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Review

# Dopamine and extinction: A convergence of theory with fear and reward circuitry

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ABSTRACT

Research on dopamine lies at the intersection of sophisticated theoretical and neurobiological approaches to learning and memory. Dopamine has been shown to be critical for many processes that drive learning and memory, including motivation, prediction error, incentive salience, memory consolidation, and response output. Theories of dopamine's function in these processes have, for the most part, been developed from behavioral approaches that examine learning mechanisms in reward-related tasks. A parallel and growing literature indicates that dopamine is involved in fear conditioning and extinction. These studies are consistent with long-standing ideas about appetitive–aversive interactions in learning theory and they speak to the general nature of cellular and molecular processes that underlie behavior. We review the behavioral and neurobiological literature showing a role for dopamine in fear conditioning and extinction. At a cellular level, we review dopamine signaling and receptor pharmacology, cellular and molecular events that follow dopamine receptor activation, and brain systems in which dopamine functions. At a behavioral level, we describe theories of learning and dopamine function that could describe the fundamental rules underlying how dopamine modulates different aspects of learning and memory processes.



## 1. Introduction

A key insight from behavioral approaches to learning is that multiple theoretical processes contribute to the acquisition and extinction of learned behaviors. Over the years, theories have described effects on processing of the conditioned stimulus (CS), the unconditioned stimulus (US), the context in which learning occurs, and the associative connections that form among stimuli, responses, and outcomes. Neurobiological studies have revealed that dopamine signaling is involved in many of the different theoretical processes that underlie learning. Recent experiments examining the role of dopamine in acquisition and extinction of learned fear demonstrate that learning in aversive situations may be modulated by an engagement of appetitive systems, supporting long-held assumptions about appetitive–aversive interactions in learned behavior (Dickinson & Dearing, 1979; Dickinson & Pearce, 1977; Konorski, 1967).

In this review, we focus on recent evidence demonstrating the different ways in which dopamine signaling may modulate learning during extinction of fear. We first review some of the ways in which dopamine has been treated at a theoretical level. Dopamine is involved in the circumstances that produce learning (e.g., prediction error, coding of stimulus salience); it mediates the content of that learning (e.g., hedonic value of associations); and it modulates the expression of learning in performance (e.g., response vigor, memory retrieval). We consider the complexity of dopamine signaling at receptor, molecular, and neural systems levels and suggest that some of the reward-related processes that rely on dopamine may drive the learning of extinction contingencies.

## 2. The many roles of dopamine in learning

A central tenet of the neurobiology of reward is that dopamine plays a key role in different processes modulating reward-seeking behaviors. Due to the complexity of signaling that arises from the projections to and from dopamine neurons, there are several different theoretical explanations for dopamine's role in these behaviors. These theories parallel learning theories that have focused on different aspects of Pavlovian and operant processes in behavior. In particular, theories have focused on the nature of reinforcement and how motivational state alters the impact of an outcome on learning processes (e.g., Dayan & Balleine, 2002), how the conditioned reinforcing value of previously neutral stimuli may come to control behavior (e.g., Belin, Belin-Rauscent, Murray, & Everitt, 2013), and how the discrepancy between the expected and obtained outcomes in a given situation drives learning (e.g., Iordanova, 2009).

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Theories that focus on dopamine's role in reinforcement have described mechanisms through which dopamine increases stimulus–response associations when those responses lead to rewarding experiences (Wise, 2004). A consequence of reinforcement is that stimuli that have been reinforced will generate both proximal motivated behaviors (approach or avoidance), as well as distal motivated behaviors (allocating resources for effortful approach or avoidance of a goal stimulus; Salamone & Correa, 2012). Ettenberg (2004) separates motivation from reinforcement by defining motivation as the process that initiates goal-seeking behavior, while reinforcement is the consequence of operant behavior that alters the probability that a behavior will be repeated under similar conditions.

Theories that focus on the way that dopamine alters the conditioned value of previously neutral stimuli suggest that reward alters how organisms process environmental cues. The incentive salience theory describes mechanisms by which dopamine transmission in the nucleus accumbens assigns value to reward-related stimuli and dissociates hedonic value from behaviors directed toward goal stimuli (Berridge & Robinson, 2003; Flagel et al., 2010). The incentive salience theory is useful for understanding the maintenance of drug addiction, as tolerance develops to the rewarding effects of drugs but drug-seeking behavior becomes sensitized to drug-paired stimuli.

Cues associated with reward come to evoke responding and further learning to the extent that they signal unexpected outcomes. The prediction error model of dopamine function describes dopamine neuron activation linked to predictive models generated from associative learning events. Violations of predicted outcomes alter dopamine neuron firing, leading to alterations in motivated behaviors (Schultz & Dickinson, 2000). Triggering a dopamine response can induce learning under conditions, such as blocking, in which learning normally fails (e.g., Steinberg et al., 2013). These behavioral theories are supported by cellular and molecular evidence that dopamine receptor activation induces signaling cascades that are involved in the long-term consolidation of appetitive or aversive memories (Lauzon, Bechard, Ahmad, & Laviolette, 2013).

Although these theories have been useful for understanding how dopamine is involved in reward learning, behavioral theories of the role of dopamine in aversive learning remain poorly defined. Fear conditioning occurs rapidly, often after few pairings of a CS with a shock US. During extinction, the fear response is suppressed as the organism learns that the CS no longer predicts the shock. Extinction does not erase the original fear memory, but creates a new representation that allows the animal to adapt behavioral responses to previously conditioned stimuli (Rescorla, 2001). Several researchers have proposed mechanisms by which dopamine may modulate aversive learning (Horvitz, 2000; Redgrave, Prescott, & Gurney, 1999; Salamone, 1994) and technological advances such as optogenetics or fast-scan cyclic voltammetry could clarify the exact contribution of dopamine in particular aspects of fear-related behaviors. Characterizing the role of dopamine in fear is particularly interesting because dopamine release within reward circuitry may alter the subjective value assigned to fearful stimuli, in addition to directly affecting memory consolidation (Horvitz, 2000; Pezze & Feldon, 2004). Thus, there are multiple mechanisms through which dopamine may alter the establishment, maintenance, expression, and extinction of fear. These include altering the conditions through which fear occurs (e.g., prediction error), altering the content of the association (e.g., attaching rewarding hedonic value to previously fearful stimuli), and altering the expression of the memory (e.g., changing the conditions under which conditioned fear occurs in behavior).

The varied role of dopamine in appetitive and aversive learning is not surprising given the distribution of dopamine receptors in the central nervous system (Mansour & Watson, 1995), where dopamine is found throughout regions important for aversive and reward memory. This creates a complicated pattern of regional activity that could have different behavioral outcomes depending on the behavioral experience. In addition to regional activation patterns causing different theoretical processes to be engaged, analyses of dopamine function in learning are complicated by the different intracellular signaling cascades that are triggered by receptor binding of dopamine. Just as the competition between excitation and inhibition at behavioral and regional levels can change the long-term behavioral consequence of a learning experience, so too can competition between excitatory and inhibitory intracellular signals.

## 3. Dopamine receptor signaling and pharmacology

The three questions that have motivated much of the behavioral research on learning (Rescorla & Holland, 1976) are recapitulated at a cellular level when it comes to assessing dopamine function. What are the conditions that cause activation of different dopamine receptor subtypes? How are those conditions translated into molecular changes that lead to learning? How are those subtypes involved in expression of learning in behavior? Although the specific answers to these questions are elusive, a great deal is now known about dopamine receptor signaling and pharmacology and how they relate to learning.

A major complexity in understanding the role of dopamine in learning processes is that there are multiple dopamine receptor subtypes that activate different second messenger signaling cascades (Fig. 1). Although differences among receptor subtypes are widely documented and are often described in terms of different learning processes, it is important to consider that one receptor subtype can have multiple molecular effects, which may result in different behavioral endpoints. These effects may be excitatory or inhibitory and may occur through different second messengers.

One of the challenges in research on cellular effects of dopamine receptors is determining the relation between inhibitory and excitatory processes at molecular and behavioral levels. Dopamine signaling involves clear interactions between these processes, revealed in effects of activating the two main subfamilies of dopamine receptors. D1-like receptors, comprised of D1 and D5 dopamine receptors, activate the stimulatory G proteins $G\alpha_s$ and $G\alpha_{olf}$. D2-like receptors, which include the D2, D3, and D4 receptors, activate the inhibitory G proteins $G\alpha_i$ and $G\alpha_o$ (Beaulieu & Gainetdinov, 2011). Generally, activation of stimulatory G proteins stimulates adenylate cyclase activity and cyclic adenosine monophosphate (cAMP) production, while activation of inhibitory G proteins decreases adenylate cyclase activity. D1 receptors in the nucleus accumbens and neostriatum primarily activate $G\alpha_{olf}$ stimulatory G proteins while D1 receptors in hippocampus and cerebral cortex activate $G\alpha_s$ stimulatory G proteins. The classical view of dopamine receptor activity has focused on intracellular signaling through adenylate cyclase and cAMP activity, both of which are widely recognized to play central roles in learning. For example, inhibitory interactions between dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) and protein phosphatase-1 (PP1) are important for intracellular regulation of neural plasticity (Gould & Manji, 2005) and DARPP-32 activity has been identified as a critical component in detecting convergent dopamine and glutamate signals leading to long-term synaptic plasticity (Valjent et al., 2005).

There is considerable evidence, however, that in addition to modulating cAMP activity, D1-like receptors operate through activation of phospholipase C (PLC). PLC activity has been implicated in the formation of fearful memories (Buckley & Caldwell, 2004;