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REVIEW

Calculating utility: preclinical evidence for cost–benefit analysis by mesolimbic dopamine

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Abstract
Rationale Throughout our lives we constantly assess the costs and benefits of the possible future outcomes of our actions and use this information to guide behavior. There is accumulating evidence that dopamine contributes to a fundamental component of this computation—how rewards are compared with the costs incurred when obtaining them.
Objective We review the evidence for dopamine's role in cost–benefit decision making and outline a simple mathematical framework in which to represent the interactions between rewards, costs, behavioral state and dopamine.
Conclusions Dopamine's effects on cost–benefit decision making can be modeled using simple utility–function curves. This approach provides a useful framework for modeling existing data and generating experimental hypotheses that can be objectively and quantitatively tested by observing choice behavior without the necessity to account for subjective psychological states such as pleasure or desire. We suggest that dopamine plays a key role in overcoming response costs and enabling high-effort behaviors. A particularly important anatomical site of this action is the core of the nucleus accumbens. Here, dopamine is able to modulate activity originating from the frontal cortical systems that also assess costs and rewards. Internal deprivation states (e.g., hunger and thirst) also help to energize goal-seeking behaviors, probably in part by their rich influence on dopamine, which can in turn modify decision making policies.

Keywords Dopamine · Accumbens · VTA · Prefrontal cortex · Decision · Neuroeconomics

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Introduction

Over the past decades, there was significant progress delineating the neural mechanisms involved with reinforcement and outcome processing with dopamine being central to many accounts of goal-directed behavior. Although the classical formulation of dopamine release providing a signal mediating the hedonic pleasure of primary rewards such as food, water and sex was largely refuted (Berridge and Robinson 1998; Salamone and Correa 2002; Wise 2004), there is a large body of evidence demonstrating a prominent role for mesocorticolimbic dopamine in modulating instrumental behavior, particularly those types of responses triggered by environmental stimuli. Low levels of dopamine antagonism or selective depletions of dopamine in the core of the nucleus accumbens cause changes in the motivation of animals to pursue rewards and the manner in which they allocate their responses without affecting food intake or affective reactions to the appetitive value of such reinforcers (Berridge and Robinson 1998; Ikemoto and Panksepp 1999; Salamone and Correa 2002; Kelley 2004).

Similarly, dopamine manipulations also consistently alter behavioral activation following the presentation of predictive cues. There is also a well-established literature connecting dopamine cell firing and reinforcement with increases in activity observed at the time of presentation of a predictive cue when a reward is received unexpectedly or when the obtained outcome is higher than the animal's expectation (Schultz and Dickinson 2000; Schultz 2006). While we have glossed over the distinctions between different elements that make up goal-directed behavior and reward (Berridge and Robinson 2003; Balleine 2005), it nonetheless seems safe to say that dopamine signals are likely to be closely involved in the process of motivating an animal to choose the optimal response in a given situation (Dayan and Balleine 2002; McClure et al. 2003). This decision making process requires animals to consider the consequences of selecting one action over another. These consequences include both rewards and costs. While there was much research into the neurobiology of reward processing, research into cost representations was less forthcoming.

Here, we assess the role of dopamine for mediating cost–benefit analysis, which is essential for ongoing decision making that drives action selection. We should note that this paper does not address dynamic learning paradigms and therefore does not attempt to either validate or invalidate the role of phasic dopamine release in temporal difference and other theories of learning (Rescorla and Wagner 1972; Montague et al. 1996; Schultz et al. 1997; Sutton and Barto 1998; Waelti et al. 2001). Instead, we focus on the acute psychomotor activating properties of dopamine on proximal behavior during stationary tasks where we can infer that the animal's perception of the operational requirement and outcome has already been established.

A neural representation of future rewards

Brain pathways involved in cost–benefit decision making must receive and utilize representations of potential future rewards. This information needs to be prescient: to use environmental stimuli to provide foresight into the likely outcome of an action before committing resources to that action. It needs to be adaptive: to use recent history to update assessments of the capacity of external stimuli to predict reward; and it needs to be quantitative: to account for outcomes of different reward magnitudes and likelihood before allocating responses. Wolfram Schultz and colleagues have demonstrated the capacity of dopamine neurons in the midbrain to respond to environmental stimuli that predict future rewards by phasic (~200 ms) neurophysiological activation (Ljungberg et al. 1992; Mirenowicz and Schultz 1994). These responses are adaptive, as exemplified during the acquisition of a reaction–time task where the phasic change in activity of dopamine neurons progressively develop (over ~15 trials) to an auditory stimulus as monkeys learn that this cue predicted a reward (Mirenowicz and Schultz 1994). These neurons quantitatively encode the magnitude of future rewards in their firing rate (Tobler et al. 2005) and also account for the likelihood of reward by scaling the response proportionally to the probability of reward delivery when weaker cues are presented that predict reward only a fraction of the time (Fiorillo et al. 2003). Furthermore, brief, phasic activation of dopamine cell body regions can promote reward-seeking behavior (Phillips et al. 2003) and inactivation of these brain areas impairs immediate responses to reward-predicting cues (Yun et al. 2004). Therefore, these findings suggest that midbrain dopamine neurons carry a phasic signal that fulfils the necessary criteria for broadcasting information about future rewards that can be used in cost–benefit decision making processes.

The reward-prediction signal in the nucleus accumbens

An additional requirement for a reward signal to be used in cost–benefit decision making is that it be available to brain areas implicated in these behaviors. Indeed, dopamine neurons project heavily to the forebrain areas implicated in decision making such as the prefrontal cortex and nucleus accumbens. However, although phasic responses to reward-predicting stimuli are encoded by as many as 70% of the dopamine-containing cells in the midbrain (Schultz 1998), this still leaves a significant proportion (30% or more) of the population that is unresponsive to these stimuli. It is important to note that dopaminergic projections to the nucleus accumbens, prefrontal cortex and other areas such as the amygdala are anatomically and functionally distinct, arising from separate subsets of dopamine neurons (Swanson 1982; Bassareo et al. 1996; Ford et al. 2006; Margolis et al. 2006). Hence, extracellular electrophysiological recordings alone cannot readily determine whether phasic dopamine reward-predictions reach any particular target.

Therefore, to test whether dopaminergic reward-predicting signals are sent to the nucleus accumbens, chemical recordings of neurotransmission are required. Alas, conventional neurochemical recording techniques (e.g., microdialysis) are orders of magnitude too slow to isolate putative phasic chemical signals elicited by behavioral stimuli. However, the use of voltammetric methods to measure brain chemistry in situ, as conceptualized by Ralph Adams (Kissinger et al. 1973), has provided a means to overcome this experimental barrier. While voltammetric

techniques have been used in awake rodents for two decades, early applications lacked chemical specificity (see Salamone 1996; Fillenz 2005). However, the recent advent of fast-scan cyclic voltammetry for the detection of dopamine during behavioral activation (Rebec et al. 1997; Robinson et al. 2001) or behavioral tasks (Phillips et al. 2003; Roitman et al. 2004; Stuber et al. 2005) has provided more selective chemical detection of dopamine (Phillips and Wightman 2003) while matching the temporal resolution of the neurophysiological changes. In these latter studies, increases in dopamine were most robustly observed in the core of the nucleus accumbens to discriminative (Roitman et al. 2004) or conditioned (Phillips et al. 2003; Stuber et al. 2005) stimuli. These stimuli precede rewards and predict their availability or delivery and therefore confirm that prescient encoding of rewards by dopamine transmission is conserved in the nucleus accumbens core. These chemical signals are also dynamically adaptive, as they decline during extinction but are restored upon subsequent reinstatement of the stimulus–reward pairing (Stuber et al. 2005). While quantitative encoding of future rewards by these chemical signals is largely untested, preliminary data from our laboratory suggest that this attribute will also be preserved in the core of the nucleus accumbens (J. O. Gan and P. E. M. Phillips, unpublished data). Therefore, it appears that the dopamine-mediated reward-prediction signal is robustly preserved in the nucleus accumbens and transmitted in the form of dopamine release.

Dopamine and subjective reward preference

But how does this accumbens dopamine signal influence behavior? Early hypotheses suggested that it provides the experience of pleasure during reward thereby reinforcing preferences for rewarding outcomes like food and drugs of abuse. This link between dopamine and reward was popularized in the 1970s, most notably in the "anhedonia hypothesis" proposed by Roy Wise et al. (1978). While this seminal hypothesis was challenged and revised (Berridge and Robinson 1998; Salamone and Correa 2002; Wise 2004), it has provided the preeminent framework for the study of dopamine's role in reward-related behavior. Nonetheless, evidence against a *unique* role for dopamine in euphoria and subjective reward preference comes in several forms. First, there seems to be a mismatch between dopamine neuronal activity and times when we would expect hedonia. For instance when a reward is predicted, there is an increase in the firing rate of midbrain dopamine neurons on presentation of the predictive stimulus, but not at the time of reward receipt. Does this suggest that just the anticipation of the reward is pleasurable rather than the receipt of the reward itself? This is a provocative concept, but is difficult to test experimentally. Also, there is a ramping up of dopamine cell firing between uncertain reward predictors and outcomes (Fiorillo et al. 2003). This would not be a time we would expect to be especially pleasurable. Next, putative measures of hedonia are not altered by dopamine impairment. Rodents produce orofacial taste reactions to palatable liquids delivered intraorally that are considered to reflect hedonic processes (Berridge 2000). While global dopamine depleting lesions (Berridge et al. 1989) or high-dose systemic dopamine receptor antagonists (Pecina et al. 1997) disrupt feeding, they do not change these orofacial responses. Finally, lack of dopamine doesn't impact relative reward preferences. Rats with almost complete nucleus accumbens core dopamine depletion still choose larger rewards (four food pellets) over smaller rewards (two food pellets) when the response requirement for either option is minimal (Salamone et al. 1994). This is also true when a dopamine receptor antagonist is site-specifically injected into the core of the nucleus accumbens (Salamone et al. 1994) or administered systemically at a low dose (Salamone et al. 1994; Denk et al. 2005). Moreover, even with a higher response requirement (but equal for each reward option) rats still demonstrate a behavioral preference for larger rewards after low-dose systemic dopamine antagonism (Denk et al. 2005). One caveat of some of these studies, raised by Wise (2004), is that the animals had previously experienced the rewards with an intact dopamine system and thus the measures of hedonia or preference during dopamine disruption may reflect pre-extinction conditioned associations of physical qualities of the agent, such as taste with primary reinforcement. This view is supported by the observation that in the presence of a dopamine antagonist, orofacial reactivity to *repeatedly* delivered sucrose progressively declines, somewhat analogous to an extinction paradigm (Leeb et al. 1991).

However, the most definitive evidence on the subject of reward processing in the absence of dopamine comes from Richard Palmiter and colleagues who engineered mice whose "dopamine" neurons are incapable of synthesizing dopamine (Zhou and Palmiter 1995). These animals survive if supplemented daily with a dopamine precursor from which they can synthesize dopamine (L-DOPA), but if this is withheld for even 1 day, dopamine drops to negligible trace levels in their brains. These dopamine-deficient mice are severely retarded in goal-directed behavior overall. In fact with ad libitum food access they will hardly feed and will die of starvation unless nutrition is provided intraorally (or presumably by other means that have minimal response costs). Nonetheless, there is conservation of some components of reward processing. For instance, these mice show preferences towards sucrose compared to water in a two-bottle choice task (Cannon and Palmiter 2003) indicating

that dopamine is not required for the immediate perception of reward value. Although total fluid consumption was much lower in dopamine-deficient mice compared to wild types, the relative intake of sucrose over water was comparable to wild types and dopamine-deficient mice actually had higher licking rates and bout lengths on the few occasions when they initiated drinking bouts. One interpretation of this finding is that dopamine depletion impaired the animals' drive to approach the spout, but not their preference for consuming it once within reach. This group has also reported that these mice are capable of forming conditioned place preferences for morphine (Hnasko et al. 2005) and learning reward locations (Robinson et al. 2005) in the absence of dopamine. In each of these experiments, the animals did not have prior experience with the context with an intact dopamine status and so these findings do not reflect preconditioned responses.

Collectively, these data suggest that while dopamine encodes the magnitude of future rewards and is essential for normal goal-directed behavior, it is not required for the formation of immediate subjective preferences between qualitatively or quantitatively different rewards, as evidenced by measures of consummatory behavior.

Using dopamine to overcome costs

If subjective pleasure and/or preference is not the *primary* role of dopamine in reward processing, what computations do account for its unequivocal involvement in instrumental behavior? To economists or behavioral ecologists studying decision making, focusing purely on the reinforcing side of motivation disregards a vital component of choice behavior, namely, that most responses incur certain costs before the goal can be attained. For a marmoset, for instance, for whom gum and sap from trees is a primary constituent of its diet, one cost is the amount of time the animal has to wait patiently for this local food source to appear and be renewed (Long and Platt 2005; Stevens et al. 2005). For another foraging animal, such as a tamarin or starling, the cost may be an energetic one, incurred as the animal travels from one starting location to a patch where it believes that a foodstuff may be found (Bautista et al. 2001; Stevens et al. 2005). Research into the neural mechanisms that process such costs was much less forthcoming than that investigating reinforcement. However, implicit in many of the motivational theories of dopamine function, and stated most unequivocally by Salamone et al. (2006) and in a recent computational model by Niv et al. (2005), is that dopamine may also play a role in the evaluation of response costs, particularly those which entail an energetic or activational component.

Several studies have demonstrated that low-dose administration of dopamine antagonists or selective depletions of dopamine in the core of the nucleus accumbens can suppress responding for reward when the response has a large work component interposed between the response and the outcome, such as a high lever-press ratio requirement or lengthy maze traversal (Caine and Koob 1994; Ikemoto and Panksepp 1996; Aberman and Salamone 1999). Conversely, the same treatments have little or no effect if only a single lever response is required or if animals are placed adjacent to the reward. In isolation, these deficits could be attributed to gross motivational or motoric alterations as observed after high doses of systemically administered dopamine antagonists or depletions/antagonism of dopamine in areas such as the ventrolateral striatum (Salamone et al. 1993). However, it is notable that nucleus accumbens core dopamine depletions do not have any effects on movements such as grasping or food handling or on the duration of lever responses (Salamone et al. 1993; Nowend et al. 2001).

Moreover, a series of studies by Salamone and colleagues in which animals choose between investing effort for a larger or more palatable reward (high reward–HR–option) and a more easily obtained, but less palatable or smaller quantity of food (low reward–LR–option) has indicated that dopamine plays a crucial role in response allocation, allowing animals to overcome energetic constraints to obtain better outcomes. In both operant and T-maze situations, systemic injections of dopamine antagonists at doses, which did not affect free food intake or food preference or selective nucleus accumbens core dopamine depletions caused animals to shift from choosing to work to obtain the HR to selecting the LR option, which required less energetic expenditure (reviewed in Salamone and Correa 2002; Salamone et al. 2006). This was not caused by gross motor and performance deficits as the effect was not observed when the LR option was either unrewarded or unavailable.

While choosing to obtain the HR tends to entail the animal having to wait longer to receive the reward and it needing to put in effort, it seems unlikely that the factor of time was a significant component of this effect. When faced with two options, one of which gives a small immediate reward and the other a larger reward delayed by a period of time, animals with dopamine depletions targeted to the nucleus accumbens make no more impulsive choices than controls (Winstanley et al. 2005). Moreover, it appears that responding for delayed rewards is only affected by targeted nucleus accumbens dopamine depletions if there is a work component to the reinforcement schedule. Animals with dopamine lesions of the core of the nucleus accumbens are impaired on variable interval (VI) schedules, which have an attached work component but appear relatively unaffected

when the VI schedule is unaccompanied by an additional fixed-ratio lever response requirement (Correa et al. 2002; Mingote et al. 2005). Likewise, the infusion of D_1 or D_2 receptor antagonists into the nucleus accumbens does not affect the amount of time the animals are willing to wait for reward in a progressive delay task (Wakabayashi et al. 2004). These results are all in accord with an increasing body of evidence, which suggests that investing effort over time or waiting for reward are behaviorally and neuroanatomically dissociable (Stevens et al. 2005; Walton et al. 2006).

While the above studies imply a fairly specific role for dopamine in overcoming energetic costs, the extent to which dopamine has a more general role in bridging response costs is presently unclear. Nucleus accumbens dopamine does not appear to be instrumental in overcoming time delays, as discussed above, but dopamine acting at other anatomical loci may be important. Evidence for this position comes from studies in which *systemic* injections of D_2 receptor antagonists (either haloperidol or raclopride) were shown to cause animals to make more impulsive choices (Wade et al. 2000; Denk et al. 2005). Similarly, systemic administration of D-amphetamine, an indirect dopamine agonist, can result in animals tolerating longer delays to gain a high reward rather than accepting a smaller, but immediate, reward (Richards et al. 1999; Cardinal et al. 2000). Moreover, while 6-hydroxydopamine lesions of the nucleus accumbens do not directly affect delay-discounting, they do block the ability of the 5-HT agonist 8-OH-DPAT to increase impulsive decisions (Winstanley et al. 2005) indicating that dopamine in the nucleus accumbens actually has a subtle but more complex role relating to this task. Despite this caveat, these data suggest that dopamine acting in areas other than the nucleus accumbens may be most important in dealing with time delays.

In addition to physical work and time delays, response costs associated with obtaining rewards could be probabilistic (i.e., uncertainty) or come in the form of aversive consequence of the outcome. With respect to uncertain outcomes, there is evidence that the nucleus accumbens may be an important neural component of risk taking behavior (Kuhnen and Knutson 2005). However, to date, the role of mesolimbic dopamine in processing risk and uncertainty remains largely untested. Nonetheless, anecdotal evidence for the role of dopamine in risk taking comes from numerous case reports describing the development of pathological gambling in Parkinson's patients after their treatment regimen was switched to dopamine agonists (e.g., Avanzi et al. 2004; Dodd et al. 2005; Szarfman et al. 2006). Moreover, Fiorillo et al. (2003) demonstrated that dopamine cells code the uncertainty between a stimulus and its outcome with activity levels greatest at the highest levels of uncertainty (probability 0.5) and suggest that this information may be employed during risky decisions. Aversive consequences of obtaining a reward normally reduce responding for that reward. Disruption of this process (particularly for long-term future aversive consequences) is central to the pathology of compulsive behaviors including drug addiction (Deroche-Gamonet et al. 2004; Vanderschuren and Everitt 2004). However, the ability of dopamine to change response allocations when rewards are paired with aversive consequences is largely unexplored.

In summary, dopamine may have a universal role in overcoming response costs to obtain rewards. Extensive empirical data support this role for response costs that impose physical effort. However, despite some evidence that dopamine may also contribute to time delay costs, other modes of response cost are chiefly unexplored.

Determining reasonable cost expenditure for rewards

To provide a conceptual framework to understand the relationship between dopamine and the cost expenditure to obtain rewards, we have employed basic utility functions (Fig. 1) akin to those used by economists to model human decisions. At this time we will use the general term "cost" to describe phenomena such as physical effort, time delays, probability or aversive consequences that are imposed upon reward options and discount their net value. It is intended that we can provide a uniform framework, which can subsequently be used to determine the anatomical loci of dopamine's involvement of specific modes of response cost. Naturally, this framework could also be used to study additional neural substrates other than dopamine.

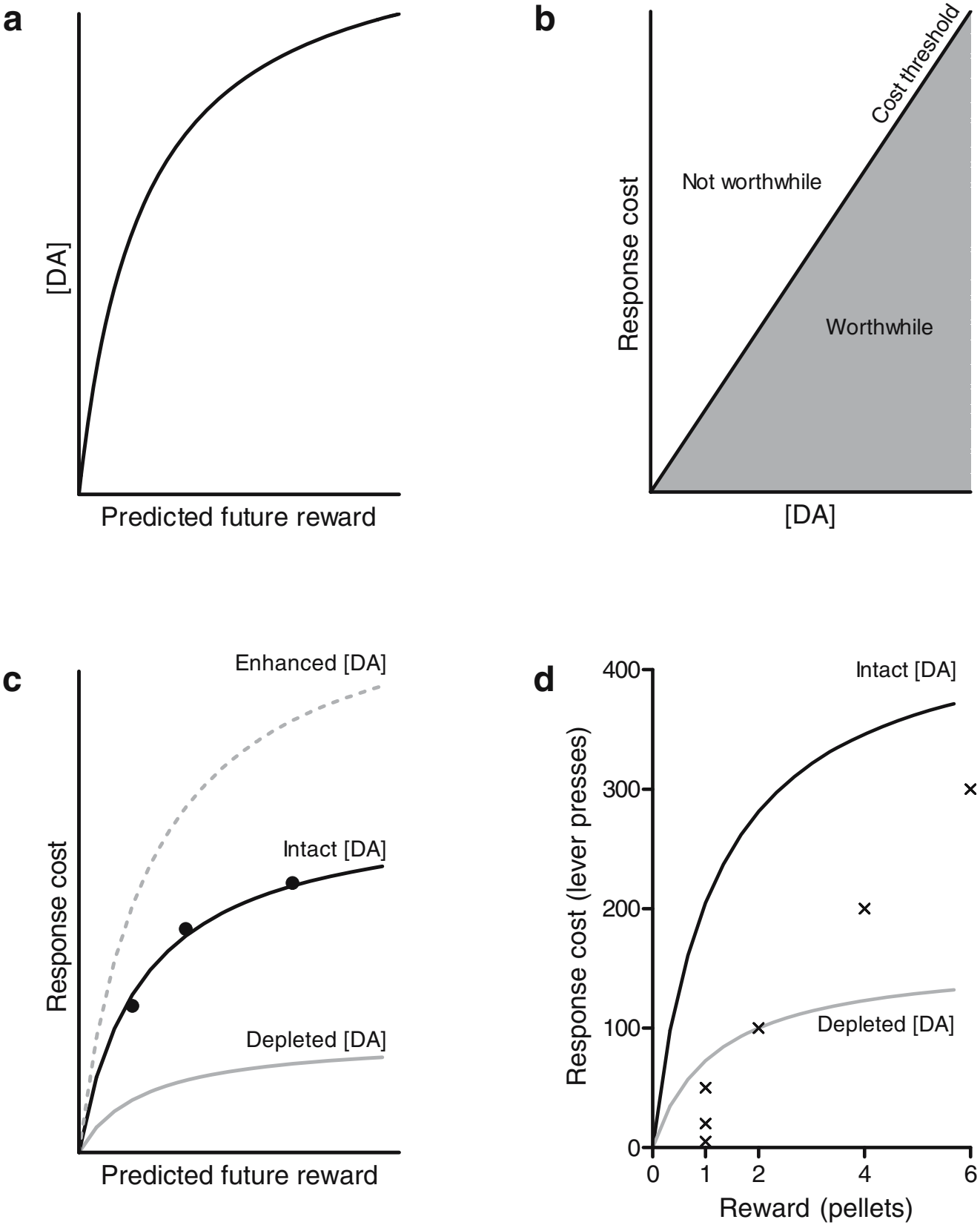
In the first instance we need to account for dopamine's ability to encode future reward magnitudes. Such a function is presented in Fig. 1a showing a monotonic relationship between expected reward and (phasic) extracellular dopamine concentration. This curve is proposed to be concave down to account for decelerated gains with higher rewards (see Marsh and Kacelnik 2002; Pompilio et al. 2006) in accordance with Weber's Law (thresholds for discrimination are proportional to the value being discriminated)—to economists, this is the concept of diminishing marginal utility. The horizontal asymptote is constrained by the limited dynamic range of the dopamine system and its inputs. Experimental evidence as to the exact shape of this curve has not yet been obtained and hence we have not made the subsequent discussion dependent on this. Next, we need to account for the effect of dopamine on cost expenditure thresholds where reduced dopamine function via depletion or antagonism decreases the maximum work (breakpoint) an animal will exert to obtain a reward. We have presented this as a linear function, meaning that the cost expenditure threshold will be proportional to the

dopamine concentration. Again, the exact relationship between dopamine levels and cost thresholds was not experimentally determined and while we have provisionally assumed a linear relationship, the subsequent discussion will not be radically altered as long as the relationship is monotonic. This function divides reward options based on the phasic dopamine concentrations they elicit and the costs required to obtain them. Options that fall below (and to the right of) the threshold curve are deemed to have surplus utility, are "worthwhile" and will generally be chosen, while those above (and to the left of) the threshold have deficit utility, are "not worthwhile" and will generally be rejected. These graphs capture the ideas that higher reward expectations produce larger phasic dopamine concentrations (Fig. 1a) and hence higher cost thresholds (Fig. 1b).

By combining the functions from Fig. 1a and b we can obtain a behavioral utility function (Fig. 1c) that determines the threshold cost expenditure (breakpoint) based on the expectation of outcome (black line). Again, options that fall below the threshold (surplus utility) will generally be selected and those above it (deficit utility) will generally be rejected. The further an option falls from the threshold line, the greater the surplus or deficit utility and the more often that option will be selected or rejected, respectively with options that fall on the line being selected half of the time. However, we have not attempted to precisely quantitate the response allocation with respect to the distance from the threshold line. Because this curve models behavioral choice, its form can be tested much more easily than the previous graphs, which characterize purely internal brain function (Fig. 1a and b). For example we carried out a preliminary validation of the shape by observing breakpoints in a progressive ratio schedule in two rats working for one, two or four 45-mg food pellets (Bio-Serv, NJ). These data fit the proposed form of the curve very well and are shown on the graph as filled circles (Fig. 1c). While this curve is purely a behavioral cost–benefit analysis function, we generated it on the basis that dopamine mediates this relationship between expected reward, cost expenditure and behavioral choice. Therefore, this construct dictates that manipulating dopamine will change the cost threshold function and therefore choice behavior of the animal. The gray lines in Fig. 1c are the predictions of such manipulations. The solid gray line represents a hypothetical 67% dopamine depletion (or antagonism). In this case, the allocation of choices based on response cost would be altered, so that far fewer options are selected (area under curve) compared to the intact dopamine scenario. Conversely, with a hypothetical 67% enhancement of dopamine function (dotted gray line), there would be a much larger allocation of choices to obtain rewards.

By introducing real numbers to the axes we can evaluate the model using empirical behavioral data (Fig. 1d). It should be noted that the cost threshold curve presented in Fig. 1d on real axes represent realistic breakpoints for dopamine-intact, food-deprived rats. We used this model to simulate a study carried out by Salamone et al. (2001), which showed that targeted dopamine depletion in the core of the nucleus accumbens selectively retarded high-ratio responding. Those data are difficult to explain by existing computational models because reward density was constant for four of the response schedules, FR (fixed-ratio) 50 for 1 food pellet, FR-100 for 2 pellets, FR-200 for 4 pellets and FR-300 for 6 pellets (FR-5 and FR-20 for 1 pellet were also tested), yet dopamine depletion still selectively affected the high response ratio options. These schedules are shown in Fig. 1d as crosses on the graph. Options that fall below the cost threshold curve should be selected and those above ignored. The simulation predicts that when dopamine is intact, rats will respond for any of the schedules offered. With dopamine depletion, the model predicts that rats will still work for FR-5/1, FR-20/1 and FR-50/1 schedules, but rarely choose FR-200/4 or FR-300/6. In this simulation, the FR-100/2 schedule falls on the threshold curve suggesting that this option would be at the point of indifference and rats may choose it about half of the time. Remarkably, this simulation accurately accounts for the behavior observed by

Fig. 1 Putative role of nucleus accumbens dopamine in determining the maximum response cost that will be expended to obtain a reward. **a** Phasic dopamine release in the nucleus accumbens encodes the magnitude of predicted future rewards. This relationship is expressed as a hyperbolic function $(y = y_{\max} \times x/(k + x))$ to account for the prevailing idea that animals perceive reward magnitude with decelerating gains. **b** We propose that this dopamine signal is used to monotonically set the threshold (breakpoint) beyond which the net outcome is no longer worthwhile. **c** The functions from **a** and **b** can be nested to obtain behavioral utility curves that describe maximum response costs that will be expended as a function of reward magnitude. This cost–threshold function is altered when dopamine transmission in the nucleus accumbens is manipulated. Higher or lower dopamine levels are permissive of greater (*dotted gray line*) or lesser (*solid gray line*) cost expenditure to obtain a reward compared to the intact state (*solid black line*), respectively. The concave shape of these curves is consistent with the average breakpoint data from progressive ratio responding for one, two or four 45-mg food pellets (Bio-Serv, NJ) from two rats (T. C. Jhou and P. E. M. Phillips, unpublished data; *filled circles*). **d** The threshold curves from **c** (intact and dopamine depleted) were expressed with real units and used to model the effects of dopamine depletion on constant-reinforcement-density responding observed by Salamone et al. (2001). The *crosses* represent the fixed-ratio reinforcement schedules used in that study. The animal should only choose to engage in schedules where the response cost of a reward falls below the threshold line. With intact nucleus accumbens dopamine the rats work for all of the available rewards, whereas after nucleus accumbens dopamine depletion they work for the low ratios (FR-5, FR-20 and FR-50 for one food pellet), but become indifferent to working for FR-100 for two pellets and do not work at all on the higher-ratio schedules (FR-200 for four pellets and FR-300 for six pellets). This simulation is in good concordance with the results obtained by Salamone et al. (2001)


a
[DA]
Predicted future reward
b
Cost threshold
Not worthwhile
Worthwhile
Response cost
[DA]
c
Enhanced [DA]
Intact [DA]
Depleted [DA]
Response cost
Predicted future reward
d
Intact [DA]
Depleted [DA]
Response cost (lever presses)
400
300
200
100
0
0
1
2
4
6
Reward (pellets)

Salamone et al. (2001). It seems, therefore, that this type of framework can be useful in reconciling the role of dopamine in cost–benefit decision making.

Involvement of the prefrontal cortex in cost–benefit decision making

While numerous studies now show some role for mesolimbic dopamine systems in allowing animals to surmount their natural cost aversion in which immediate, certain or easily obtained rewards tend to be preferred (with some notable exceptions: see Kacelnik and Marsh 2002; Matsushima et al. 2003), dopamine does not act in isolation in the processing of costs and the calculation of utility. Increasingly, there is converging evidence from both animal and human studies for a prominent and perhaps dissociable role for different parts of the prefrontal cortex in cost–benefit decision making. Using a similar effort-related T-maze to the one devised by Salamone and colleagues, studies have demonstrated that anterior cingulate cortex lesions cause a bias away from choosing a HR option that required climbing a barrier in the presence of an easily obtained available LR (Walton et al. 2002; Walton et al. 2003; Schweimer and Hauber 2005). This is an analogous, if not even more prominent, effect to that observed after nucleus accumbens core dopamine depletions. However, while disrupting mesolimbic dopamine causes a general retarding of responding when work is necessary, anterior cingulate cortex lesions only seem to affect the investment of effort when there is another available rewarded option (Schweimer and Hauber 2005). This suggests that the anterior cingulate cortex may play a role in evaluating the costs and/or benefits of each course of action in the context of available alternatives and setting a decision criterion for when it is worth overcoming response constraints.

Like dopamine in the core of the nucleus accumbens, the role of the anterior cingulate cortex in overcoming response costs also appears to show some specificity, as lesions to this structure cause no changes in sensitivity to time delays, i.e., impulsivity (Cardinal et al. 2001). However, one prefrontal area that does appear to play a role in delay discounting is the orbitofrontal cortex. Nonetheless, there is a large degree of confusion over its precise function as one study has demonstrated an increase in impulsive choices after orbitofrontal cortex lesions (Mobini et al. 2002) and another the opposite finding of an increased ability to tolerate delays (Winstanley et al. 2004). Similar regions of prefrontal cortex were also implicated in aspects of economic decision making by human neuropsychological and neuroimaging studies. Patients with damage to the ventromedial prefrontal cortex (including parts of both orbitofrontal and anterior cingulate cortex) can exhibit impulsive and risk taking behavior and were recently shown to be poor at discerning when they lack relevant information to make a decision (Bechara et al. 1999; Rogers et al. 1999; Berlin et al. 2004; Hsu et al. 2005). One functional magnetic resonance imaging study has shown the activation of the lateral orbitofrontal cortex when linking an action with an immediately available outcome but not when learning to obtain a large future reward by overcoming small, immediate losses (Tanaka et al. 2004) and another found rostral anterior cingulate/medial orbitofrontal cortex and ventral striatum activations when choosing to obtain a small amount of money without delay rather than a deferred but larger reward (McClure et al. 2004).

Integration of the functions of dopamine and the prefrontal cortex

The anterior cingulate cortex and other parts of the prefrontal cortex are the recipient of dopamine innervation from the ventral tegmental area. Given the plethora of studies connecting dopamine with overcoming response costs (including those that administered dopamine antagonists systemically) and this analogous function of the anterior cingulate cortex, a logical hypothesis would be that *mesocortical* dopamine would be paramount to this effect. However, dopamine-depleting lesions of the anterior cingulate cortex had no effect on performance on the barrier T-maze task (Walton et al. 2005, though see Schweimer et al. 2005). The importance of prefrontal dopamine on other types of decision making is also ambiguous with levels of the dopamine metabolite DOPAC being increased in the orbitofrontal cortex of animals performing a delay-discounting task (Winstanley et al. 2006), but selective dopaminergic lesions of this region caused animals to become less impulsive if there were delays between the choice and delivery of either the high or low rewards (Kheramin et al. 2004).

An alternative way to reconcile the role of dopamine in cost–benefit analysis with that of the prefrontal cortex is by considering their anatomical convergence. Many frontal cortical regions send excitatory projections to areas of the striatum where they communicate with medium-sized spiny neurons, forming synaptic connections that are in close apposition to those from ascending dopaminergic projections from the midbrain (Sesack and Pickel 1992). The prevailing hypotheses on the cellular function of dopamine suggest that it acts to gate these excitatory signals and increase signal-to-noise by enhancing strong inputs and suppressing weaker inputs (reviewed by O'Donnell 2003; Nicola et al. 2004). We suggest that a cost–benefit decision making policy is set in the prefrontal regions and is

transmitted to specific parts of the striatum where dopamine may act to bias this signal.

Specifically, efferents from the anterior cingulate project to the core of the nucleus accumbens (Brog et al. 1993)—the exact region where dopamine depletion reduces effortful choices (Sokolowski and Salamone 1998). It seems, therefore, that the crux of dopamine's anatomical selectivity in this process is the prefrontal afferents upon which it converges. It remains to be discovered whether there will be anatomical specificity of dopamine's (or other neuromodulators') effects related to other modes of response costs that will be defined by the projection field of other specialized corticostriatal pathways.

This concept that dopamine biases decision making policies represented in the prefrontal cortex can be simulated with a utility function. This time, we will consider that a decision making policy, formulated and represented in the prefrontal cortex is characterized by a cost-discounting utility curve (Fig. 2). The black line describes the way in which increasing cost discounts the net value of a reward (shown normalized to its pre-discount value). When no response costs are imposed, the outcome holds its gross utility. However, as response costs increase, the net utility falls. Once the net utility drops below zero (dotted horizontal line), the outcome becomes unfavorable. We model the effect of changes in dopamine concentration by a change in the slope of this curve. This is manifested as reduced discounting of net utility by response costs when dopamine levels are high (dotted gray line) and increased discounting when dopamine is low (solid gray line). As such, animals choose more transactions where cost expenditure is higher when dopamine levels rise. As can be seen from the divergence of the curves and consistent with

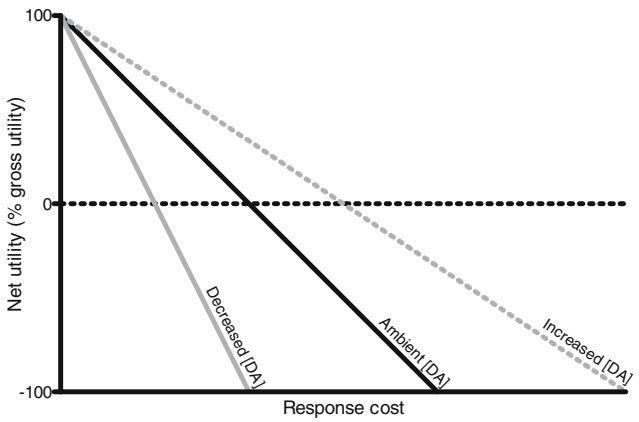


Fig. 2 Cost-discount utility–functions. The *black line* represents the function set up by the prefrontal cortex at ambient dopamine levels. The *dotted gray line* shows the biasing of the curve by an increase in dopamine. Under this condition, rewards will show less depreciation of their net utility when response costs are increased. The converse condition is represented by the *solid gray line* where dopamine is lowered below ambient levels. Now the net utility undergoes heavy discounting when response costs are increased

experimental data (Salamone and Correa 2002), rewards that have high response costs are most affected by changes in dopamine.

From this straightforward account, we can make predictions on the roles of ambient (tonic) and phasic dopamine activity on decision making. This simple model has no preferential role for either tonic or phasic dopamine (and therefore does not account for the possibility of the activation of different subpopulations of receptors), but differentiates them only by their concentration and time profiles. Thus, we suggest that either mode of dopamine transmission should act with the same valence on cost–benefit decision making, but with the obvious difference in temporal duration. Tonic dopamine should impose a steady state cost–benefit bias that may reflect the general status of an animal (see below) and baseline decision making policy. As such, elevated ambient dopamine levels may have a priming role in decision making, modulating all ongoing frontocortical-derived activity to influence behavior. The specificity of such an effect will be contingent upon the specific descending information from the prefrontal cortex. Conversely, phasic dopamine should provide a reactive signal to discrete environmental stimuli that has a short-lasting effect, providing a window of opportunism where cost-prone options may be included in response allocations. This effect should have temporal specificity to the eliciting stimulus. We would suggest that this opportunistic behavior would be most prominent when predictors of rewards are outside habitual routines and are themselves unpredicted because it is at these times that phasic dopamine response to reward predictors are most robust (Ljungberg et al. 1992; Schultz et al. 1993). A form of this behavior may also be evidenced by Pavlovian-instrumental transfer experiments in which ongoing instrumental behavior is potentiated when reward-predictive cues are presented (Balleine 2005). This behavioral mode should encourage the experience of low availability but potentially costly commodities and promote novelty seeking—a trait intimately linked to dopamine activity (Marinelli and White 2000).

Accounting for internal states

To hypothesize that dopamine biases cost–benefit analyses raises a question of redundancy. Why would we need dopaminergic systems to modify a decision making policy that was already set up by executive areas of the brain? We have speculated that dopamine may add a reactive (opportunistic) component to cost–benefit analysis to take advantage of items that become available unexpectedly. In addition, decision making policies should respect changing physiological and cognitive priorities. Dopamine transmission may provide one mechanism that bridges internal states with

executive function. Internal states such as hunger, thirst, sexual arousal or stress affect the allocation of resources an organism devotes to obtaining rewards. Allostatic systems that govern these internal states may exert some of their effects on behavior via dopaminergic mechanisms (Wilson et al. 1995). Receptors for several peptides that regulate food intake, ghrelin, orexin (hypocretin), insulin and leptin are abundantly expressed in tyrosine hydroxylase-expressing cells in the ventral tegmental area and substantia nigra pars compacta (Figlewicz et al. 2003; Narita et al. 2006; Zigman et al. 2006). Leptin, a satiety signal released by non-depleted adipose cells inhibits basal and feeding-evoked dopamine release in the nucleus accumbens (Krugel et al. 2003); while ghrelin and orexin, which promote feeding, enhance dopamine signaling (Jiang et al. 2006; Borgland et al. 2006) and augment cocaine-induced hyperactivity (Wellman et al. 2005; Borgland et al. 2006). Hence, food deprivation may increase an animal's cost threshold for obtaining food via activation of the dopaminergic systems. Acute stress may have a similar impact on decision making because corticotropin-releasing factor, a stress-related peptide, acts in the ventral tegmental area to potentiate excitatory transmission in dopamine neurons (Ungless et al. 2003) and modifies motivated behaviors (e.g., Fulton et al. 2002; Pecina et al. 2006). Because these internal states may be able to change both tonic and phasic dopamine transmissions (perhaps differentially), they are likely to adapt the baseline decision making policy and impact the ability for environmental stimuli to transiently modify that policy to create a window of opportunism. This might be particularly useful in times of deprivation for maintaining seeking and selecting rare opportunities when they are presented, despite their costs (like overpriced food at the airport). Collectively, these internal states provide a means by which decision making policy can be adapted to the current needs of the organism, adding ecological flexibility to motivated behaviors.

Summary

Midbrain dopamine neurons are phasically activated by reward-predicting environmental stimuli to encode neural representations of future rewards. This information is transmitted to the core of the nucleus accumbens and rather than using it primarily to perceive subjective preferences, it is used in cost–benefit analysis to derive appropriate response allocations. In the nucleus accumbens, dopamine acts on medium-sized spiny neurons to modulate converging information that originates from the prefrontal cortex. By this means it is able to bias decision making policies that are represented in those pathways. We suggest that phasic dopamine release that is evoked by unexpected reward-predicting stimuli provides a window of opportunistic drive where the threshold cost expenditure to obtain the reward is increased. This type of behavior may be particularly useful and therefore promoted at times of increased ecological drive dictated by internal states. With the use of simple utility–function curves, a conceptual framework can be developed to generate experimental hypotheses on the function of dopamine and related neurobiological processes. This has the great advantage of high testability because with this approach, dopamine's role in reward-related cognition can be examined using decision making behavior without the necessity to assume psychological states.

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