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Role of brain dopamine in food reward and reinforcement

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The ability of food to establish and maintain response habits and conditioned preferences depends largely on the function of brain dopamine systems. While dopaminergic transmission in the nucleus accumbens appears sufficient for some forms of reward, the role of dopamine in food reward does not appear to be restricted to this region. Dopamine plays an important role in both the ability to energize feeding and to reinforce food-seeking behaviour; the role in energizing feeding is secondary to the prerequisite role in reinforcement. Dopaminergic activation is triggered by the auditory and visual as well as the tactile, olfactory, and gustatory stimuli of foods. While dopamine plays a central role in the feeding and food-seeking of normal animals, some food rewarded learning can be seen in genetically engineered dopamine-deficient mice.

Keywords: food; reward; reinforcement; dopamine

1. INTRODUCTION

While the cognitive and behavioural disturbance we call 'hunger' is innate, the appetites for specific foods are learned. Undifferiented hunger is controlled largely by fluctuations of peripheral and hypothalamic peptides (Saper *et al.* 2002; Horvath & Diano 2004) and thirst is controlled by fluctuation in vagal input (Kraly *et al.* 1975) triggered by hypovolemia (Fitzsimons 1961) and by dehydration of cells in the lateral preoptic area of the hypothalamus (Blass & Epstein 1971; Peck & Novin 1971), However, neither hunger nor thirst results in unconditioned goal-directed behaviour (Changizi *et al.* 2002). Chance encounters with the sweet (Pfaffmann 1960) or salty (Denton 1982) taste of preferred foods or with the oral cooling by ingested fluids (Mendelson & Chillag 1970; Freed & Mendelson 1974) are required before goal-directed behaviour results from the interaction of internal need states with the salience of environmental cues (Bindra 1972). The infant recognizes (Steiner *et al.* 2001) and can learn to seek out (Johanson & Hall 1979) sweet tastants, but the appetite for a specific food is controlled by the interaction of the hunger-associated peptide levels with the brain circuitry that codes the animal's reinforcement history with that food. Until it has received reinforcing feedback from various foods, the infant indiscriminately mouths both food and non-food objects. The monkey's appetite for a yellow banana depends on the prior learning of the association of the sight of the yellow banana skin with the sweet taste of the white banana meat (Wise 2004*b*) and with the post-ingestive consequences of the ingested fruit (Le Magnen 1959). Similarly, the vitamin-deficient rat does not innately know what foods contain the deficient vitamin. Rather, the vitamin-deficient rat progressively loses its food neophobia until, by sampling new foods randomly, it chances on and ingests a food with the missing vitamin (Rodgers & Rozin 1966; Rozin & Rodgers 1967; Rozin 1969). The specific preference for a particular substance is only established when the post-ingestional consequences of the repleting food stamp in or 'reinforce' the tendency to approach that food (Rozin & Kalat 1971). Similarly, food- or water-seeking behaviours develop only after the animal has had the paired experience of hunger with eating or thirst with drinking, respectively (Changizi *et al.* 2002).

Our understanding of the brain circuitry through which various rewards control behaviour began with the findings that rats would learn to work for the direct electrical stimulation of the brain (Olds & Milner 1954) or for the pharmacological stimulation of the brain by psychomotor stimulant drugs (Pickens & Harris 1968). The finding that the rewarding effects of brain stimulation (Liebman & Butcher 1974; Fouriezos & Wise 1976) and of psychomotor stimulants (Yokel & Wise 1975; de Wit & Wise 1977) was blocked or attenuated by dopamine antagonists first implicated brain dopamine in reward function. Similar attenuation of food reward by dopamine antagonists (Wise *et al.* 1978*a*,*b*) first implicated brain dopamine in the control of behaviour by natural rewards.

2. IMPORTANCE OF DOPAMINE FOR NON-FOOD REINFORCEMENT

Dopamine antagonists impair learning (Wise & Schwartz 1981) and, by extinguishing them, previously learned (Wise *et al.* 1978*a*,*b*) instrumental responding for food. Several lines of study confirm that they do so by blunting reward function itself (Wise 1982, 2004*a*; Beninger 1983; Smith 1995) rather than, as has been suggested (Mason *et al.* 1980; Koob 1982; Tombaugh *et al.* 1982; Salamone 1986), by simply impairing performance capacity.

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One contribution of 16 to a Theme Issue 'Appetite'.

The earliest evidence that dopamine plays an important role in motivational function was that brain stimulation and psychomotor stimulants were simply ineffective as reinforcers in animals treated with response-sparing doses of dopamine antagonists. Intravenous amphetamine and cocaine failed to maintain responding when tested under the influence of dopamine antagonists, despite evidence of adequate response capacity. Indeed, in this case animals respond at higher than normal rates before ceasing to respond following pretreatment with dopamine antagonists (Yokel & Wise 1975, 1976; de Wit & Wise 1977; Ettenberg *et al.* 1982).

In the case of brain stimulation reward, responding is generally lower when animals are treated with dopamine antagonists; however, several conditions reveal that the low response rates are due to ineffectiveness of the reinforcer and not incapacitation of the animal. First, responding decreases progressively, both within sessions and across sessions, in animals pretreated with dopamine antagonists (Fouriezos & Wise 1976; Fouriezos *et al.* 1978; Franklin 1978; Franklin & McCoy 1979). When animals pretreated with moderate doses of dopamine antagonists are required to traverse an alleyway for access to the response lever that delivers the stimulation, performance is initially normal and deteriorates after several trials. Moreover, lever-pressing in the goal box deteriorates before running speed or latency to leave the start box; thus brain stimulation loses its ability to maintain responding in the goal box before the animals stop running to obtain it (Fouriezos *et al.* 1978). Second, after animals have stopped responding for brain stimulation reward under conditions of dopamine blockade, a reward-predicting environmental stimulus can, temporarily, reinstate normal performance; thus it appears that the decrement in responding results from the progressive loss of the expectancy of reward rather than from the immediate loss of response capacity (Fouriezos & Wise 1976; Franklin & McCoy 1979; Gallistel *et al.* 1982). Finally, when animals are tested in a 'rate–frequency' paradigm (an analogue of a dose–response paradigm), it is the stimulation frequency required to motivate the animal, rather than the maximum response rate that can be obtained from the animal, that is altered by dopamine blockade; animals can respond normally, but they require a higher stimulation 'payoff' if they are to keep doing so (Franklin 1978; Gallistel & Karras 1984). Finally, if dopamine-blocked rats are trained to earn rewarding brain stimulation in two ways (traverse a runway or press a lever) and are then tested in the two tasks sequentially, the animals initiate responding normally in the second task despite having ceased to respond normally in the first task; thus response capacity in the second task is unimpaired despite cessation of responding in the first task (Gallistel *et al.* 1982). Thus, while performance may be partially impaired by treatment with dopamine antagonists, data from several paradigms confirm that these drugs attenuate the ability of the stimulation to sustain normal performance before they interfere with the animal's capacity to generate such performance.

3. IMPORTANCE OF DOPAMINE FOR FOOD REINFORCEMENT

The concept of reinforcement is, at its core, a concept of how stimulus (Pavlov 1928) and response (Thorndike 1933) associations are formed and how they serve as the basis of habit acquisition (Skinner 1938). Food does not serve as a normal reinforcer in animals pretreated with dopamine antagonists; such treatment causes, for example, a dose-dependent decrease in how quickly animals learn to lever-press for food (Wise & Schwartz 1981). Under pretreatment with low doses of the dopamine antagonist animals eventually reach the normal performance asymptote; however, they require more trials to do so. With higher pretreatment doses learning is slower and may not reach the same performance asymptote. With yet higher doses there is no evidence of learning.

While the concept of reinforcement is most frequently used to explain response learning (Thorndike 1933; Skinner 1935; Hull 1937), it was first used in relation to stimulus learning (Pavlov 1928). Stimulus learning is now known to contribute significantly to response learning (Rescorla & Solomon 1967; Bindra 1972) and dopamine is thought to play a role in both (Wise 1989). Most studies of the reinforcing efficacy of food reward deal with the ability of the reward to maintain rather than to establish instrumental behaviour; without reinforcement both stimulus associations (Pavlov 1928) and response associations (Skinner 1933) extinguish.

When well-trained animals are tested under the influence of dopamine antagonists, food loses the ability to maintain normal responding. Whereas normal responding is initiated, responding slows progressively both within sessions and across sessions (Wise *et al.* 1978*b*; Dickinson *et al.* 2000). Similar progressive loss, both within and across trials, can be seen in the ability of food to maintain free feeding (Wise & Raptis 1986). The response slowing resembles what is seen in extinction conditions (when the normal reward is withheld), and is generally interpreted as a reflection of the impoverishment or 'devaluation' of food reward in the dopamine-impaired animal (Wise *et al.* 1978*a*,*b*; Xenakis & Sclafani 1981, 1982; Geary & Smith 1985). (See Salamone *et al.* (2005) for a dissenting opinion and Wise (2004*a*) for rebuttal.)

Few alternative hypotheses have been offered to explain the progressive response deficits seen when animals are tested under conditions of dopamine blockade. There is the suggestion that the progressive deficit might reflect a susceptibility to fatigue (or some other progressive within-trial performance impairment) caused by dopamine antagonists. This hypothesis can be ruled out from a variety of findings. First, the deficits are not only progressive within-trials; responding decreases progressively across repeated tests that are spaced days apart, with normal levels of responding between the days when the dopamine antagonist is given (Fouriezos *et al.* 1978; Wise *et al.* 1978*b*; Wise & Raptis 1986). Second, animals trained under intermittent dopamine blockade, like animals under intermittent reinforcement, respond more, not less, when tested for habit strength during extinction trials (Ettenberg & Camp 1986). There is no suggestion

of any fatigue-like effect in this paradigm. Finally, when animals are trained in single daily trials to traverse a runway for food, dopamine blockade does not interfere with latency or running speed on the trial when the dopamine antagonist is given; rather, performance is impaired only on the *following* day, when the animals are free of the antagonist (McFarland & Ettenberg 1998). Fatigue due to dopamine blockade can explain neither the normal performance on the treatment day nor the slow performance on the day after treatment; here performance is impaired by the animal's memory of the previous day's experience and not by the pharmacological treatment itself.

Another suggested alternative for the progressive within-trial slowing of feeding and responding for food was that the slowing reflected the effects of enhanced satiety rather than the effects of blunted reward. This suggestion has been falsified in three ways. First, the same within-session progressive deficits are seen when dopamine-blocked animals are offered non-nutritive saccharin as when they are offered nutritive food reward; no such deficits are seen in control animals that do not receive the dopamine antagonist (Wise *et al.* 1978*a*). Second, within-session progressive deficits are seen when ingested sucrose is not absorbed but is, rather, drained through an open gastric fistula (Geary & Smith 1985). Third, the satiety hypothesis (like the fatigue hypothesis) cannot explain the fact that performance decreases across successive tests as a function of how much experience the animal has previously had with food in the dopamine-blocked condition (Wise *et al.* 1978*b*; Wise & Raptis 1986) and not as a function of experience with dopamine blockade in the absence of food (Wise *et al.* 1978*b*). Thus, it appears to be the memory of the food experience in the dopamine-blocked condition, not the experience of dopamine blockade itself, that determines the decline in responding between trials in the dopamine-blocked animal.

When animals are tested with a number of sucrose concentrations, dopamine-blocked animals respond to a given concentration as if it were weaker than normal (Xenakis & Sclafani 1981; Geary & Smith 1985; Bailey *et al.* 1986; Schneider *et al.* 1986, 1990). Thus, normal sucrose lick rates are shown in dopamine-blocked animals if the concentration of the sucrose solution is increased to 10% from the normal 5%. The devaluation of sucrose reward—the treatment of high concentrations as if they were lower—is seen either in animals pretreated with either D1- or D2-type dopamine receptor blockade (Schneider *et al.* 1986). Thus, like many dopamine-mediated behaviours (Clark & White 1987), performance for sweet reward appears to require co-activation of D1- and D2-type receptors.

The hypothesis that dopamine transmission is important for food reward implies that food reward elevates dopamine levels, as do, for example, some drug rewards (Hurd *et al.* 1989; Pettit & Justice 1989; Wise *et al.* 1995*a*,*b*; Ranaldi *et al.* 1999). Indeed, food reward (Hernandez & Hoebel 1988) and food reward-associated stimuli (Bassareo & Di Chiara 1999) do elevate dopamine levels in the nucleus accumbens. Indeed, just as μ and δ opiate agonists are rewarding in proportion to their ability to elevate dopamine levels (Devine *et al.* 1993; Devine & Wise 1994), so are different sucrose concentrations rewarding in proportion to their ability to elevate dopamine levels in the nucleus accumbens (Hajnal *et al.* 2004).

4. RECENT ISSUES

An important role for dopamine in reward function has been well established for many years, but several fine points continue to be discussed in the literature. Is dopamine absolutely necessary for reward? Is dopamine more important for the expectancy of reward before it is delivered or for the impact of reward after it is delivered? Is the dopamine in nucleus accumbens more important for reward than the dopamine in other brain regions? Some of these recent issues are best resolved by consideration of the early literature.

First, studies involving pharmacological blockade of dopamine receptors have suggested a necessary role for dopamine in the reward function (Wise & Rompré 1989; Wise 2004*a*). Recent studies with genetically engineered mice challenge this strong position. First, deletion of the tyrosine hydroxylase (*TH*) gene with rescue of noradrenergic function results in mice that are born superficially normal and eat and gain weight for 10–15 days, at which time their eyes normally open and they begin nibbling and foraging for solid food. Unless treated with L-DOPA, they then lose weight, usually dying by 4 weeks of age (Zhou & Palmiter 1995). If treated with L-DOPA, however, they are alert and active for about 8 h after their daily treatment, eating enough during this period to maintain themselves (Szczypka *et al.* 1999). Restoration of *TH* expression in the caudate nucleus but not in the nucleus accumbens is sufficient to restore normal feeding in the *TH* knockout animals (Szczypka *et al.* 2001).

If these dopamine-deficient mice are maintained by daily L-DOPA treatment but tested when showing Parkinsonian akinesia, 18 or 28 h after the previous L-DOPA maintenance injection, they show normal sucrose and saccharin preferences over water, and drink more of these solutions than water in single bottle tests even after any trace levels of residual dopamine are purged by treatment with the dopamine-releaser amphetamine (Cannon & Palmiter 2003). Such animals show between-session (but not within-session) learning in a water escape task (Denenberg *et al.* 2004). If aroused with caffeine, such animals can learn a side-preference (but not reverse it) for food reward in a T-maze (Robinson *et al.* 2005). These findings establish that, whatever its importance in normal animals, normal dopamine function is not an absolutely necessary condition for rudimentary instrumental learning.

Another recent issue is whether dopamine is important for the motivation to seek anticipated food or rather for the reinforcing effects of food once it has been earned and received (Berridge & Robinson 1998; Salamone & Correa 2002). Food rewards have both kinds of effect (Wise 1989, 2004*b*). The primary effect would appear to be the ability to reinforce learning, as evidenced by: (i) the fact that animals do not learn food-seeking responses when their dopamine systems

are blocked (Wise & Schwartz 1981); (ii) the fact that the effects of finding a piece of food when the dopamine system is blocked are more evident on the day after the dopamine blockade than on the day of the dopamine blockade (McFarland & Ettenberg 1998); and (iii) the fact that food-seeking habits extinguish when animals are tested under dopamine blockade (Wise *et al.* 1978*a*,*b*).

However, secondary to its role in the reinforcement history of the animal, dopamine clearly does have a role in the motivation of reward-seeking behaviours. While food-seeking is thought to be initiated by hunger, it is food-predictive or 'incentive–motivational' environmental cues in the environment that release and guide the behaviour. The incentive–motivational salience of these stimuli depends upon the prior dopamine-dependent reinforcement of their association with the reward. Again, the McFarland & Ettenberg (1998) study clearly illustrates the point. Their trained animals left the start box promptly and ran the runway quickly except on the day *after* they obtained food in the goal box while under the influence of the dopamine antagonist haloperidol. Thus incentive–motivation—the process by which reward-predictive cues activate and motivate an animal—depends on a dopamine-dependent history of association (reinforcement) between the cues and the reward they predict.

In addition, a 'priming' presentation of a reward sample (rather than of a conditioned predictor) can arouse an animal and motivate it to seek more of the priming stimulus. Salted peanuts and potato chips are good examples of rewards that are particularly good at priming further reward-seeking. A taste of such rewards is particularly effective at renewing reward-seeking behaviours after they have been given-up because they are no longer rewarded (Skinner 1938). Administering dopamine agonists is among the most effective ways to reinstate extinguished reward-seeking (de Wit & Stewart 1981, 1983; Wise *et al.* 1990).

Questions about the role of dopamine in reward function have also arisen from evidence that dopamine seems unimportant for the facial responses to oral presentation of sweet tastants (Berridge *et al.* 1989; Pecina *et al.* 1997). If one was to assume correspondence between the facial expression of 'liking' food and the ability of that food to serve as a reinforcer, this finding would pose a challenge to the view that dopamine is important for the ability of food to stamp in stimulus and response associations. The assumption of correspondence between the facial expression of liking and the hedonic response to reinforcement is, however, open to serious question.

Initial studies of the orofacial responses of humans to various tastants identified unique reactions to sweet, sour, and bitter stimuli (Steiner 1973). In rodents, the reactions to sweet and bitter stimuli are clearly distinguishable and have been classified as 'ingestive' and 'aversive' fixed action patterns (a misnomer, as it is the stimulus, not the action pattern, that is aversive) (Berridge & Grill 1984). The rodent orofacial responses to sweet and bitter tastants are, essentially, the licking of lips associated with the acceptance of a fluid and the gagging and chin-rubbing associated with fluid rejection, respectively. Following Schneirla's (1959) argument that approach and withdrawal responses are the only objective terms applicable to all motivated behaviour in all animals, Berridge & Robinson (2003) have suggested that these oral fixed action patterns reflect the hedonic assessments—liking or disliking—of various tastants. What is not clear, however, is how well the fixed action patterns of ingestion and rejection, expressed in decorticate rats (Grill & Norgren 1978; Hall & Bryan 1981) and anencephalic children (Steiner 1973), correlate with the higher-level subjective hedonic responses to and objective reinforcement induced by various foods.

The recent arguments of Berridge & Robinson (1998) that dopamine is important for the wanting of rewards but not the liking of rewards is based on several assumptions about the relation of the taste reactivity test to generalized emotional states. First, there is the assumption that the brainstem reactions to taste stimuli determine the hedonic response to those stimuli (Berridge 2000). This assumption begs the question of how humans learn to like bitter tastants like coffee and broccoli. Second, there is the assertion that the liking of a tastant need not be conscious (Berridge & Robinson 1998; Berridge & Winkielman 2003); in this view, whether the subject likes or dislikes a tastant is more directly evident to an outside observer than to the subject itself. This may well be true, but the possibility raises the question of why subjective lay terms like 'wanting' and 'liking' should be substituted for the more traditional motivational labels 'drive,' 'incentive–motivation' and 'reinforcement.' Third, there is the implicit assumption that all rewards are pleasant; this assumption is falsified by the fact that animals can be trained to work for aversive footshock (Kelleher & Morse 1968) and that initial injections of heroin, while extremely habit-forming, are often reported to be aversive (Haertzen 1966). Finally, there is the assumption that the mechanism of wanting and liking of tastants can be generalized to other rewards such as sexual interactions and addictive drugs (Robinson & Berridge 2003).

In order to see the relevance of subjective wanting and liking for the behavioural control by the motivating and reinforcing effects of food reward, it is important to distinguish between the wanting and liking of an abstract concept such as 'sweets' and the wanting and liking of a specific food morsel that is currently available to the peripheral senses. While Berridge & Robinson (2003) hold that you can both want and like a given tastant (like chocolate fudge) at the same time, you cannot experience at the same time the wanting and liking of *a given specific morsel of food*. If you do not yet have the morsel you can want it without knowing for certain that you will like it; if you have it in your mouth you can like it but it is no longer available to want. Inasmuch as it is a real morsel and not an imagined category that controls behaviour at a given time, we can, for behavioural analysis, identify wanting with the state of mind of an animal prior to earning a given food morsel and identify liking as the state of mind once the reward has been earned and is being sensed. From this perspective, the animals in the McFarland & Ettenberg (1998) study discussed above want the food pellet

before they have tasted it on the haloperidol treatment day. If there is a deficit in the wanting of food in these animals, it is a deficit in wanting the *next* pellet, the one offered on the day *after* the pellet eaten during haloperidol treatment. In as much as the animals ran normally on the haloperidol treatment day and failed to do so on the day following the haloperidol treatment, it seems an inescapable conclusion that they wanted the food despite dopaminergic dysfunction. This separation of food-seeking into discrete trials allows us to see that haloperidol treatment disrupts food-seeking only after the animal has had the opportunity to taste the food under the influence of the dopamine blocker. As discussed above, it would appear that the importance of dopamine for the wanting of food on a given day exposure results from the role dopamine played in the prior liking of food on earlier exposures (whether it be days, trials, morsels, or bites). It is the prior liking of (or reinforcement by) a foodstuff—a dopamine-dependent function—that establishes a subsequent craving for that foodstuff (Rozin & Kalat 1971).

Another challenge of the view that dopamine plays an important role in food reinforcement stems from the unwarranted assumption that all the reward-relevant dopamine functions occur in nucleus accumbens (Salamone *et al.* 2001). While a good deal of work implicates nucleus accumbens in the rewarding effects of psychomotor stimulants (Roberts *et al.* 1977; Ikemoto *et al.* 1997; Roberts *et al.* 1980), and while it is nucleus accumbens dopamine fluctuations, for the most part, that have been correlated with drug reward and food reward (Di Chiara & Imperato 1988; Hernandez & Hoebel 1988; Hurd *et al.* 1989; Pettit & Justice 1989; Wise *et al.* 1995*a*,*b*; Ranaldi *et al.* 1999; Bassareo & Di Chiara 1999), and while protein synthesis in nucleus accumbens impairs instrumental learning for food reward (Baldwin *et al.* 2002), it nonetheless remains the case that lesions of the dopamine projection to nucleus accumbens do not cause feeding deficits (Ungerstedt 1971; Ervin *et al.* 1977), while lesions of the dopamine projections to the dorsal striatum do (Ungerstedt 1971). Moreover, it is genetic restoration of dopamine function in the dorsal striatum, not in nucleus accumbens, that rescues feeding in dopamine-deficient knockout mice (Szczypka *et al.* 2001). While lesions of nucleus accumbens disrupt cocaine self-administration more than they disrupt heroin self-administration (Pettit *et al.* 1984), ventral tegmental lesions that damage nigrostriatal as well as mesolimbic fibres disrupt both behaviours (Bozarth & Wise 1986). While nucleus accumbens injections of opiates (Olds 1982; Goeders *et al.* 1984) or psychomotor stimulants (Hoebel *et al.* 1983; Carlezon *et al.* 1995; Carlezon & Wise 1996; Ikemoto *et al.* 1997) are rewarding, injections of cocaine into the medial prefrontal cortex (Goeders & Smith 1983, 1986) or olfactory tubercle (Ikemoto 2003), or injections of opiates into the ventral tegmental area (Bozarth & Wise 1981; Devine & Wise 1994; Zangen *et al.* 2002), are also rewarding. Thus, nucleus accumbens is not the exclusive seat of dopamine-dependent reward function, and nucleus accumbens lesions should not be expected to disrupt all rewards.

Another recent issue is whether activation of dopamine neurons represents reward, prediction of reward, or an error signal reflecting the difference between earned and expected reward. The issue arises from electrophysiological studies of Schultz and collaborators, suggesting that dopaminergic neurons respond to rewards as long as they are not fully predictable, but transfer to conditioned stimuli predicting reward once the predictive significance has been learned (Schultz 1986; Romo & Schultz 1990; Ljungberg *et al.* 1991, 1992; Schultz *et al.* 1993). It is naive, of course, to expect that dopamine would play a specialized role in only one of these functions.

Moreover, Schultz's (Schultz 2002) distinction between 'reward-predicting' and 'rewarding' stimuli in these studies merits closer analysis. First, the rewarding event is not consistently defined in the various studies of Schultz's monkeys. In these studies, the reward was sometimes identified with presentation of the rewarding object rather than with the oral contact with the reward or with the post-ingestional consequences of that reward that truly constitute the rewarding event. In some studies, the primary rewarding stimulus was a piece of apple presented in a cup at arm's reach; in others it was a drop of fruit juice presented in a spout near the animal's mouth. In the case of the juice, the rewarding event was assumed to be the delivery of the juice rather than the taste of the juice; presumably, in this case, latencies were short enough that the presentation of the reward and the tasting of the reward were almost concurrent. In the case of pieces of apple, however, dopamine responses were noted when the monkey touched the food and again when the monkey tasted the food. Here, the tactile rather than the taste contact was taken as the rewarding event. Whether receipt of reward was defined by the touch of the apple pieces or the delivery of the juice, dopamine neurons responded to what was designated as the rewarding event in early stages of training but to what was designated as the reward-predicting event (sound and sight of latch opening in the case of the apple reward and sight of illumination of a light cue in the case of the juice reward) and *not*, after a great deal of training (thousands of training trials) to the 'reward' itself.

Clarification of the influence of training in these studies comes from subsequent studies in which the effectiveness of the reward-predictive cues was varied. When visual or auditory cues, or both, predicted reward with 100% certainty, the responses of dopamine neurons shifted from the reward itself (as defined above) to the reward-predictive environmental stimuli (Schultz 1986; Romo & Schultz 1990; Ljungberg *et al.* 1991, 1992; Schultz *et al.* 1993; Fiorillo *et al.* 2003). In the case where presentation of the reward was predicted by both auditory and visual stimuli, the responses of dopamine neurons to the reward-predictor (latch-opening) was weakened when the visual stimulus (sight of the door) was occluded (Schultz 1986). When a visual stimulus predicted reward with 75, 50, or 25% probability, responsiveness to the visual stimulus decreased and responsiveness to the tactile or taste stimulus increased accordingly (Fiorillo *et al.* 2003). This finding suggests the need for a closer examination

of the distinction between reward and reward-prediction (Wise 2004*b*). While food might be considered a 'primary' reward (Schultz 1986), food is identified by each of the five senses and it is only in the taste of sweet foods (and perhaps the taste of salt in the case of sodium deficiency; Quartermain *et al.* 1967) that a strong argument can be made that the sensory experience of food is innately rewarding (Steiner 1974; Hall & Bryan 1981) in the absence of learned association with its post-ingestive consequences (Le Magnen 1959; Rozin & Kalat 1971; Messier & White 1984; Sclafani 2004). To the degree that it is the post-ingestional effects of a food that is reinforcing, however, as is the case with the rewarding effects of minerals or vitamins for deficient animals, the sensory experience of a given foodstuff becomes a reinforcer in its own right: a *conditioned* reinforcer (Robbins 1978). Certainly, the touch of a piece of apple is a learned reinforcer for Schultz's very well trained monkeys (Schultz 1986), as, it would appear, are the click or sight of the opening door behind which food is to be found (Schultz 1986). Even the sweet taste of saccharin appears to be a learned reward (Messier & White 1984). Thus, Schultz's distinction between reward-predictors and primary reward is fuzzy distinction; the visual or auditory awareness of the availability of food, if it is a 100% predictor, is certainly as primary as the tactile awareness of that availability, and it is arguably as primary as the olfactory or gustatory awareness of foods that satisfy a mineral deficiency. The fact that dopamine neurons no longer fire in response to the taste of apple when that taste has been predicted by the feel of the apple or the click that predicts the feel is completely consistent with the fact that food-predicting stimuli can become conditioned reinforcers in their own right so long as dopamine function is not impaired during the association of the conditioned stimulus with the food (Beninger & Phillips 1980; Taylor & Robbins 1986).

This does not negate the fact that the phasic activation of dopamine neurons occurs in proportion to the discrepancy between the expected reward and the observed reward, or that such information participates in the learning associated with reinforcement. It should be noted, however, that the short-latency activation of dopamine neurons by visual stimuli occurs before the eye moves to fixate a peripheral visual stimulus. Thus dopamine neurons are likely to be only reporters of the discrimination made by the inferior colliculus between reward-predictive or otherwise salient stimuli and various stimulus events that bear no relation to rewarding events (Dommett *et al.* 2005).

5. CONCLUSIONS AND PERSPECTIVES

Brain dopamine plays several roles in the ability of food to serve as a reward. It is important—but apparently not completely necessary—for the reinforcement function of rewards, their ability to stamp in stimulus and response associations. Current evidence suggests that dopamine in the caudate nucleus may play a more important role than dopamine in the nucleus accumbens in the reinforcement of response habits (White & McDonald 2002; Wise 2004*a*). Past dopamine-dependent reinforcement of stimulus–reward associations is, in turn, important for the incentive–motivational energizing effect of reward-predictive cues in the environment. And, of course, some degree of basal dopamine is important for rudimentary behaviour of any kind (Hornykiewicz 1979; Stricker & Zigmond 1985). This does not mean that dopamine plays a specialized or exclusive role in reward function. Other neurotransmitter systems are certainly involved and it is not clear what subsets of dopamine neurons contribute to reward function. Reward function—and food reward in particular—is only one of the many functions in which dopamine plays an important contributing role.

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