

Is dopamine required for natural reward?

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Abstract

Reward is fundamental to the organization of behavior, and the neurotransmitter dopamine (DA) is widely recognized to be critical to the neurobiology of reward, learning and addiction. Virtually all drugs of abuse, including heroin and other opiates, alcohol, cocaine, amphetamine and nicotine activate dopaminergic systems. So called “natural” rewards such as food, positive social interactions and even humor, likewise activate DA neurons and are powerful aids to attention and learning. Sweet solutions are a well-characterized natural reward. When a source of sugar is encountered, animals will consume substantial amounts, return to it preferentially, and will work to obtain access. Dopamine systems are activated in animals drinking sugar solutions, and lesions of dopaminergic neurons or pharmacological blockade of DA receptors seem to reduce the reward value of both sweet tastes and drugs of abuse. However, we have recently demonstrated that genetically modified mice that cannot make DA (DD mice) manifest normal sucrose preference. During preference tests, mutant mice initiated licking less frequently than did normal mice, but the rate of licking by DD mice for sweets was actually higher than that of normal mice, indicating that their motor ability to lick is intact. We conclude that DA is not required for the hedonic response to sweets nor for their discrimination. This brief and slightly humorous review discusses these findings in the context of current and historical answers to the question, “What is the role of DA in reward?”

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1. Introduction

Because humor and enjoyment are powerful aids to attention and learning [1–4], one could hypothesize that scientific progress would be greatly expedited if we were all simply funnier. Case studies suggest that this may be true (Fig. 1A). Scientific application of this insight by those of us who study the role of dopamine (DA) in reward is particularly appropriate, as humor (like most good fun or pleasant stimuli) has been demonstrated to activate the “mesolimbic reward circuit” [5]. Dopamine neurons within this circuit also respond to food [6–10], play [11], positive family and social interactions [12–14], sexual interaction [15–18], winning money [19], drugs [7,20–23], music [24], video games [25], pretty faces [26], and even monogamous pair-bonding (at least among voles) [27]. Given the wealth of data correlating DA and rewarding stimuli, it is easy to understand why the idea that DA is the brain’s “pleasure chemical” has become a pervasive idea in modern neuroscience.

We have recently reported that facets of reward are intact in mice that are congenitally unable to produce DA [28]. However, the dominant paradigm (along with the practice of referring to dopaminergic pathways as the “brain’s reward circuit”) seems to be persisting. In fact, a recent feature film, “Dopamine,” was named after “the natural amphetamine our bodies produce when we’re falling in love” [29]. Doubtless the filmmaker would have changed the title to “ γ -aminobutyric acid” or “agonists at μ ,” if only our paper had been published in time. However, if the romantic notion that brain reward circuits speak only in the language of DA seems old-fashioned to some, it remains likely that DA is important to reward processes in intact individuals. The persistence of reward processes in mutants lacking DA suggests that DA is not entirely necessary for these reward processes and, in addition, may make it possible to refine the hypothesized role of DA in normal animals during reward-related tasks and learning about rewards.

2. What is “reward”?

A reward (*n.*), like a twinkie [1], can be held in your hand. Or, you can reward (*v.*) your dog with a twinkie for

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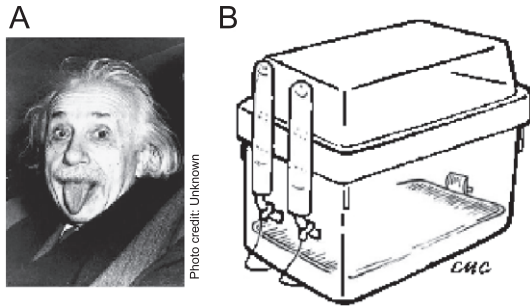


Fig. 1. (A) Physicist and Nobel Laureate Albert Einstein. (B) A “lickometer” cage modified for mice, as described in Ref. [28].

bringing your paper. In addition, the twinkie may be rewarding to (*adv.*) your dog if your dog finds the twinkie rewarding (*adj.*). A “reward” can also refer to something that is never external to the brain (e.g., your dog might find electrical brain stimulation more reinforcing than a twinkie). Rewards can be “natural,” while drugs and electrical brain stimulation are not considered natural rewards (although twinkies, “smarties,” saccharin pellets and fruit loops are). Finally, reward is a concept related to the hedonic, or pleasurable, properties of a stimulus [30], devised by psychologists to represent processes of the brain. It is the processes of reward in the brain that we study (unless, of course, you study fruit loops).

Perhaps the best operational definition of reward is that “rewards are . . . the environmental incentives we tend to return to after having previously contacted them” [31]. This is clearly true, but is not the whole truth. For example, this definition cannot account for the hedonic experience of reward. With notable exceptions [32], the hedonic value of a stimulus is not directly assessed by most tests of reward. Instead, most tests devised to take the measure of reward do so indirectly (via the assumption that changes in present performance reflect degrees of, or variations upon, prior reward processes). As such, they require the animal to perform a superfluity of tasks that are mostly irrelevant to the processes of reward, as well as foreign to the species-specific behaviors of the animal, e.g., when a mouse walks up to a bar and presses it a certain number of times on a given schedule based on intermittent visual or auditory cues in order to receive intravenous drug. These tasks often involve many different brain processes, so that it is helpful to begin by identifying the aspects of the task that are not brain reward processes. In the simple and ethologically relevant example of food reward experienced with a novel food, the ability to sense the food by sight, smell, hearing, taste, touch, pheromones or magnetic fields is not reward, nor is the motor ability to move to or obtain the food. Learning and memory related to the event are brain processes separate from reward. (Many things that are learned and remembered are not rewarding, and learning is not required for something to be rewarding.) Therefore, the ability to remember and recall the food, cues associated

with the food, or whether the food was good is distinct from reward processes. Rather, brain reward processes are those that mediate the hedonic experience of rewards, and those that attribute response-sustaining incentive value to rewards and reward-associated cues.

While the subjective experience of reward can be singular, the neurobiology of reward can probably be parsed into at least two processes. First, the animal eats the food, and finds it good (or hedonic/rewarding/reinforcing). The “goodness” of this experience is a reward process that can be studied in animals within certain temporal and sensory constraints [32]. For example, the “goodness” of the sweet taste of sucrose, placed directly on the tongue, elicits an immediate reaction that can be quantified. Many reinforcing events are not as easy to detect. The noncaloric sweetener saccharin is considered quite good on the tongue, but lacks good postingestive consequences [33]. Likewise, animals can detect the absence of a single essential amino acid (EAA) in their diet, and when another diet is provided containing the missing EAA, the postingestive experience is reinforcing [34]. It would be difficult to attempt to quantify the affective reaction in these cases, because both temporal and subjective specificity are lacking. From these examples, it also should be clear that a rewarding experience does not need to be either conscious or subjective.

An animal capable of learning and memory can associate previously neutral cues (including the sight, smell, taste and spatial location of the food) with the “goodness,” or reward value, of the food. This learning can help the animal to obtain the same reward again. In addition, if the experience with the food was rewarding, some cues seem to be imparted with the ability to elicit approach, making the next trip to the food source more likely. In other words, this second brain reward process sets the “reward value” that can maintain future responding via the addition of incentive value to previously neutral cues. A distinction between reward processes and processes of learning is readily apparent here. While reward and learning are often associated, they are separable: an animal may learn that a previously neutral cue predicts food, but that knowledge is not what imparts the cue with the ability to trigger approach. (Desire is not usually the product of the rational application of knowledge, as any drug addict can attest.) Rather, it is the processes of reward that turn predictors into “reward predictors” that are evidently desirable in of themselves. In summary, reward processes include hedonic processes and the processes whereby a previously neutral cue becomes an incentive.

3. What is the role of DA in reward?

Although the neurotransmitter DA is widely regarded as critical to the neurobiology of reward processes [6,31,35–39], the precise role of DA has been vigorously contested and revised [36,40–46]. The anhedonia hypothesis stated

that DA mediates the hedonic value of rewards. This idea has been highly influential [29,47], and an important impetus to research, though vigorously challenged [36,39,42–44,46]. Other theories for the role of DA in reward include that DA is a teaching signal that highlights prediction errors during reward-related learning [37], that DA imparts salience to environmental incentives [36,48] and that DA is required for the ability to overcome behavioral constraints, such as work-related response costs [46]. A related, but different, question is whether DA is actually required for reward. We attempted to address this question using a genetic approach: the DA-deficient (DD) mouse.

Our genetically modified (or “designer”) mice that lack DA [49] are cataleptic, hypoactive and hypophagic as compared to their generic littermate controls. Although these mice are physically able to move, find and eat food and to return to the same food source again, they do so very infrequently; DD mice will die of starvation in the midst of readily available, palatable foods [49]. To prevent this we can give them daily DA replacement [28,49]. We have already noted that reward processes are often inferred from complex behaviors. For the hypoactive DD mice, the additional processes required by complex tasks may be confounding, or simply not possible. In order to minimize these difficulties, we tested the performance of DD mice with a task they are capable of performing, licking (Fig. 1). Sucrose, a well-established natural reward [50,51], has a specific taste, minimal odor and texture, and does not require grasping or chewing. Because solutions of sucrose elicit hedonic responses in newborn human infants [52] and in 3-day old rat pups [53], it is probable that little if any learning is necessary in adults and juveniles for the taste of sucrose to be rewarding. Finally, the reward processes elicited by sucrose correlate with activation of dopaminergic neurons and release of DA [54,55]. Mice provided with both sucrose and water demonstrated significant preference for sucrose, regardless of whether they were DA deficient [28]. In other words, both DD and control mice licked at the sucrose-containing spout more than they licked at the water-containing spout. However, the pattern of intake by DD mice was markedly different. While DD mice initiated drinking very infrequently, they drank longer and faster than the controls [28]. Preference for the noncaloric sweetener saccharin was also robust, which suggests that calories are not required for preference in the absence of DA (Fig. 2).

4. Do DD mice manifest impairments of hedonic experience, incentive salience or response capacity?

Blockade of DA action by lesion or antagonists has been reported to reduce the reward value of both food and drugs of abuse without limiting motor ability or sensory perception [9,31,56]. In fact, the anhedonia hypothesis was initially offered as an alternative to the idea that DA is merely

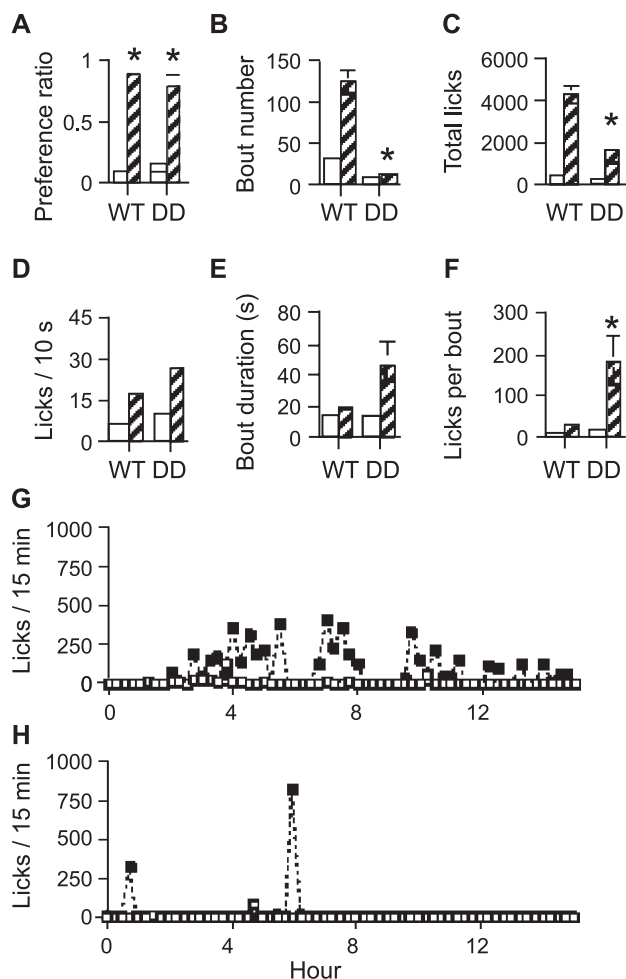


Fig. 2. In the absence of releasable DA, DD mice prefer saccharin to water. WT ($n=7$) and DD ($n=8$) mice were given the choice of saccharin (hatched bars) or water (open bars). (A) Both groups demonstrated significant preference for saccharin ($P<.01$). (B and C) DD mice had fewer bouts and total licks at the saccharin tube as compared to WT mice ($P<.01$). (D–F) Saccharin elicited more licks per bout in DD as compared to WT mice ($P<.01$), but did not elicit a significantly higher lick rate or bout duration in DD mice. Both WT and DD mice had lower lick rate when drinking saccharin than when drinking sucrose ($P<.01$). (G and H) Licking patterns of representative individual control (G) or DD (H) mice given the choice of saccharin (filled squares) and water (open squares).

required for the motor performance of reward-related tasks. Wise and colleagues argued that motor impairments caused by DA receptor blockers (or neuroleptics) could not adequately account for the diminished performance of animals that had experienced food reward in the presence of these drugs [39]. For example, under the influence of these drugs, the latency to begin eating solid food pellets (or running towards a goal box containing food) was not impaired, while the speed and maintenance of performance was diminished, on average. In other words, across a series of trials, the maximal performance achieved by a neuroleptic-treated animal was not reduced. Rather, the incidence of inappropriate or ineffectual responses was much greater in the presence of DA receptor blockade. In one aspect, this is

reminiscent of our observations of the DD mice, because they are surprisingly active during the overnight test, yet rarely initiate intake. But, it is difficult to directly compare observations from a fundamentally different task with our own observations of licking behavior. In fact, licking behavior may not respond to neuroleptic treatment in a manner comparable to extinction or reward dilution [57,58].

Unconditioned licking of sweet solutions has been evaluated under the influence of dopaminergic drugs in rats [6,57–61]. The maximal lick rate of 10% sucrose achieved by rats treated with raclopride, a D2 antagonist, or with SCH23390, a D1 antagonist with activity at 5HT-2 and -1C receptors, was not diminished, in agreement with our observations that mice lacking DA can lick normally. Raclopride increased the interval between bouts of licking, an observation that is consistent with the effects of D2 antagonists on meal patterns in rats [62], and our own observations of DD mice. However, raclopride also produced a modest decrease in cluster size (or the number of licks in a given bout of drinking) [6], perhaps analogous to the diminished persistence of feeding observed in pimozide-treated rats. This particular observation is surprising because D2 antagonists, including raclopride, increase meal size in rats eating pelleted chow [62], and DD mice demonstrate enhanced bout size. In addition, our unpublished observations suggest that a noncataleptic combination of SCH23390 and the selective D2 antagonist sulpiride increase bout size and duration for 16% (0.5 M) sucrose during the first 6 h of an overnight test in normal mice. Many possible explanations could be given for this apparent discrepancy. Receptor antagonists and genetic deletions of the ligand are clearly different. For example, the DA receptor blockade provided by neuroleptic drugs is acute, incomplete, and may favor some DA receptors over others. In addition, many of these drugs also act via nondopaminergic systems, such as serotonin receptors, which may also influence feeding behavior. Neuroleptics like pimozide, given at the same doses that have been reported to reduce reward value (1.0 mg/kg), have been reported to cause a conditioned taste aversion [63], perhaps through their action at DA receptors, or via nondopaminergic actions at 5HT7 receptors and Ca^{2+} channels. Thus, aversive consequences of the drug could explain why hungry rats reduced the rate or persistence of their intake. The rate of bar pressing or licking for sucrose, which increases as a function of sucrose concentration, is changed by pimozide treatment similar to the effect of adulteration of the sucrose with the aversive taste of quinine [59,64]. This does not imply that pimozide shifts palatability for the sucrose [56], but may imply that it is, itself, aversive. On the other hand, procedural differences, such as the length of sucrose exposure, deprivation condition or experience and sucrose or drug concentration may account for this difference.

A compelling case has been made that the hedonic aspects of reward do not require DA, as near-absolute depletion of DA in the nucleus accumbens (NAcc) does

not reduce positive affective reactions [36]. It seems unlikely that the increased bout size and duration of DD mice is due to an altered (in this case increased) hedonic response directly related to the lack of DA. However, the large bout size, long bout duration, and increased lick rate of the chronically underweight DD mice may be caused by their increased motivation to consume the reward as an indirect consequence of DA deficiency. For example, because DD mice maintain chronically low body weight, the sweet taste of sucrose may elicit a greater hedonic or motivational response in the DD mice than in the controls. This could be addressed by the observation of taste reactivity patterns.

However, it was the performance of the DD mice that suggested greater reward value (and performance and hedonic reactivity are not invariably correlated [65,66]). The absolute level of reward-related (and other) behaviors by the DD mice was low compared to controls. Does this necessarily imply that processes of reward in the DD mice are diminished? We do not think so, because the absolute level of performance is more likely to reflect constraints on the ability to perform the task than alterations in reward value. On the other hand, changes in the rate of responding of a comparable magnitude and in an appropriate direction (e.g., increased responding) are likely to reflect changes in reward processes [39]. We suggest that the DD mice adjusted their responding for rewards appropriately, though within the constraints of a lower basal and maximum response capacity.

To give one additional example in support of this idea, we have recently observed that DD mice are able to form a conditioned flavor preference (CFP) to a flavor previously associated with caloric reinforcement (sucrose) over a flavor associated only with sweet taste (saccharin). The ability of DD mice to express the CFP suggests that the sucrose preference we have observed in DD mice is not necessarily the residual of an “innate” taste preference for sweets, but may be based on rewarding caloric consequences. Of greater pertinence to the question at hand, both controls and DD mice will initiate a significantly greater number of larger, longer bouts at the flavor previously associated with caloric reward. Thus, DD mice appear surprisingly capable of responding to rewards in appropriate ways. They will increase their intake when a reward is present, will preferentially consume the reward in ways that suggest high reward value in normal animals (rapid, extended licking), will return preferentially to a previously encountered source of reward, and can even associate previously neutral or less preferred cues with rewarding consequences. Although the absolute level of intake by DD mice is much less than that of controls, the appropriate magnitude and direction of their reward-related performance suggests that their reward-related motivation is at least partially intact. The simplest explanation for these observations is that the deficits manifested by DD mice reflect either reduced motivation or capacity to obtain the reward (or both).

5. You can't always get what you want: response capacity and motivation

One idea about the role of DA in reward processes is that DA circuits attribute incentive salience to stimuli [36]. This hypothesis recognizes two distinct processes of reward, the hedonic experience, referred to as “liking,” and the ability of cues associated with the reward to elicit approach, i.e., the incentive salience, or “wanting” of the reward. Based on empirical observations, it appears that these processes are mediated by separable neurobiological mechanisms, thus “you do not always want what you like, or like what you want” [36]. While this may not seem intuitive based on common subjective experience of reward, in more extreme circumstances, humans do report an awareness of the separable nature of these reward processes. For example, a heroin addict describes [67]: “When you are addicted, there is no euphoria when you shoot up. You only want heroin.” The attribution of incentive salience in this model is hypothesized to depend on DA released at the time of performance.

Our data are consistent with the incentive salience hypothesis insofar as DD mice do not robustly seek out the sucrose. Because incentive salience has been operationally defined as the ability of the stimulus to elicit approach behavior [36], it combines motivation and response capacity. However, the increased motivation of DD mice to consume the sucrose, which we inferred from the experiments described above [28], led us to conclude that the deficit may be primarily one of response capacity.

Sensorimotor impairments have been suggested to account for the reduced reward-related (and other) behaviors after dysregulation or removal of DA, e.g., after 6-OHDA lesions. Normal sensorimotor states involve integration of intention, action and sensory feedback. For example, moving a limb through space in order to reach an object requires some mechanism to ensure that sensory (e.g., proprioceptive and visual) inputs and motor outputs are congruent with the intended goal. However, the sensorimotor ability of DD mice to lick, and to move in general, appears sufficient. In fact, we have observed DD mice during the overnight preference tests, when they can become quite active, to climb the cage walls, traverse the widely spaced metal grid floor with little difficulty, and to run against the corner between two cage walls (a common activity in mice that seems to require considerable sensorimotor ability to keep from falling over or through the floor by misplacing a paw on the wire grid). Our observations of these mice in general, and of their abilities during this particular task, seem to exclude a motor or sensorimotor deficit as the root cause of their reduced total intake.

Although we have not tested this hypothesis directly, it also seems unlikely that they are unwilling to work, in general. To give one example, we have observed that DD mice spend considerable energy and coordinated movement to sniff at a hole in the cage top of a polycarbonate

enclosure, a behavior that normal mice also engage in. This activity requires the mouse to support the weight of its body off the cage floor by holding the upper cage rim with the forepaws, usually while kicking with the lower paws and balancing with the tail, in order to position the nose at the 1-cm-diameter hole. They will engage in this activity for extended periods (many minutes), often interrupted by short breaks during which they circle the cage. They also continue to engage in this behavior when a reward, such as sucrose or liquid diet, is readily available. In fact, we have observed that they engage in these activities more often when they are food deprived. Unless DD mice manifest a motor, sensorimotor or work-related activational deficit specific to certain reward processes, it seems possible that these ideas cannot adequately explain their behavior.

Therefore, we hypothesized that the DD mice are not sufficiently able to direct their behavior towards appropriate goals. This idea is predicated, in part, on other observations we have made of the DD mice. For example, mice lacking DA will initiate a normal number of drinking bouts for sucrose after virally mediated restoration of DA signaling only in the caudate-putamen (CPu) (Ref. [68] and our unpublished observations). This may be surprising because in this model, no DA is available in the NAcc. This would suggest that DA in the CPu alone is adequate for normal levels of reward-related performance. In a more recent work, we have suggested that regulated striatal DA (particularly in the CPu where viral transduction rescues adequate feeding behavior) may mediate the translation of homeostatic integration into appropriate behavior, independent of motor ability [69].

To illustrate the distinction between motor (or sensorimotor) ability and the proposed ability to direct behavior appropriately, it is useful to compare the effects of DA depletion of the CPu to removal of the CPu itself. Depletion of DA from the striatum results in profound hypophagia and hypoactivity, whereas surgical removal of the entire striatum, which also results in profound and irreversible hypophagia, is instead accompanied by intense, unfocused hyperactivity [70,71]. These phenomena are apparent in human disease states; Parkinsonian patients lose striatal DA innervation, which results in catalepsy, whereas death of striatal neurons in Huntington's disease is marked by uncontrolled choreiform movements. Thus, striatal DA is not necessary for motor behavior per se, but is necessary to direct motor behavior towards appropriate goals. We suggested that the hypophagia resulting from unregulated striatal DA (e.g., after AMPH) is not caused primarily by loss of appetite or motor ability, but is instead caused by “an altered brain state in which animals cannot respond selectively” [72] or with appropriate frequency, particularly to integrated homeostatic and motivational drives [69]. This putative neural process, which allows appropriate, selective behavior, falls between the general categories of motivation and motor ability. For lack of a better term, we refer to it as the ability of the animal to “goal-direct.” An inability of

DD mice to direct their behavior in spite of motor ability, hedonic experience and reward and caloric motivation would suggest that DA is necessary in order to goal-direct, and that remaining CNS pathways are unable to compensate for the loss of DA to this process.

Furthermore, we suggest that the relative inability of DD mice to respond with appropriate behavior, or to goal-direct, is not strictly limited to reward-related situations. For example, when the lid of a home cage containing a nesting hut is removed, normal mice will quickly move to the hut, but DD mice rarely do. Like Parkinsonian patients and 6-OHDA lesioned rats, they display “paradoxical kinesia” in response to a stressor, so that during injection or in response to being handled they may demonstrate an abrupt suspension of catalepsy, and elude capture almost as well as littermate controls. This paradoxical kinesia (so called because much of the time Parkinsonian patients, and DD mice, seem incapable of moving) is usually initiated only after the mouse is touched, although they are alert and aware of approach before physical contact. Their relative inability to behave normally in apparently aversive or neutral situations suggests that their deficit may not be restricted to rewarding situations.

Although it is possible that DA is also involved in the hedonic and motivation aspects of reward-related tasks, our own data and that of others suggest that these processes are at least partially intact in the absence of DA. To bow to the demands of parsimony, we considered whether the proposed deficit in goal direction could completely account for their low level of absolute intake. Therefore, we hypothesized that, in DD mice, incentive salience (“wanting”) may be dissociated from the process(es) necessary to act on that motivation. (While “you do not always want what you like, or like what you want,” [36] perhaps, in addition, “you can’t always get what you want” [73].) And, if the proposed ability to goal-direct is not specific to processes of reward, the present data may be used to further refine the definition of reward processes, and to refute the necessity of DA to the neurobiology of reward.

However, it is also possible that DD mice are highly capable of performance in other reward-related tasks, and that the primary deficit is in their motivation to do so (although we suggest that some reward-related motivation is demonstrated by DD mice). Even if this is not the case, can the proposed deficit of DD mice to goal-direct, as presently defined, adequately account for all observations in animals treated with neuroleptics? To give a single example, it is well known that extinction of food-reward-related behavior will occur after many successive unrewarded trials, and that a single rewarded (or “priming”) trial can reinstate high levels of subsequent performance. If a neuroleptic drug is given at the time of the rewarded trial, this reinstatement can be blocked, even when the subsequent trial to assess performance is conducted on the following day, long after the effects of the drug have abated [74]. It could be argued that response reinstatement is not mediated

by the same mechanisms that initially attributed a motivational valence to the rewarded task, or that the neuroleptic drug had aversive consequences that counteracted any perceived reward value. But it also seems valid to suggest that DA signaling, which was attenuated by the neuroleptic, is important for the reward processes that would have attributed greater incentive value to task-related cues for the subsequent trial. If DA is required only for the ability of the animal to direct its behavior towards the goal, how could interference with this process via reduced DA signaling reduce the response-reinstating properties of the reward? Perhaps Ralph Waldo Emerson was literally correct that “the reward of a thing well done is having done it.” Or, the ability to alter present performance based on the aversive or rewarding consequences of prior events may reflect, in part, the degree to which prior performance was directed to appropriate goals.

Finally, perhaps the behavior of DD mice reflects multiple deficits in these and other processes. Our colleagues Mark Szczytko and Michelle Brot have observed that viral restoration of DA signaling to the NAcc, without transduction of the CPU, also partially restored volume intake in the sucrose preference task [68]. Could this reflect greater attribution of incentive salience, or willingness to overcome work-related response costs, than we observed in the DD mice? Further studies may be better able to address these possibilities. While the deficiencies of lesioned and mutant individuals reflect an inability to compensate for what has been removed, in the absence of deficit, the converse cannot be assumed: that which is not necessary nevertheless may play a role in the normal individual. It seems probable that DA, if not required for certain reward processes, may be important to reward processes in intact individuals. The practice of referring to dopaminergic pathways as a part of a “brain reward circuit” therefore seems to be in no immediate danger.

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