participants modulates the magnitude of a prediction error learning signal, suggesting that increases in dopaminergic function lead to choices being perceived as more rewarding (64). Similar manipulations in PD patients hint at specific impairments in learning from positive outcomes when in an unmedicated state (but intact learning from negative outcomes), and normal learning from positive (but not negative) outcomes when treated with dopaminergic agonists (11,13,16). Interestingly, in some individual cases of PD, administration of dopaminergic agonists targeting the dorsal striatum can lead to enhanced impulse control impairments such as increased gambling behavior (65–67), posited to be due to an overflow of dopamine in the ventral striatum (68–70). Neuroeconomic approaches of modeling dopaminergic learning signals raise interesting possibilities for future clinical research involving BG dysfunction (13,16) that allow for extensions beyond the classification of a particular impairment (e.g., learning deficits in feedback-based tasks in PD) to identification of the mechanism underlying such impairment (e.g., learning deficits due to prediction error impairments and medication status). An exciting future direction is the incorporation of multiple learning signals arising from distinct structures, such as the MTL, that underlie different forms of learning signals which participate in goal-directed behavior.

Medial Temporal Lobe, Declarative Learning, and Reward-Related Contributions

When deciding to try out the new grocery store in town, an individual may rely not only on past experiences with the local shop but also on declarative information obtained regarding the new store. One may read a positive review about the wide array of food available at the new store or be informed by a friend about the great selection of produce (Figure 1). This type of declarative information, thought to be dependent on the integrity of the MTL, is a major influence on our decisions. The MTL consists of many substructures, including the hippocampus, entorhinal cortex, parahippocampus, and perirhinal cortices (71). Collectively, these substructures support multiple types of declarative learning including memory for facts and events (21), novelty detection (72,73), mediating flexible transfer of knowledge (31,74,75), as well as spatial learning and navigation (76,77). Studies in nonhuman animals and patient populations with damage to the MTL have demonstrated the importance of this structure in forming new declarative memories and flexibly applying knowledge in new scenarios (6,14,31,78).

More recently, the hippocampus has been highlighted in reward-related studies (79–86). In comparison to the substantial existing evidence of the involvement of distinct MTL structures in various aspects of declarative memory, however, there is still less known about the role of the hippocampus in reward-related learning and decision making. One important consideration with regard to the hippocampus and reward processing is its connectivity with corticostriatal circuits (44,83). Specifically, the hippocampus is anatomically connected with the striatum (87,88) and it has been suggested that cortical mechanisms may mediate the interaction between them (89). The potential functional significance of these interactions is illustrated in specific learning contexts, such as spatial learning (81). In such context, distinct but parallel contributions to successful path navigation have been proposed for the hippocampus, involved in prospection or the representation of future paths; the ventral striatum, involved in the valuation of future rewards; and the dorsal striatum, tracking action-related task components, that together aid decision making (77).

The hippocampus also receives projections from midbrain dopaminergic structures (90, 91) and an alternative, perhaps complementary view, is that dopaminergic modulation provides a learning signal for both the hippocampus and the striatum (75,89). Whether these dopaminergic signals exert similar or distinct influences on both these structures is currently an intriguing question for neuroeconomics. A popular hypothesis posits that a distinct function of dopaminergic input into the hippocampus facilitates the entry of information into long-term memory by novelty detection (73). Consistent with this idea, dopamine has been thought to play a key role in adaptive memory and determining what information is learned and subsequently remembered (e.g., those associated with a high reward value) (79,83,86).

This connectivity between the hippocampus and midbrain dopaminergic centers is also involved in mediating the association between different environmental contexts and reward (92) and the ability to generalize prior learned associations into future decisions (74). Research on neuropsychiatric populations has specified a double dissociation between patients with PD and those with hippocampal atrophy during initial learning (impaired in PD) and the subsequent ability to transfer (impaired in hippocampal patients) during an associative learning task (31), highlighting the role these regions play in learning and flexibly using information. Interestingly, hippocampal damage does not typically correlate with deficits in performance in some learning tasks associated with dopamine and striatal function, such as trial-and-error feedback-based learning (14,93). Moreover, during instrumental conditioning tasks with delayed reinforcement, rats with lesions of the hippocampus actually display better learning than control animals (94), perhaps because such lesions hinder the formation of context–outcome

associations, focusing instead on action–outcome contingencies dependent on corticostriatal systems.

A potential similar function of dopaminergic modulation in both the hippocampus and striatum may be the encoding of prediction error learning signals during specific learning contexts. In associative learning tasks, learning-related spiking activity is correlated with a reward-predictive value signal in monkey hippocampal neurons (82), whereas in human probabilistic learning paradigms, activity in the hippocampus has been suggested to track differences between positive and negative outcomes (95) potentially encoding a feedback-based model-derived reward prediction error signal (96) in parallel with corticostriatal systems. A challenge for neuroeconomics currently is understanding the functional and temporal significance of this learning signal because the human hippocampus has also been associated with coding for the uncertainty of cue–outcome associations (97), a novelty response (98,99), and a mismatch signal (100,101). The few reports that exist thus far advocating an association between the hippocampus and outcome prediction (95,96,102) do not necessarily claim that the hippocampal activity exclusively correlates with a scalar prediction error, because plausible alternative models, such as a mismatch signal or an unsigned prediction error, were not tested. Rather, these initial reports point to neuroeconomic approaches as a potential tactic for advancing these questions for future consideration. It is likely that the nature of a learning signal coded in the hippocampus depends on the learning context (e.g., probabilistic task with declarative and nondeclarative elements) and the anatomic location and functional connectivity of loci of activation (e.g., CA1 subfield of the hippocampus has been linked with tracking associative mismatches) (100). Nevertheless, understanding the contributions of the dopaminergic learning signal encoded in the hippocampus may present new directions in decision-making research and translational applications for neuropsychiatric disorders by highlighting how humans flexibly use information in novel contexts to guide future choices.

Interactive Memory Systems During Decision Making

It is theorized that the inadequacy of a single learning and memory system's ability to deal with a complex situation may have led to the evolution of multiple memory systems (5). To illustrate this in the context of decision making and neuroeconomics more specifically, one can consider "the trust game," a classic paradigm in behavioral economics used to investigate risky decision making and social interactions (103). Briefly, in its simplest form, the game involves a one-shot interaction between two players, where the first player, the proposer, is given an initial sum of money (e.g., $20) and decides whether to keep it and end the game or invest some or all of that money with the second player, the responder. Any amount invested gets tripled (e.g., $60), and the responder now decides whether to share (or not) some of the investment back to the proposer (e.g., each player gets $30). It is a risky proposition but a potentially profitable one for the proposer who has to show "trust" in their partner. Adaptations of this game to neuroimaging settings involving repeated interactions evoke trial-and-error learning and suggest that reputation building is dependent on learning signals being processed in the striatum (104–106), with a shift in the magnitude of the BOLD signal in the striatum to the earliest prediction of a trustworthy interaction based on the development of reputation (106), akin to the shift observed in reinforcement learning models of prediction error signals (54,57).

The concept of multiple memory systems can be applied to these complex learning and decision-making situations in which other types of information can influence decisions. For instance, a proposer may have either good or bad priors with respect to the responder, such as knowledge about their ethical and business practices. In this situation, the additional information affects the belief about probability of reciprocation and decisions to trust (104,105,107). Furthermore, learning signals in the striatum involved in updating predictions based on current outcomes are diminished when prior declarative information is present, as if a proposer places less weight on the current experience or outcome due to the value assigned to the prior information (105).

One hypothesis is that declarative knowledge may bias decision making in this case, potentially overriding exploration of alternatives favored by trial-and-error learning mechanisms and suggesting that dynamic, perhaps competitive, interactions between the MTL and BG that can affect future choices. This is consistent with evidence from probabilistic learning studies proposing that these memory systems may compete during some learning scenarios (108,109). An alternative hypothesis is that MTL and BG may at times cooperate during learning situations, thus allowing compensation for a faulty system in a state in which the brain is diseased (110,111) or when such an interaction is behaviorally relevant (112).

A third idea is that the nature of the interactions between MTL and BG involves parallel processing of information, with the interactions being competitive or cooperative depending on task demands (25,113,114). This debate across the theory of multiple memory systems regarding the nature of the interactions between the MTL and BG can profit from neuroeconomics research and the setting conjectured by experimental paradigms such as the trust game. For example, in the trust game, the dynamic interactions between the MTL and BG could be perceived as competitive; however, reinforcement learning signals have been observed during probabilistic learning tasks in both structures (96,102), conceivably suggesting parallel engagement or even a cooperative interaction between these regions. Introducing instructed knowledge (e.g., knowledge of probabilities) to a probabilistic learning paradigm diminishes the reinforcement learning signals in these regions, concurrent with an increase in activity in the dorsolateral prefrontal cortex (95), posited to mediate the interaction between the MTL and BG (89). Thus, parallel processing within these distinct neural circuits in the MTL and BG, which are influenced by dopaminergic input and shaped by cortical modulation, may underlie learning and decision-making processes that occur during complex social interactions such as the trust game.

Further Considerations

Several models posited to underlie decision-making processes have been highlighted in the literature and merit brief discussion (3,4,9,115). One dual system account of decision making, for example, distinguishes between a cognitively based, controlled system (deliberative system) and an automatic, emotional system (impulsive system), acutely important during intertemporal choice (116–119). Deliberative processes have been posited to involve prefrontal and parietal cortices, whereas automatic processes have been linked with subcortical regions such as the striatum ([4,119]; although see [116]). Another influential model highlights goal-directed and habitual learning as two key systems involved in guiding choice behavior (115,120), with goal-directed learning involving the anterior caudate nucleus and medial prefrontal regions, and habitual learning associated with the posterior putamen (48,49,115). Current work is also exploring a distinction between reinforcement learning error signals related to reward prediction, referred to as model-free, and expectations regarding current states given previous choices, referred to as model-based (121,122).

Integrating these models in a cohesive account of how distinct neural systems involved in learning, such as the striatum (typically highlighted across models) and the hippocampus (observed less often), can inform decision making is an important future endeavor. A recent proposal posits four key decision-making systems in the brain: goal-directed (dorsolateral PFC and dorsomedial striatum), habitual (dorsolateral striatum), episodic (MTL), and Pavlovian (123). These distinct systems help guide decisions independently but may also interact to steer choices depending on the context of the decision.

Because this review primarily focused on the potential contributions of learning signals associated with the BG and MTL to decision making, less discussion was attributed to other important regions that contribute to learning and decision making—namely, the amygdala and the prefrontal cortex (124,125). The amygdala is a critical structure for aversive learning (126) and emotional memory (127) that has implications for decision making in particular contexts, such as when decisions involve ambiguity (128) or are framed as gains or losses (129). Interestingly, the amygdala is another potential link between interactions of the MTL and BG because it has been shown to modulate activity in these structures during specific learning tasks (e.g., win-shift and win-stay, respectively) (130). Thus, a clear future direction is how learning signals originating from the amygdala can influence the MTL and BG during decision-making processes.

In contrast, the involvement of the PFC in decision-making processes has been well documented (4,9,115). Both dorsolateral and ventromedial prefrontal cortical regions, in particular, have been associated with the representation of goal values (9) and integrating reward-related information along with a striatal and dopaminergic network (131), consistent with the previously highlighted theories of cortical modulation of MTL and BG interactions (89). Future research using computational models of learning signals will prove useful in further understanding the relationship between PFC regions and the striatum during action–outcome learning (95) as potentially informed by corticohippocampal connections that mediate rule governance (132).

Conclusion

Understanding how neural structures underlying distinct learning and memory systems interact has profound potential to inform neuropsychiatric disorders, especially in populations in which decision making is adversely affected by the disease or disease treatment (e.g., pathological gambling and PD) (65–67). The advent of functional magnetic resonance imaging has allowed for extension of elegant animal models and patient studies in support of multiple learning and memory systems, although a debate remains with respect to how underlying neural structures—namely, the BG and MTL—interact to facilitate learning and decision making. The emergence of neuroeconomic approaches, such as the application of signals derived from models of cognitive processes that are used to more carefully identify neural mechanisms promises to shed light on this debate and extend this knowledge beyond basic principles of learning that inform decision making to other important forms of learning common to humans (e.g., instructed and observational learning) (95,133). The evolution of neuroeconomics-based models and paradigms and initial efforts of their application in neuropsychiatric populations bodes well for future advances in understanding the connectivity and interactions of neural mechanisms involved in learning, memory, and decision making to promote more efficient diagnosis and treatment options.

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1. Glimcher PW, Camerer C, Fehr E, Poldrack RA (2009): *Neuroeconomics Decision Making and the Brain*. London: Academic Press.
2. Dayan P, Niv Y (2008): Reinforcement learning: The good, the bad and the ugly. *Curr Opin Neurobiol* 18:185–196.
3. Frank MJ, Cohen MX, Sanfey AG (2009): Multiple systems in decision making: A neurocomputational perspective. *Curr Direct Psychol Sci* 18: 73–77.
4. Sanfey AG, Loewenstein G, McClure SM, Cohen JD (2006): Neuroeconomics: Cross-currents in research on decision-making. *Trends Cogn Sci* 10:108–116.
5. Sherry DF, Schacter DL (1987): The evolution of multiple memory systems. *Psychol Rev* 94:439–454.
6. Squire LR, Zola SM (1996): Structure and function of declarative and nondeclarative memory systems. *Proc Natl Acad Sci U S A* 93:13515–13522.
7. Balleine BW, Delgado MR, Hikosaka O (2007): The role of the dorsal striatum in reward and decision-making. *J Neurosci* 27:8161–8165.
8. Middleton FA, Strick PL (2000): Basal ganglia output and cognition: Evidence from anatomical, behavioral, and clinical studies. *Brain Cogn* 42:183–200.
9. Rangel A, Camerer C, Montague PR (2008): A framework for studying the neurobiology of value-based decision making. *Nat Rev Neurosci* 9:545–556.
10. Cools R, Barker RA, Sahakian BJ, Robbins TW (2001): Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain* 124:2503–2512.
11. Frank MJ, Seeberger LC, O'Reilly R C (2004): By carrot or by stick: Cognitive reinforcement learning in parkinsonism. *Science* 306:1940–1943.
12. Peterson DA, Elliott C, Song DD, Makeig S, Sejnowski TJ, Poizner H (2009): Probabilistic reversal learning is impaired in Parkinson's disease. *Neuroscience* 163:1092–1101.
13. Schonberg T, O'Doherty JP, Joel D, Inzelberg R, Segev Y, Daw ND (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* 49:772–781.
14. Shohamy D, Myers CE, Hopkins RO, Sage J, Gluck MA (2009): Distinct hippocampal and basal ganglia contributions to probabilistic learning and reversal. *J Cogn Neurosci* 21:1821–1833.
15. Shohamy D, Myers CE, Onlaor S, Gluck MA (2004): Role of the basal ganglia in category learning: How do patients with Parkinson's disease learn? *Behav Neurosci* 118:676–686.
16. Rutledge RB, Lazzaro SC, Lau B, Myers CE, Gluck MA, Glimcher PW (2009): Dopaminergic drugs modulate learning rates and perseveration in Parkinson's patients in a dynamic foraging task. *J Neurosci* 29:15104–15114.
17. Lang AE, Lozano AM (1998): Parkinson's disease. First of two parts. *N Engl J Med* 339:1044–1053.
18. Lang AE, Lozano AM (1998): Parkinson's disease. Second of two parts. *N Engl J Med* 339:1130–1143.
19. Packard MG, Knowlton BJ (2002): Learning and memory functions of the basal ganglia. *Annu Rev Neurosci* 25:563–593.
20. Squire LR (1992): Declarative and nondeclarative memory: Multiple brain systems supporting learning and memory. *J Cogn Neurosci* 4:232–243.
21. Squire LR (2004): Memory systems of the brain: A brief history and current perspective. *Neurobiol Learn Mem* 82:171–177.
22. Reber PJ, Knowlton BJ, Squire LR (1996): Dissociable properties of memory systems: differences in the flexibility of declarative and nondeclarative knowledge. *Behav Neurosci* 110:861–871.
23. Packard MG, Hirsh R, White NM (1989): Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. *J Neurosci* 9:1465–1472.
24. Packard MG, McGaugh JL (1992): Double dissociation of fornix and caudate nucleus lesions on acquisition of two water maze tasks: Fur-

ther evidence for multiple memory systems. *Behav Neurosci* 106:439–446.
25. White NM, McDonald RJ (2002): Multiple parallel memory systems in the brain of the rat. *Neurobiol Learn Mem* 77:125–184.
26. Alvarez P, Zola-Morgan S, Squire LR (1995): Damage limited to the hippocampal region produces long-lasting memory impairment in monkeys. *J Neurosci* 15:3796–3807.
27. Zola-Morgan S, Squire LR (1985): Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. *Behav Neurosci* 99:22–34.
28. Zola-Morgan S, Squire LR (1984): Preserved learning in monkeys with medial temporal lesions: Sparing of motor and cognitive skills. *J Neurosci* 4:1072–1085.
29. Corkin S (1984): Lasting consequences of bilateral medial temporal lobectomy—clincal course and experimental findings in HM. *Semin Neurol* 4:249–259.
30. Knowlton BJ, Mangels JA, Squire LR (1996): A neostriatal habit learning system in humans. *Science* 273:1399–1402.
31. Myers CE, Shohamy D, Gluck MA, Grossman S, Kluger A, Ferris S, *et al.* (2003): Dissociating hippocampal versus basal ganglia contributions to learning and transfer. *J Cogn Neurosci* 15:185–193.
32. Shohamy D, Myers CE, Grossman S, Sage J, Gluck MA, Poldrack RA (2004): Cortico-striatal contributions to feedback-based learning: converging data from neuroimaging and neuropsychology. *Brain* 127: 851–859.
33. Henke K (2010): A model for memory systems based on processing modes rather than consciousness. *Nat Rev Neurosci* 11:523–532.
34. Bondi MW, Kaszniak AW (1991): Implicit and explicit memory in Alzheimer's disease and Parkinson's disease. *J Clin Exp Neuropsychol* 13:339–358.
35. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N (1989): Neuropsychological evidence for multiple implicit memory systems: A comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *J Neurosci* 9:582–587.
36. Meeter M, Radics G, Myers CE, Gluck MA, Hopkins RO (2008): Probabilistic categorization: How do normal participants and amnesic patients do it? *Neurosci Biobehav Rev* 32:237–248.
37. Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD, *et al.* (1993): Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia* 31:627–644.
38. Reber PJ, Squire LR (1999): Relaxing decision criteria does not improve recognition memory in amnesic patients. *Mem Cogn* 27:501–511.
39. Wilkinson L, Lagnado DA, Quallo M, Jahanshahi M (2008): The effect of feedback on non-motor probabilistic classification learning in Parkinson's disease. *Neuropsychologia* 46:2683–2695.
40. O'Doherty JP, Hampton A, Kim H (2007): Model-based fMRI and its application to reward learning and decision making. *Ann N Y Acad Sci* 1104:35–53.
41. Sutton RS, Barto AG (1998): *Reinforcement Learning*. Cambridge, MA: MIT Press.
42. Rescorla RA, Wagner AR (1972): A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In: Black AH, Prokasy WF, editors. *Classical Conditioning II: Current Research and Theory*. New York: Appleton Century Crofts, 64–99.
43. Delgado MR (2007): Reward-related responses in the human striatum. *Ann N Y Acad Sci* 1104:70–88.
44. Haber SN, Knutson B (2010): The reward circuit: Linking primate anatomy and human imaging. *Neuropsychopharmacology* 35:4–26.
45. Montague PR, Berns GS (2002): Neural economics and the biological substrates of valuation. *Neuron* 36:265–284.
46. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004): Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science* 304:452–454.
47. Poldrack RA, Prabhakaran V, Seger CA, Gabrieli JD (1999): Striatal activation during acquisition of a cognitive skill. *Neuropsychology* 13:564–574.
48. Tricomi E, Balleine BW, O'Doherty JP (2009): A specific role for posterior dorsolateral striatum in human habit learning. *Eur J Neurosci*. 29:2225–2232.
49. Yin HH, Knowlton BJ (2006): The role of the basal ganglia in habit formation. *Nat Rev Neurosci* 7:464–476.
50. O'Doherty JP (2004): Reward representations and reward-related learning in the human brain: insights from neuroimaging. *Curr Opin Neurobiol* 14:769–776.
51. Tricomi EM, Delgado MR, Fiez JA (2004): Modulation of caudate activity by action contingency. *Neuron* 41:281–292.
52. Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM (2004): Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci* 27:468–474.
53. Knutson B, Taylor J, Kaufman M, Peterson R, Glover G (2005): Distributed neural representation of expected value. *J Neurosci* 25:4806–4812.
54. Schultz W, Dayan P, Montague PR (1997): A neural substrate of prediction and reward. *Science* 275:1593–1599.
55. D'Ardenne K, McClure SM, Nystrom LE, Cohen JD (2008): BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. *Science* 319:1264–1267.
56. McClure SM, Berns GS, Montague PR (2003): Temporal prediction errors in a passive learning task activate human striatum. *Neuron* 38: 339–346.
57. O'Doherty JP, Dayan P, Friston K, Critchley H, Dolan RJ (2003): Temporal difference models and reward-related learning in the human brain. *Neuron* 38:329–337.
58. Knutson B, Adams CM, Fong GW, Hommer D (2001): Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci* 21:RC159.
59. Delgado MR, Nystrom LE, Fissell C, Noll DC, Fiez JA (2000): Tracking the hemodynamic responses to reward and punishment in the striatum. *J Neurophysiol* 84:3072–3077.
60. Haruno M, Kawato M (2006): Different neural correlates of reward expectation and reward expectation error in the putamen and caudate nucleus during stimulus-action-reward association learning. *J Neurophysiol* 95:948–959.
61. Schonberg T, Daw ND, Joel D, O'Doherty JP (2007): Reinforcement learning signals in the human striatum distinguish learners from nonlearners during reward-based decision making. *J Neurosci* 27:12860–12867.
62. Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ (2006): Cortical substrates for exploratory decisions in humans. *Nature* 441:876–879.
63. Foerde K, Shohamy D (2011): The role of the basal ganglia in learning and memory: Insight from Parkinson's disease. *Neurobiol Learn Mem* 96:624–636.
64. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD (2006): Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature* 442:1042–1045.
65. Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE (2005): Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 62:1377–1381.
66. Molina JA, Sainz-Artiga MJ, Fraile A, Jimenez-Jimenez FJ, Villanueva C, Orti-Pareja M, *et al.* (2000): Pathologic gambling in Parkinson's disease: A behavioral manifestation of pharmacologic treatment? *Mov Disord* 15:869–872.
67. Voon V, Fox SH (2007): Medication-related impulse control and repetitive behaviors in Parkinson disease. *Arch Neurol* 64:1089–1096.
68. Cools R, Barker RA, Sahakian BJ, Robbins TW (2001): Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex* 11:1136–1143.
69. Gotham AM, Brown RG, Marsden CD (1988): "Frontal" cognitive function in patients with Parkinson's disease "on" and "off" levodopa. *Brain* 111:299–321.
70. Swainson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW (2000): Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: Possible adverse effects of dopaminergic medication. *Neuropsychologia* 38:596–612.
71. Squire LR, Stark CE, Clark RE (2004): The medial temporal lobe. *Annu Rev Neurosci* 27:279–306.
72. Knight R (1996): Contribution of human hippocampal region to novelty detection. *Nature* 383:256–259.
73. Lisman JE, Grace AA (2005): The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron* 46:703–713.
74. Shohamy D, Wagner AD (2008): Integrating memories in the human brain: Hippocampal-midbrain encoding of overlapping events. *Neuron* 60:378–389.

75. Wimmer GE, Shohamy D (2011): The striatum and beyond: Hippocampal contributions to decision making. In: Delgado MR, Phelps EA, Robbins TW, editors. *Attention and Performance XXII*. Oxford: Oxford University Press.
76. Burgess N, Maguire EA, O'Keefe J (2002): The human hippocampus and spatial and episodic memory. *Neuron* 35:625–641.
77. van der Meer MA, Johnson A, Schmitzer-Torbert NC, Redish AD (2010): Triple dissociation of information processing in dorsal striatum, ventral striatum, and hippocampus on a learned spatial decision task. *Neuron* 67:25–32.
78. Corkin S (2002): What's new with the amnesic patient H.M.? *Nat Rev Neurosci* 3:153–160.
79. Adcock RA, Thangavel A, Whitfield-Gabrieli S, Knutson B, Gabrieli JD (2006): Reward-motivated learning: Mesolimbic activation precedes memory formation. *Neuron* 50:507–517.
80. Johnson A, Redish AD (2005): Hippocampal replay contributes to within session learning in a temporal difference reinforcement learning model. *Neural Netw* 18:1163–1171.
81. Johnson A, van der Meer MAA, Redish AD (2007): Integrating hippocampus and striatum in decision-making. *Curr Opin Neurobiol* 17: 692–697.
82. Okatan M (2009): Correlates of reward-predictive value in learning-related hippocampal neural activity. *Hippocampus* 19:487–506.
83. Shohamy D, Adcock RA (2010): Dopamine and adaptive memory. *Trends Cogn Sci* 14:464–472.
84. Wirth S, Avsar E, Chiu CC, Sharma V, Smith AC, Brown E, *et al.* (2009): Trial outcome and associative learning signals in the monkey hippocampus. *Neuron* 61:930–940.
85. Wittmann BC, Bunzeck N, Dolan RJ, Duzel E (2007): Anticipation of novelty recruits reward system and hippocampus while promoting recollection. *Neuroimage* 38:194–202.
86. Wittmann BC, Schott BH, Guderian S, Frey JU, Heinze HJ, Duzel E (2005): Reward-related FMRI activation of dopaminergic midbrain is associated with enhanced hippocampus-dependent long-term memory formation. *Neuron* 45:459–467.
87. Brog JS, Salyapongse A, Deutch AY, Zahm DS (1993): The patterns of afferent innervation of the core and shell in the "accumbens" part of the rat ventral striatum: Immunohistochemical detection of retrogradely transported fluoro-gold. *J Comp Neurol* 338:255–278.
88. Groenewegen HJ, Vermeulen-Van der Zee E, te Kortschot A, Witter MP (1987): Organization of the projections from the subiculum to the ventral striatum in the rat. A study using anterograde transport of Phaseolus vulgaris leucoagglutinin. *Neuroscience* 23:103–120.
89. Poldrack RA, Rodriguez P (2004): How do memory systems interact? Evidence from human classification learning. *Neurobiol Learn Mem*. 82:324–332.
90. Samson Y, Wu JJ, Friedman AH, Davis JN (1990): Catecholaminergic innervation of the hippocampus in the cynomolgus monkey. *J Comp Neurol* 298:250–263.
91. Swanson LW (1982): The projections of the ventral tegmental area and adjacent regions: A combined fluorescent retrograde tracer and immunofluorescence study in the rat. *Brain Res Bull* 9:321–353.
92. Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G (2011): Linking context with reward: A functional circuit from hippocampal CA3 to ventral tegmental area. *Science* 333:353–357.
93. Filoteo JV, Maddox WT, Davis JD (2001): Quantitative modeling of category learning in amnesic patients. *J Int Neuropsychol Soc* 7:1–19.
94. Cheung TH, Cardinal RN (2005): Hippocampal lesions facilitate instrumental learning with delayed reinforcement but induce impulsive choice in rats. *BMC Neurosci* 6:36.
95. Li J, Delgado MR, Phelps EA (2011): How instructed knowledge modulates the neural systems of reward learning. *Proc Natl Acad Sci U S A* 108:55–60.
96. Dickerson KC, Li J, Delgado MR (2011): Parallel contributions of distinct human memory systems during probabilistic learning. *Neuroimage* 55:266–276.
97. Vanni-Mercier G, Mauguiere F, Isnard J, Dreher JC (2009): The hippocampus codes the uncertainty of cue-outcome associations: An intracranial electrophysiological study in humans. *J Neurosci* 29:5287–5294.
98. Fyhn M, Molden S, Hollup S, Moser MB, Moser E (2002): Hippocampal neurons responding to first-time dislocation of a target object. *Neuron* 35:555–566.
99. Kumaran D, Maguire EA (2009): Novelty signals: A window into hippocampal information processing. *Trends Cogn Sci* 13:47–54.
100. Chen J, Olsen RK, Preston AR, Glover GH, Wagner AD (2011): Associative retrieval processes in the human medial temporal lobe: Hippocampal retrieval success and CA1 mismatch detection. *Learn Mem* 18:523–528.
101. Kumaran D, Maguire EA (2006): An unexpected sequence of events: Mismatch detection in the human hippocampus. *PLoS Biol* 4:e424.
102. Foerde K, Shohamy D (2011): Feedback timing modulates brain systems for learning in humans. *J Neurosci* 31:13157–13167.
103. Berg J, Dickhaut J, McCabe K (1995): Trust, reciprocity, and social history. *Games Econ Behav* 10:122–142.
104. Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E (2008): Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron* 58:639–650.
105. Delgado MR, Frank RH, Phelps EA (2005): Perceptions of moral character modulate the neural systems of reward during the trust game. *Nat Neurosci* 8:1611–1618.
106. King-Casas B, Tomlin D, Anen C, Camerer CF, Quartz SR, Montague PR (2005): Getting to know you: Reputation and trust in a two-person economic exchange. *Science* 308:78–83.
107. Chang LJ, Doll BB, van't Wout M, Frank MJ, Sanfey AG (2010): Seeing is believing: Trustworthiness as a dynamic belief. *Cogn Psychol* 61:87–105.
108. Lee AS, Duman RS, Pittenger C (2008): A double dissociation revealing bidirectional competition between striatum and hippocampus during learning. *Proc Natl Acad Sci U S A* 105:17163–17168.
109. Poldrack RA, Clark J, Pare-Blagoev EJ, Shohamy D, Creso Moyano J, Myers C, *et al.* (2001): Interactive memory systems in the human brain. *Nature* 414:546–550.
110. Dagher A, Owen AM, Boecker H, Brooks DJ (2001): The role of the striatum and hippocampus in planning: A PET activation study in Parkinson's disease. *Brain* 124:1020–1032.
111. Voermans NC, Petersson KM, Daudey L, Weber B, Van Spaendonck KP, Kremer HP, *et al.* (2004): Interaction between the human hippocampus and the caudate nucleus during route recognition. *Neuron* 43:427–435.
112. Sadeh T, Shohamy D, Levy DR, Reggev N, Maril A (2011): Cooperation between the hippocampus and the striatum during episodic encoding. *J Cogn Neurosci* 23:1597–1608.
113. Doeller CF, King JA, Burgess N (2008): Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proc Natl Acad Sci U S A* 105:5915–5920.
114. Tricomi E, Fiez JA (2008): Feedback signals in the caudate reflect goal achievement on a declarative memory task. *Neuroimage* 41:1154–1167.
115. Balleine BW, O'Doherty JP (2010): Human and rodent homologies in action control: Corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35:48–69.
116. Kable JW, Glimcher PW (2007): The neural correlates of subjective value during intertemporal choice. *Nat Neurosci* 10:1625–1633.
117. Kahneman D, Tversky A (1979): Prospect theory: An analysis of decision under risk. *Econometrica* 47:263–292.
118. McClure SM, Ericson KM, Laibson DI, Loewenstein G, Cohen JD (2007): Time discounting for primary rewards. *J Neurosci* 27:5796–5804.
119. McClure SM, Laibson DI, Loewenstein G, Cohen JD (2004): Separate neural systems value immediate and delayed monetary rewards. *Science* 306:503–507.
120. Balleine BW, Dickinson A (2000): The effect of lesions of the insular cortex on instrumental conditioning: evidence for a role in incentive memory. *J Neurosci* 20:8954–8964.
121. Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ (2011): Model-based influences on humans' choices and striatal prediction errors. *Neuron* 69:1204–1215.
122. Glascher J, Daw N, Dayan P, O'Doherty JP (2010): States versus rewards: dissociable neural prediction error signals underlying model-based and model-free reinforcement learning. *Neuron* 66:585–595.
123. Dayan P (2008): The role of value systems in decision making. In: Engel C, Singer W, editors. *Better than Conscious? Decision Making, the Human Mind, and Implications for Institutions*. Cambridge, MA: MIT Press, 51–70.
124. Kringelbach ML (2005): The human orbitofrontal cortex: Linking reward to hedonic experience. *Nat Rev Neurosci* 6:691–702.

125. Seymour B, Dolan R (2008): Emotion, decision making, and the amygdala. *Neuron* 58:662–671.
126. Phelps EA, LeDoux JE (2005): Contributions of the amygdala to emotion processing: From animal models to human behavior. *Neuron*. 48:175–187.
127. McGaugh JL (2004): The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu Rev Neurosci* 27:1–28.
128. Hsu M, Bhatt M, Adolphs R, Tranel D, Camerer CF (2005): Neural systems responding to degrees of uncertainty in human decision-making. *Science* 310:1680–1683.
129. De Martino B, Kumaran O, Seymour B, Dolan RJ (2006): Frames, biases, and rational decision-making in the human brain. *Science* 313:684–687.
130. Packard MG, Teather LA (1998): Amygdala modulation of multiple memory systems: Hippocampus and caudate-putamen. *Neurobiol Learn Mem* 69:163–203.
131. Ballard IC, Murty VP, Carter RM, MacInnes JJ, Huettel SA, Adcock RA (2011): Dorsolateral prefrontal cortex drives mesolimbic dopaminergic regions to initiate motivated behavior. *J Neurosci* 31:10340–10346.
132. Doll BB, Jacobs WJ, Sanfey AG, Frank MJ (2009): Instructional control of reinforcement learning: A behavioral and neurocomputational investigation. *Brain Res* 1299:74–94.
133. Burke CJ, Tobler PN, Baddeley M, Schultz W (2010): Neural mechanisms of observational learning. *Proc Natl Acad Sci U S A* 107:14431–14436.