

## COMMENTARIES

# Espresso Reward Learning, Hold the Dopamine: Theoretical Comment on Robinson et al. (2005)

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*Question:* Is dopamine needed for reward learning? *Answer:* No—at least, not in the brain of a caffeinated dopamine-deficient (DD) mutant mouse. That is the conclusion of an important paper in this issue by S. Robinson, S. M. Sandstrom, V. H. Denenberg, and R. D. Palmiter. Those authors demonstrate that reward learning can proceed normally in the brains of DD mice, even though they contain no dopamine at the time of learning, if the mice are given caffeine just before learning. Caffeine activates the DD mice by a nondopaminergic mechanism, allowing them to learn where to obtain food reward in a T-maze runway. Their reward-learning-without-dopamine is revealed on a subsequent test day, when dopamine function is restored by L-dopa administration. Robinson et al. conclude that dopamine is not needed for normal learning about rewards, or for hedonic “liking” of rewards during learning, but rather specifically for a motivational “wanting” component of reward, such as incentive salience.

In an important study in this issue, S. Robinson, Sandstrom, Denenberg, and Palmiter (2005) ask which component of reward is most lacking in dopamine-deficient mutant mice: reward learning, reward “liking,” or reward “wanting”? Their answer is that dopamine is necessary in order to want rewards normally, but that dopamine is not needed for learning about rewards or for liking them.

The dopamine-deficient (DD) mouse is an intriguing mutant, developed by Zhou and Palmiter (1995). Its mutation inactivates the gene that normally codes tyrosine hydroxylase, an enzyme required for neurons to produce dopamine. The mesolimbic–nigrostriatal neurons of DD mice fire action potentials with waveforms and burst properties similar to those of normal dopamine neurons when DD mice are in baseline waking state (S. Robinson, Smith, Mizumori, & Palmiter, 2004), but in DD mice those neurons are unable to synthesize dopamine without additional aid. DD mice exhibit classic symptoms of rats that have received severe 6-hydroxydopamine lesions of dopamine neurons (also similar to severe Parkinson’s disease symptoms). DD mice show akinesia, aphagia, and adipsia, so that they fail to eat or drink sufficient amounts of food or water to survive.

However, if DD mice are treated with the medication L-dopa (which is often prescribed to human Parkinson’s patients too) the mutant mice show a temporary behavioral recovery that lasts up to 9 hr. L-dopa provides an alternative biochemical route to produce dopamine without tyrosine hydroxylase, at least for a few hours.

During those hours, DD mice avidly eat and drink, and so regularly repeated doses of L-dopa keep DD mice sufficiently nourished and hydrated to be maintained in good health.

In their current study, Robinson et al. cleverly exploit the ability of L-dopa to temporarily revive dopamine production and behavioral competence. They use a two-phase experimental design. First, DD mice learn a reward task in Phase 1. On a later day, the mice are tested in Phase 2. Comparison of mice that received L-dopa in both phases to those that received it only in Phase 2 allows assessment of latent learning that occurred earlier without dopamine.

In their first experiment, Robinson et al. gave L-dopa in both Phase 1 and Phase 2. L-dopa-medicated mice learn to run down a runway and turn to one side to find a food reward, similar to control wild-type mice, and they generally eat the food rewards they find. The L-dopa-medicated DD mice performed normally, aside from slight abnormality in latency to eat, and an inability to switch directions in a reversal task after one direction had already been successfully learned (possibly a side effect of L-dopa). So Experiment 1 demonstrates that when dopamine function is rescued by L-dopa, DD mice are apparently capable of normal reward learning, “liking,” and motivation for reward.

However, the real beauty of this paper lies in the second experiment. It cleverly uses the same two-phase design to exploit latent learning acquired in the first phase, even without dopamine. The learning is expressed later in the second phase, when dopamine is present, after L-dopa is given to all DD mice to enable and equate their performance capacity.

Crucially, in Phase 1 of the second experiment, the DD mice were divided into three groups: caffeine, saline, and L-dopa groups. Neither caffeine nor saline groups had brain dopamine during Phase 1. Caffeine behaviorally activates DD mice by a nondopaminergic mechanism. Even though caffeine indirectly promotes dopamine release in normal brains, caffeine also apparently has an alternate route of behavioral arousal, perhaps via adenosine recep-

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tors, which suffices in DD mice. The statement that caffeine acts differently from dopamine in DD mice seems safe, for two reasons. First, DD mice have virtually no dopamine to be released by caffeine if they have not also received L-dopa on the same day. So when caffeine by itself behaviorally activates DD mice to run in a maze, it must be acting by a mechanism that does not involve dopamine. Further, caffeine fails to induce immediate early gene expression of Fos in neostriatum of DD mice, although L-dopa and dopamine D<sub>1</sub> receptor agonists both cause Fos expression in DD mice (Kim, Froelick, & Palmiter, 2002). Lack of Fos indicates that caffeine must activate DD mice without causing the neostriatal changes normally produced by stimulation of dopamine receptors.

### Latent Learning Without Dopamine: Crucial Results of Experiment 2

The caffeine group of DD mice are the real stars of this experiment. They received caffeine before Phase 1 training trials, and L-dopa only before Phase 2 test. Did they learn anything about rewards in Phase 1 without dopamine? Yes, the caffeine-treated DD mice did indeed learn about rewards in Phase 1 training trials. Their learning is revealed chiefly by their performance in Phase 2 (when all mice got L-dopa). During the Phase 2 test, the DD mice previously trained under caffeine make correct choices of the maze arm containing food reward as often as mice that had previously been trained under L-dopa. Yet unlike the L-dopa group, which both learned and performed with the benefit of dopamine, the caffeine group had learned entirely without dopamine.

Interestingly, the learning of the caffeine group of DD mice was revealed only once they were given L-dopa during Phase 2. It was not apparent in their performance while they actually were learning without dopamine in Phase 1. During Phase 1, the caffeine-treated mice made many mistakes in choosing the maze arm and did not improve their performance over successive trials on that day. But once the caffeine-trained mice are given L-dopa in Phase 2, they immediately make more correct choices than they had during training, and become equal in learned choice performance to the mice that received L-dopa during both training and test.

This pattern of behavior suggests that dopamine is not needed for the acquisition of reward learning or associative information needed to make predictions about reward. Instead dopamine is only needed to use already learned information to generate successful motivated performance. This is more of a motivational, or “wanting,” function than an associative or learning function (Berridge & Robinson, 1998; Cannon & Bseikri, 2004; Cardinal, Parkinson, Hall, & Everitt, 2002; Everitt, Cardinal, Parkinson, & Robbins, 2003; McClure, Daw, & Read Montague, 2003; Robinson & Berridge, 2003; Salamone & Correa, 2002; Shizgal & Arvanitogiannis, 2003).

### Intact “Liking” Too?

Robinson et al. also suggest that caffeine treated mice have normal “liking” for food reward and do not show the anhedonia predicted by hedonic hypotheses of dopamine function (Koob & Le Moal, 1997; Wise, 1985). That’s because the caffeine group of DD mice did consume nearly 90% of the food rewards they encountered during training. This suggestion is reasonable if caffeinated DD mice eat (and learn about) only rewards they “like.”

Of course, a commentary from anyone like me who believes “liking” and “wanting” are separable and distinct components of reward is obligated to point out here that voluntary consumption of a reward is a form of wanting that sometimes can mislead regarding conclusions about hedonic liking. I should point out that Robinson et al. acknowledge this too. For example, several brain manipulations are known to specifically increase incentive salience of food (reflected in food consumption or seeking behavior) without simultaneously increasing hedonic impact (reflected in liking taste-reactivity patterns elicited by sucrose). Those examples include microinjections of amphetamine or muscimol into nucleus accumbens, mutation-induced elevation of extracellular dopamine, electrical stimulation of lateral hypothalamus and medial forebrain bundle, and mesolimbic sensitization by repeated psychostimulants (Berridge & Valenstein, 1991; Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003; Reynolds & Berridge, 2002; T. E. Robinson & Berridge, 1993, 2003; Wyvell & Berridge, 2000, 2001). All those manipulations cause wanting without liking, often driving increased food consumption or seeking behavior without increasing affective liking reactions to the hedonic impact of sweet reward.

However, in my opinion (and Robinson et al.’s), those “liking–wanting” dissociations probably pose no serious problem for Robinson et al.’s conclusion that DD mice have intact “liking.” No one is about to suggest that dopamine deficiency causes excessive “wanting.” Unless it did, potential dissociations of “wanting” from liking could not lead to false inference of “liking” in DD mice. Still, the administration of caffeine in DD mice may muddy the picture a bit. Perhaps we cannot completely rule out that caffeine might have caused “wanting” without “liking,” even if there is no evidence at present that it did. We do not understand the mechanisms underlying behavioral activation of DD mice by caffeine well enough to predict whether or not incentive salience systems might be recruited independently, even if caffeine does not induce neostriatal Fos.

These considerations imply that a degree of uncertainty may remain about “liking” in DD mice, as Robinson et al. acknowledge. To obtain more complete certainty, it might be valuable to run a taste reactivity study in the future to assess whether DD mice show normal “liking” reactions to sucrose taste. They should. In the meantime, normal “liking” without dopamine in DD mice, as Robinson et al. suggest, is a reasonable interim conclusion.

### Wanting Deficit?

The only notable deficit in Phase 2 of previously caffeine-treated DD mice was an increased latency to reach the food reward. In other words, DD mice that were trained previously on caffeine proceed more slowly to their food reward even after they were finally given L-dopa. The authors plausibly suggest that this indicates a persisting “wanting” deficit, caused by the previous absence of dopamine during training. That fits with previous theoretical suggestions that conditioned stimulus (CS)+ incentive salience has to be reboosted during learning over repeated predicted encounters with reward unconditioned stimuli (Berridge & Robinson, 1998; McClure et al., 2003).

Why should Phase 1 reboosting of “wanting” matter to Phase 2 performance? To convert CS+s into attractive “motivational magnets” that induce motivated performance, incentive salience may

need to be assigned specifically to particular CSs during learning. Once incentive salience is attributed to runway CS+s, they might speed incentive performance and reduce latency to obtain food. Normally, incentive CS+s interact with mesolimbic activation to dynamically motivate behavior in a cue-dependent fashion (Wyvell & Berridge, 2000), and in a runway, CS+ stimuli encountered in series as the mouse moves down the runway might act as dynamic motivational magnets to help pull the mouse toward reward.

But incentive salience attributed to CS+s may need to be reboosted across several learning trials in order to be motivationally effective for subsequent behavior (Berridge & Robinson, 1998; McClure et al., 2003). Blocking salience reboosting has been posited to impede subsequent motivated performance (Berridge & Robinson, 1998; Berridge & Valenstein, 1991; McClure et al., 2003), which may explain why dopamine antagonist drugs sometimes cause “extinction mimicry” effects on rewarded instrumental performance in normal animals (Wise, 1985, 2004). For DD mice without dopamine during training, presumably less incentive salience became assigned in Phase 1 to the brain’s representation of the runway location of food reward. As a persisting consequence, caffeine-treated DD mice may have to begin from a lower level of “wanting” assigned to CS+s in the runway even on the Phase 2 day when L-dopa is given. They may have to progressively attribute and reboost incentive salience to runway cues for reward in Phase 2, just as the L-dopa-trained DD mice had to do in Phase 1. In short, a “wanting” deficit in Phase 1, caused by dopamine lack in caffeine-treated DD mice, may help explain why latency remains slower in their beginning trials of Phase 2 after dopamine is replaced.

### Other Dopamine Mutant Votes

Beyond the data of Robinson et al., we can briefly compare evidence from other previous studies of dopamine mutant mice (Cannon, Abdallah, Tecott, During, & Palmiter, 2004; Cannon & Bseikri, 2004; Cannon & Palmiter, 2003; Coelho et al., 2004; Denenberg, Kim, & Palmiter, 2004; Peciña et al., 2003; Sanders, Cagniard, Manning, & Zhuang, 2003; Szczypka et al., 2001; Zhuang et al., 2001). Robinson et al. provide the strongest evidence so far that dopamine is not needed for reward learning, but their conclusion of normal learning seems consistent with results from earlier studies of DD mutant mice (Cannon & Bseikri, 2004; Cannon & Palmiter, 2003; Denenberg et al., 2004). For example, Cannon and Palmiter previously found that DD mice show a preference for sucrose solution over water, even in the absence of L-dopa medication (Cannon & Palmiter, 2003). Unmedicated DD mice drank very rarely and very little, but when they did initiate a drinking bout, the DD mice selected a spout that contained sucrose (see Figure 1). Their choice of sucrose over water suggested that DD mice do register both the greater hedonic impact of sucrose and the basic reward learning needed to locate the correct spout.

Studies of hyperdopaminergic mutant mice, which have excessive extracellular dopamine resulting from either knock-down or knock-out of the dopamine transporter (DAT) gene, also have produced results consistent with the conclusions of Robinson et al., albeit in reverse (Coelho et al., 2004; Peciña et al., 2003; Sanders et al., 2003; Zhuang et al., 2001). For example, Peciña et al. found that DAT knockdown mutant mice (DAT = 10% wild-type levels,

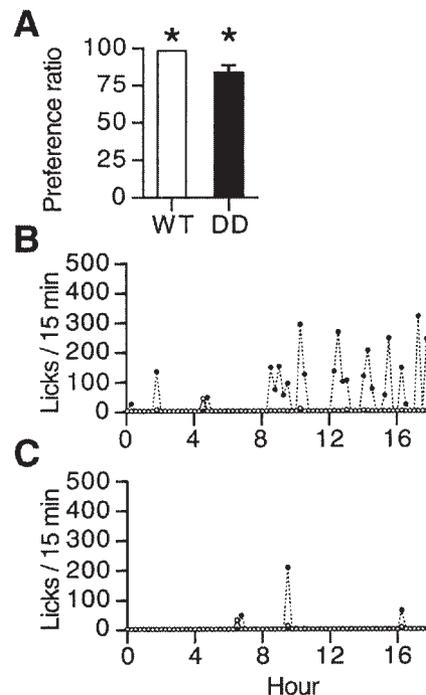


Figure 1. Cannon and Palmiter (2003) showed that unmedicated dopamine-deficient (DD) mice prefer food over water. A: Preference ratio of food to water intake was equally high for wild-type control (WT) and DD mice. However, WT mice drank far more often in absolute terms (B) than DD mice (C). Error bars represent standard error. Reprinted from “Reward Without Dopamine,” by C. M. Cannon and R. D. Palmiter, 2003, *Journal of Neuroscience*, 23, p. 10830, with permission of the Society for Neuroscience. \* $p < .05$

and neostriatal extracellular dopamine = 170% wild-type levels) showed elevated “wanting,” expressed as higher motivation to obtain a sweet reward in a one-choice runway paradigm (Peciña et al., 2003). Hyperdopaminergic mutant mice obtained their reward faster, with fewer pauses en route, and were more resistant to distractions, showing greater focus on obtaining reward than wild-type mice (see Figure 2; Peciña et al., 2003). However, hyperdopaminergic mutants showed normal or suppressed orofacial “liking” reactions to the hedonic impact of sucrose taste in a taste reactivity paradigm, despite their higher motivation for sweet reward (see Figure 3). Thus hyperdopamine mutant mice showed higher “wanting” but definitely not higher “liking” (whether learning was changed was not so clear from that study).

Converging evidence for specifically enhanced “wanting” motivation for reward, and not enhanced learning, in hyperdopaminergic DAT knockdown mutant mice also comes from separate studies by Zhuang and colleagues (Sanders et al., 2003). For example, Sanders et al. found that hyperdopaminergic DAT knockdown mutant mice persisted in lever pressing at higher levels for instrumental reward in a breakpoint paradigm, as the progressive ratio schedule elevated the work demand (breakpoint). The hyperdopaminergic elevated breakpoint is consistent with the hypothesis of higher incentive salience or “wanting” for reward in DAT knockdown mice (Sanders et al., 2003). Yet the learning abilities of DAT knockdown mutant mice so far appear to be

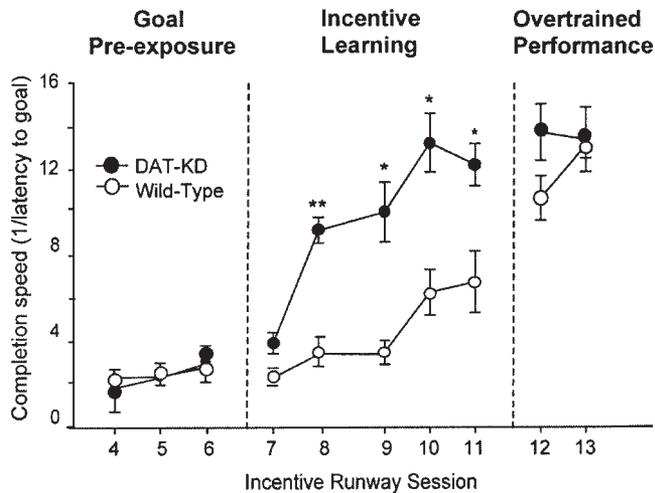


Figure 2. Peciña et al. (2003) showed that hyperdopaminergic mutant mice (dopamine transport knock-down [DAT-KD]) have elevated wanting motivation to obtain sweet reward in a runway task compared with wild-type control mice, reflected in mutants' faster task completion. Those hyperdopaminergic mutants have knockdown of dopamine transporter to 10% wild-type levels, and therefore have higher extracellular striatal dopamine (170% wild-type level). Error bars represent standard error. Reprinted from "Hyperdopaminergic Mutant Mice Have Higher 'Wanting' but Not 'Liking' for Sweet Rewards," by S. Peciña, B. Cagniard, K. C. Berridge, J. W. Aldridge, and X. Zhuang, 2003, *Journal of Neuroscience*, 23, p. 9397, with permission of the Society for Neuroscience. \* $p < .05$ . \*\* $p < .01$ .

normal, and not enhanced (Sanders et al., 2003; X. Zhuang, personal communication, October 2004).

Taken together, these various dopamine mutant studies all point to the same conclusion. Dopamine seems consistently to determine "wanting" for rewards, but not "liking" or learning for the same rewards.

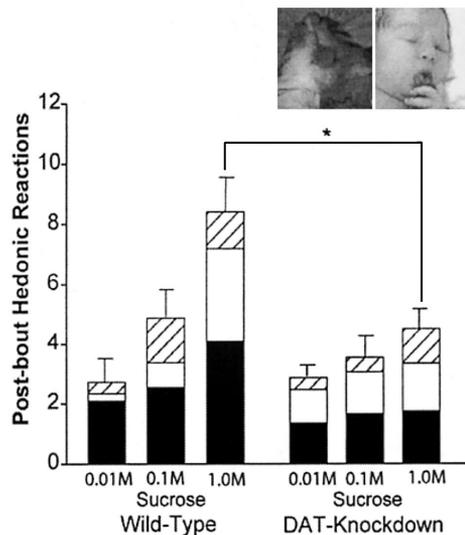
### Caveats

#### *Unintended Consequences of Congenital Mutations?*

Mutant mice are fascinating neuroscience tools, but come with their own special caveats. The most recognized limitation is the possibility that a targeted mutation may have unintended additional effects, including counteradaptations during development that oppose the original congenital mutation effect, or that otherwise rewire neural circuits in a way that regains some relevant functions. For these reasons, neuroscientists eagerly await the introduction of inducible mutants, in which a dopamine abnormality could be induced by experimenters when the mouse is adult.

Still, in the meantime, there are reasonable grounds for confidence that current conclusions from existing dopamine mutants will stand. The existing dopamine mutants behave as they ought to, supporting the hypothesis that their brain dopamine function is changed as intended. DD mice have extensive Parkinsonian symptoms typical of massive dopamine lesions (akinesia, adipsia, aphagia), whereas hyperdopaminergic mutants are hyperactive, their behavior mimicking in some ways the effects of psychostimulants.

### A. Positive Affective Reactions



### B. Aversive Reactions

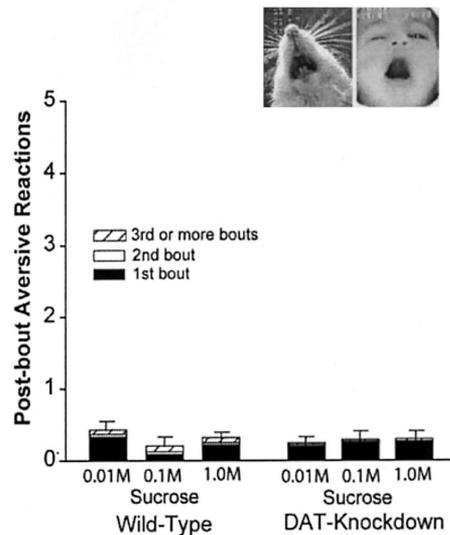


Figure 3. Peciña et al. (2003) also showed that hyperdopaminergic mutant mice (dopamine transport knock-down [DAT-KD]) do not have elevated affective liking reactions to the taste of food. Orofacial liking reactions are homologous to affective facial expressions elicited by sweet tastes from human infants. The number of liking reactions was proportional to food concentration in both DAT-KD and wild-type mice. But despite higher wanting for sweet reward and higher extracellular dopamine (170% compared with wild-type levels), DAT-KD mutant liking reactions were either unchanged or suppressed. Error bars represent standard error. Reprinted from "Hyperdopaminergic Mutant Mice Have Higher 'Wanting' but Not 'Liking' for Sweet Rewards," by S. Peciña, B. Cagniard, K. C. Berridge, J. W. Aldridge, and X. Zhuang, 2003, *Journal of Neuroscience*, 23, p. 9400, with permission of the Society for Neuroscience. \* $p < .05$ .

These features give hope that these mutants may also be giving accurate insights into the true role of dopamine in “wanting,” “liking,” and learning components of reward.

### *Dopamine as Cause Versus Dopamine Neuron Activation*

Another issue is how dopamine mutant findings relate to dopamine neuronal activity patterns. On the basis of studies of dopamine neuron activation, reinforcement learning models have recently received great attention in neuroscience as possible models of dopamine neural function (Dayan & Balleine, 2002; Kelley, 2004; Montague, Hyman, & Cohen, 2004; O’Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Schultz, 2002, 2004; Wise, 2004). Elegant studies, originally pioneered by Schultz and colleagues and later extended by others, showed that the activation of mesolimbic–striatal neurons often conforms to temporal difference and prediction error models of reward learning (Cromwell & Schultz, 2003; Ljungberg, Apicella, & Schultz, 1992; Roitman, Stuber, Phillips, Wightman, & Carelli, 2004; Schultz, 2002, 2004; Seymour et al., 2004; Tobler, Dickinson, & Schultz, 2003).

So the finding of Robinson et al. that DD mice learn to predict rewards perfectly well without dopamine may come as something of a blow to “dopamine = reward learning” theorists. Sometimes it almost seems that the correct answer to “What does dopamine do?” might mostly be “Confuse neuroscientists.”

But we should keep in mind that the question “What does dopamine do?” is asked very differently in mutant mouse studies versus electrophysiology–neurochemical–neuroimaging studies. Their questions are completely different, not just in methods, and not even just in time scale of dopamine activation, but also in substance. Electrophysiological and other dopamine activation studies ask chiefly “What are dopamine neurons doing?” (in terms of activity patterns). Mutant mouse studies ask, instead, “What do dopamine neurons achieve?” (in terms of cause and consequence). One question is about neural activation, and the other is about neural function. Of course, we may have expected the answers to be closely linked. But perhaps that link is more complex than we thought.

For all we know, the activity of dopamine-associated mesolimbic neurons may obey learning rules, even in DD mice when they lack dopamine. However, in terms of functional consequence, dopamine release is not required for normal learning to proceed. Even if dopamine activation occurs during reward learning, perhaps partly as a conditioned motivational response of the brain, dopamine is not a necessary cause for that learning to occur. This is a difference that seems to matter to the brain, and so it should matter to neuroscientists too.

### *Espresso Cup Conclusion*

In short, caffeinated DD mice show normal learning about food reward and probably normal “liking” for reward too—all without dopamine. Their chief deficit appears to be a deficiency of “wanting,” as might be suggested by the hypothesis that dopamine mediates attributions of motivational incentive salience. Thus, the valuable study by Robinson, Sandstrom, Denenberg, and Palmiter in this issue takes us all a decisive step forward in understanding the role of dopamine in reward.

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