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Dopamine Signals Learn New Tricks

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In this issue of *Neuron*, Morrens et al. (2020) show that stimulus-evoked dopamine responses are enhanced by novelty and increase the rate at which animals acquire conditioned responses. These results provide a candidate neural mechanism for latent inhibition and illustrate a new role of dopamine signals in learning.

The vast majority of dopamine neurons exhibit phasic responses to rewards that resemble fundamental learning signals: reward prediction errors. Better-than-predicted rewards evoke bursts of action potentials in dopamine neurons, whereas worse-than-predicted rewards suppress action potentials (Figure 1, top and bottom, response to reward ["R"] and no reward ["no R"] are highlighted in the blue shaded regions). Prediction errors are required for learning (Rescorla and Wagner, 1972), and recent optogenetic studies have demonstrated that phasic dopamine reward responses are necessary and sufficient for associative learning (Chang et al., 2016; Steinberg et al., 2013). Rewards, however, are not the only events that drive dopamine responses. Dopamine neurons also respond to conditioned stimuli (CS)—visual cues, odors, sounds, or even vibrotactile stimuli—that *predict* rewards (Figure 1, middle and bottom, "CS," orange shaded region) (Schultz, 2015). CS-driven dopamine responses occur after behavioral training associates a CS with reward (Schultz et al., 1993), but CS-driven responses also occur following novel stimuli (Lak et al., 2016). The behavioral functions of CS-driven dopamine responses are hotly debated and remain largely unknown. An exciting new report shows that CS-driven dopamine responses promote faster learning (Morrens et al., 2020).

In this issue of *Neuron*, Morrens, Aydin, et al. used novel and familiar odorant CS to investigate the behavioral functions of novelty-driven dopamine responses (Morrens et al., 2020). The authors familiarized the animals to CS in a pre-exposure task in which mice were exposed to the odorants, but no rewards were delivered. As novel CS were introduced, the respiration rates of the animals were elevated for novel compared to familiar CS. During the subsequent testing phase, the animals were presented with a mixture of novel and familiar CS. Learning, as indicated by the development of anticipatory lick responses, took fewer trials for novel compared to familiar CS. Reinforcement learning models applied to the data showed a higher learning rate for novel compared to familiar CS. These behavioral effects are consistent with latent inhibition, a well-known psychological phenomenon that manifests as reduced learning of conditioned responses following prior exposure to a conditioned stimulus (Lubow and Moore, 1959). This phenomenon has been documented in a wide range of species, including mice and humans. However, the neural mechanisms responsible for latent inhibition are not known.

To investigate whether CS-driven dopamine signals play a role in latent inhibition, Morrens, Aydin, et al. used Ca^{2+} imaging to monitor signals from dopamine neurons in the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) in mice (Morrens et al., 2020). As expected, dopamine transients were initiated at the reception of

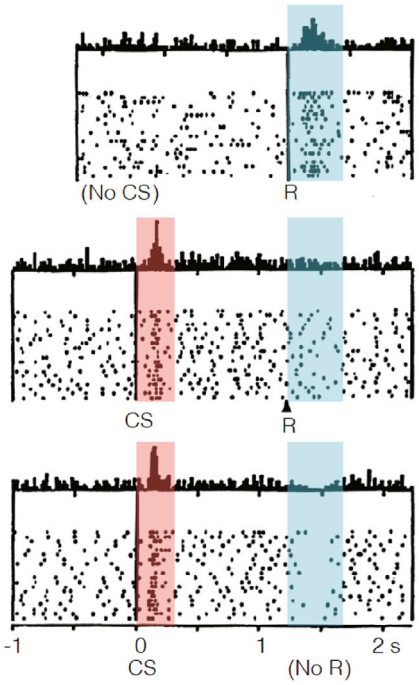

Figure 1. Dopamine Responses to Conditioned Stimuli and Rewards

Peri-stimulus time histograms (PSTHs) and raster plots of impulses demonstrate the fundamental characteristics of dopamine responses to rewards and reward predictors. Orange- and blue-shaded boxes indicate phasic dopamine responses evoked by a conditioned stimulus or reward, respectively. (Top) Activation following delivery of an unpredicted drop of juice reward ("R") demonstrates a positive reward prediction error (RPE) response. (Middle) The neuron is activated by a CS ("CS") that predicts reward, but there is no RPE or RPE response following reward ("R"). (Bottom) When the CS predicts reward but the reward is withheld on a minority of trials, the activity is silenced ("No R"). Neuronal impulses are aligned to the delivery of reward (top) or CS (middle and bottom). This figure was modified and reproduced with permission from Schultz et al. (1997).

unpredicted water and novel CS. Interestingly, the magnitudes of responses to novel odorant CS were correlated with the amount of time that mice explored that odor, suggesting a relationship between the dopamine response and the "intrinsic value" of the odorant cue. The response to novel CS diminished as the odorant became familiar, and the correlation between CS-evoked responses and exploration time disappeared. These results indicate that novel odorant stimuli enhance the CS-driven dopamine response. Moreover, they suggest that the physical properties of CS can influence both the behavioral and neurobiological correlates of learning.

Further, Morrens, Aydin, et al. used cell-type-specific optogenetic manipulations in dopamine neurons to demonstrate a causal relationship between CS-driven dopamine responses and learning (Morrens et al., 2020). Optogenetic activations and inhibitions simulated the neuronal effects of novelty and familiarity, respectively. Optogenetic activations of dopamine neurons during the presentation of familiar odorant cues decreased the number of trials to acquisition of the conditioned response. In short, optogenetic activations caused faster learning. On the other hand, optogenetic inhibition of dopamine neurons during the presentation of novel cues blocked the faster learning typically seen with novel stimuli. Thus, preventing novelty-enhanced activations caused behavioral effects that mimicked latent inhibition.

Inspired by previous findings that relate frontal cortex dopamine concentrations to latent inhibition (Nelson et al., 2010), Morrens, Aydin, et al. asked whether the behavioral effects of novelty-evoked CS dopamine activations are mediated through their effects on the frontal cortex (Morrens et al., 2020). Indeed, phasic optogenetic activation of dopamine terminals in the frontal cortex alone promoted faster acquisition of conditioned responding. These results provide evidence that phasic dopamine release, specifically in the frontal cortex, accelerates learning to novel cues.

Overall, the study by Morrens, Aydin, et al. provides fundamental new insights into how dopamine signaling contributes to reward learning (Morrens et al., 2020). The key manipulation used in this study was pre-exposure of odorant CS in the absence of reward. This pre-exposure paradigm likely familiarized the animals to a set of particular CS and reduced novelty. Alternatively, it is possible that the pre-exposure paradigm causes learning of "CS-no reward" association. If this were the case, the subsequent slower association between "CS-reward" could be due to competition between the two associations. This seems unlikely, as the recorded photometry signals did not detect phasic suppressions to familiar CS. However, fiber photometry records from many neurons at once and Ca^{2+} signals have poor temporal resolution, so this question may need to be revisited in future studies.

An interesting direction for future research relates to the temporal dynamics of CS-evoked responses. Namely, are there two, or potentially more, independent signals with distinct behavioral functions embedded within CS-evoked dopamine responses? Theory and experiments indicate that the CS-evoked responses (Figure 1) are described by the exact same reward prediction error algorithm that defines dopamine reward responses (Schultz et al., 1997). Moreover, prior electrophysiological recordings have shown that CS-evoked novelty signals and the CS-evoked prediction error signals occur consecutively in time. The novelty response, like most salience-based dopamine responses, arises 60–70 ms following CS presentation. Prediction error signals take longer to develop and are usually observed 150–250 ms following CS presentation. What part of CS-evoked dopamine responses is required to produce accelerated learning? If it is solely the novelty component, then optogenetic activations and inhibitions focused on the interval between 0 and 150 ms from stimulus onset might produce the same results as the longer duration stimulations used by Morrens, Aydin, and colleagues. If this ends up being the case, what is the behavioral role of the CS-evoked prediction error response?

Regardless of the answers to future questions, these exciting results provide direct evidence that dopamine signals have more to do with learning than we previously knew. Phasic reward responses have long been associated with learning. However, the behavioral functions of CS-evoked phasic responses were less well known. The present study shows that CS-evoked dopamine signals promote CS-reward associations, reveals a candidate neural mechanism for latent inhibition, and, like all good studies, highlights important questions for future studies to address.

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