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OUTLOOK

What does dopamine release reveal about latent inhibition?

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Summary
A recent paper by Kutlu et al. (2022) argues that changes in dopamine release during stimulus pre-exposure reflect non-associative changes in attention to the conditioned stimulus that are causally related to latent inhibition effects. Associative accounts of pre-exposure-induced changes in associability suggest, however, that such conclusions may be premature.

Main body

Of the many associative theories of learning advanced over the decades, the most successful has been Rescorla and Wagner's (1972) US processing theory (R-W). On this view, learning is most adaptive when animals accurately predict the events – the Unconditioned Stimuli (USs) – with which they are primarily concerned, for example, food, water, predators, poisons etc., and, therefore, the aim of learning is to reduce errors in predicting those USs, i.e., the discrepancy between the predicted US and that which actually occurs. This theory has been particularly successful in predicting competitive learning phenomena, such as blocking and overshadowing, and, indeed, its primary operator, the US prediction error, has been associated with the phasic activity of dopamine neurons in the midbrain; which is greatest to unpredicted USs, declines during learning, and stops altogether if a predicted US does not occur.

Nevertheless, despite this success, there have always been significant issues with the theory. Chief amongst these is the failure to predict the effects of treatments that alter the associability of the Conditioned Stimuli (CSs) animals use to predict USs, findings which have fed CS processing theories. Perhaps the simplest example of such an effect is Latent Inhibition (LI); i.e., the retardation of conditioning produced by prior exposure to the CS. Although R-W added the assumption that such a treatment might cause a decline in the *salience* of that stimulus, they provided no mechanism for that change. This vacuum was filled by a number of alternative theories, from simple non-associative accounts based on habituation-induced changes in attention to the CS (Lubow, 1973), to more complex associative views, such as Wagner's (1978) argument that pre-exposure results in a CS-context association that interferes with subsequent CS processing. Deciding between these distinct kinds of theory has proven complicated; however, one recent approach has been to consider the role of dopamine in these effects. Does dopamine contribute to changes in CS processing during pre-exposure or only when the CS is paired with a US during conditioning?

In a recent paper, Kutlu et al. (2022) set out to parse these prominent accounts of LI using optical techniques to observe and control dopamine release in the Nucleus Accumbens core (NAcc), a logical place to start given the role of striatal dopamine in associative learning and stimulus processing generally. In stage 1, mice were pre-exposed to a novel auditory or visual stimulus (X) in a novel context over a number of days before they received pairings of X with footshock in the same context during stage 2. A novel stimulus (A) was also paired with shock in stage 2 and a third stimulus (B) was presented without any consequence. Unsurprisingly, at test, the mice showed a clear LI effect, freezing significantly more in response to the novel CS-A than to either the pre-exposed X or the unpaired B. With this LI effect in hand, the authors employed fiber photometry to measure real-time dopamine release in the NAcc (using the fluorescent dopamine sensor dLight1.1) during stages 1 and 2. A relatively large dopamine release event was elicited by the first exposure to the novel X during pre-exposure, which declined over trials and, perhaps tellingly, did not recover in a second session of pre-exposure. Furthermore, when the pre-exposed X was subsequently presented prior to footshock in stage 2, dopamine release was reduced relative to that elicited by the novel A and B stimuli and, although freezing emerged to both X and A, it was clearly reduced to X. Both the dopamine and LI effects were eliminated by a context shift between stages 1 and 2. The interpretation offered for these findings was, therefore, that

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dopamine responses tracked the novelty of the stimulus in its context – and that such responses were dampened by familiarity even when a pre-exposed stimulus was paired with a motivationally significant event.

To determine whether this observed profile of dopamine release in stage 2 was causal to the expression of latent inhibition, the authors then used optogenetics to either stimulate (using channelrhodopsin, ChR2) or inhibit (using halorhodopsin, NpHR) dopamine release at terminals of axons from the ventral tegmental area (VTA) in the NAcc. Stimulating dopamine release during the onset of the pre-exposed X during the first trial of fear conditioning blocked LI and freezing was acquired similarly to the novel CS-A. A similar effect was achieved by ChR2 stimulation during pre-exposure, although this was not specific to cue onset: LI was abolished whether terminals were activated at the onset of X or during the inter-stimulus interval, raising the possibility that these effects of stimulation may have been induced by a change in context processing. Nevertheless, inhibiting dopamine release by silencing the VTA-NAcc projection for the duration of stimulus presentation had no effect on performance at test if executed in stage 2 but appeared to increase the magnitude of the LI effect if applied during stage 1.

The authors argue that, collectively, these results counter Wagner's (1978) associative account because reducing dopamine release during pre-exposure should retard context-CS learning and so prevent LI, whereas increasing it should enhance both the context-CS association and LI, which is the opposite of their findings. Instead, they suggest that the reduced dopamine release in the NAcc that develops during pre-exposure and that transfers to conditioning is causal to the expression of LI and hypothesize that the dopamine activity in the NAcc modulates future behavior via changes in novelty or saliency-induced attention to X induced non-associatively through habituation during pre-exposure. Finally, to provide further evidence for this account, the authors compared the effect of the pre-exposed X versus a novel CS when presented in compound with a previously conditioned excitor in a summation test. They found that, whereas X did not affect freezing to the excitor, the novel stimulus did, suggesting that pre-exposure reduced attention to X without inducing conditioned inhibition whereas attention to the novel cue interfered with performance to the excitor, likely due to some form of external inhibition. They conclude that, together, these findings provide consistent evidence for an attentional rather than an associative account of LI.

The finding that NAcc dopamine release is elevated to a novel stimulus and declines with further presentations is interesting and consistent with changes in attention to the stimulus. However, these are changes in dopamine release in a region of the striatum previously implicated in translating motivation into action (Mogenson et al., 1993). As such, it is perhaps equally possible that these effects reflect changes in the motor movements/orienting responses elicited by the pre-exposed stimulus. Presenting measures of motor movement, particularly of orienting to the CS, alongside the changes in dopamine activity would have made a revelatory and clarifying addition to this report. It would also have been interesting to consider other associative theories that, unlike Wagner (1978), are not so obviously troubled by these data. For example, the Pearce-Hall theory (1980) proposes that both orienting to, and the associability of, a CS decline as its consequences are accurately predicted, which, during pre-exposure, means as the CS comes accurately to predict "nothing." Furthermore, this theory incorporates the US prediction error to assign associability to the CS and, indeed Fiorillo et al. (2003) found that dopamine neuron activity increased during a CS as its associative ambiguity increased (what they call entropy), which accords both with the Pearce-Hall theory and Kutlu et al.'s (2022) findings.

Nevertheless, whether the effects of CS pre-exposure on dopamine activity turn out to be due to a reduction in novelty, in CS-elicited orienting or in the US prediction error, this paper from Kutlu et al. (2022) offers an exciting example of how ground-breaking neuroscience approaches can provide a promising route to tackling lingering questions in associative and non-associative learning.

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