Neural Basis of Motivational and Cognitive Control

edited by Rogier B. Mars, Jérôme Sallet,
Matthew F. S. Rushworth, and Nick Yeung

The MIT Press

This book was set in Times Roman by Toppan Best-set Premedia Limited. Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Neural basis of motivational and cognitive control / edited by Rogier B. Mars . . . [et al.].
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-262-01643-8 (hardcover : alk. paper)
1. Motivation (Psychology)—Physiological aspects. 2. Cognition—Physiological aspects. 3. Frontal lobes. I. Mars, Rogier B.
[DNLM: 1. Motivation—physiology. 2. Cognition—physiology. 3. Frontal Lobe—physiology. QP 409]
QP409.N48 2012
612.8′233—dc22

2011010089

10 9 8 7 6 5 4 3 2 1

10 The Influence of Dopamine in Generating Action from Motivation

Mark E. Walton, Jerylin O. Gan, and Paul E. M. Phillips

There is cognitive separation between evaluating what one finds desirable or rewarding and working out how and whether to obtain such goals. Traditionally, the study of central nervous system function divided neatly between these two faculties: one approach looking at how an organism maintains the equilibrium in its internal milieu, and another focusing on the regulation of movements in the external environment.[67] Many contemporary studies of cognitive control have also tended to treat these processes as separate, and have generally concentrated on the latter faculty. Classic paradigms such as the Stroop task or Erikson flanker task provide response selection problems through the combination of distracting stimuli and deterministic task rules, and might seem to have little particular regard to how this might be influenced by the internal motivation of the participants, though see "emotional" Stroop tasks for examples of how even this task can be tacitly adapted to tap into unconscious motivations.[114]

Working from the premise that a primary function of the control of action stems from a requirement to place the organism in a position to satisfy its needs and ultimately to ensure its survival, however, this separation of systems into either "motivation" or "action" might be argued to be artificial and potentially limiting. Instead, an important question arises as to which neural systems bridge the divide between motivation and action and how they allow us to translate often competing desires into a coherent action plan. It is not difficult to imagine that such a basic and necessary behavior as deciding whether to perform an action for reward would require coordinated action across multiple brain regions. While there have been several recent candidate regions, particularly in the frontal and parietal lobes,[45,77,80] the focus of this chapter is on parts of the striatum and the dopamine projections to this region, with special emphasis on the nucleus accumbens (NAc), which was arguably the first structure proposed to act as a "limbic-motor interface."[64]

The dopamine projection to the NAc arises from a midbrain nucleus called the ventral tegmental area (VTA) and is referred to as the "mesolimbic" dopamine system, to differentiate it nominally from the fibers originating in the dorsal

substantia nigra known as the "nigrostriatal" dopamine system. This division has also been, respectively, associated with a reward versus motor functional dichotomy.[119] Although there is little doubt that mesolimbic dopamine is important for modulating behavioral control, its exact role has remained controversial. One potential reason for this is limited appreciation of the types of incentives that might drive an organism to engage in or desist with a particular course of action. Much work has looked at how the anticipation of reinforcers and rewards might guide response selection, but there has been less appreciation of other factors that may modulate choices, such as the costs of a course of action, the novelty of exploring options, or current motivational state.

In the present chapter, we address the question of what role or roles the mesolimbic dopamine projection might play in helping translate motivation into action and in allowing one course of action to be selected in the face of competing, beneficial alternatives. We first investigate how mesolimbic dopamine came to be implicated in signaling reward and motivating an animal to action. We then discuss how dopamine transmission may promote responding to environmental cues and how this may be important for promoting control of action in some situations and disinhibition in others. Finally, we consider the limitations of the dopamine signal, focusing particularly on its role in guiding decisions when the utility of an outcome depends on the expected costs to be overcome as well as, or instead of, the anticipated benefits to be obtained.

Anatomy and Physiology of Mesolimbic Dopamine

The importance of dopamine as a chemical neurotransmitter in its own right and its function in motivation and reinforcement were realized only in the second half of the 20th century.[18,116] Dopamine is a modulatory neurotransmitter, classically thought to modulate coincident glutamatergic input in neighboring terminals. Whereas glutamatergic neurons make asymmetric synapses on the heads of dendritic spines, dopaminergic neurons synapse symmetrically on dendritic shafts and the necks of spines. In fact, the dopamine innervation of the striatum is so dense, it is thought that every structure in the striatum will be within range of a concentration of dopamine sufficient to stimulate both low- and high-affinity receptors following activation of dopamine neurons.[66]

Dopamine acts on a family of G-protein–coupled receptors classified as either D1-like (D1 and D5) or D2-like (D2, D3, D4). These receptors regulate intracellular signaling cascades in a cyclic adenosine monophosphate (cAMP)–dependent manner, where D1-like receptors increase and D2-like receptors decrease cAMP production.[69] D2-like receptors are expressed both pre- and postsynaptially, whereas

D1-like-receptor expression is limited to postsynaptic locations. In addition to their action on cAMP production, D2-like receptors regulate ion-channel conductance through the G-protein βγ complex, generally reducing cell excitability; and, as was shown recently, they participate in β-arrestin-2-dependent cell signaling using the protein-kinase-B/glycogen-synthase-kinase-3 pathway.[9] Thus, while D1-like receptors are generally considered to be excitatory and D2-like receptors inhibitory, these inferences are clearly oversimplifications. DA neurons exhibit multiple firing patterns: quiescence, tonic, slow-oscillatory/pacemaker (2–10 Hz), and phasic (bursting, 15–30 Hz) firing.[42–44,58,97,113] The pacemaker-like pattern results in a "tonic" extracellular concentration of dopamine (5–20 nM) assessable on a minute-by-minute time scale with microdialysis.[113] "Phasic" firing arises from short-latency (70–100 msec), short duration (100–200 msec) bursts of dopaminergic neuron firing that result in transient elevations of extracellular dopamine up to 1 μM.[113] It is believed that the temporally distinct patterns of dopaminergic firing convey information that subserves distinct but related behaviors, although the precise roles of tonic and phasic signals and their interaction remain to be fully elucidated.[94,113]

The majority of dopamine neurons arise from ventroanterior midbrain nuclei, which include the substantia nigra pars compacta (SNc: areas A8 and A9) and VTA (area A10) (fig. 10.1). Afferent inputs into the VTA include glutamatergic input from many parts of the brain,[41] including prefrontal cortex, amygdala, lateral hypothalamus, superior colliculus, along with the adjacent pedunculopontine tegmental nucleus (PPTg) and laterodorsal tegmental nucleus (LDT).[34] The PPTg and LDT also send cholinergic and GABAergic projections to the VTA.[96] Other GABAergic projections to the VTA originate from the ventral pallidum, the NAc, and the rostromedial tegmentum, as well as from local-circuit connections within the VTA. Additionally, the VTA receives serotonergic input from the dorsal raphe and noradrenergic input from the locus coeruleus.[34] Unlike the VTA, the major inputs to the SNc are inhibitory, consisting of GABAergic innervation from the striatum, globus pallidus, ventral pallidum, and the substantia nigra pars reticulata (SNr).[63] Excitatory inputs, though in the minority, arise from the subthalamic nucleus, amygdale, and PPTg.[63,72]

Dopaminergic projections from these nuclei comprise three main projection pathways: the nigrostriatal, the mesolimbic and the mesocortical pathway (figure 10.1). The nigrostriatal and mesolimbic dopaminergic pathways heavily but differentially innervate the striatum. SNc A8 dopaminergic neurons of the nigrostriatal pathway mainly innervate the dorsolateral striatum, while mesolimbic VTA neurons mainly innervate the ventral striatum, including NAc. Other neurons of the nigrostriatal pathway originating from A9 innervate a broad, intermediate area primarily in the dorsolateral striatum but reaching areas considered in the ventromedial striatum.[51,109] This anatomical gradient from the dorsolateral to ventromedial striatum

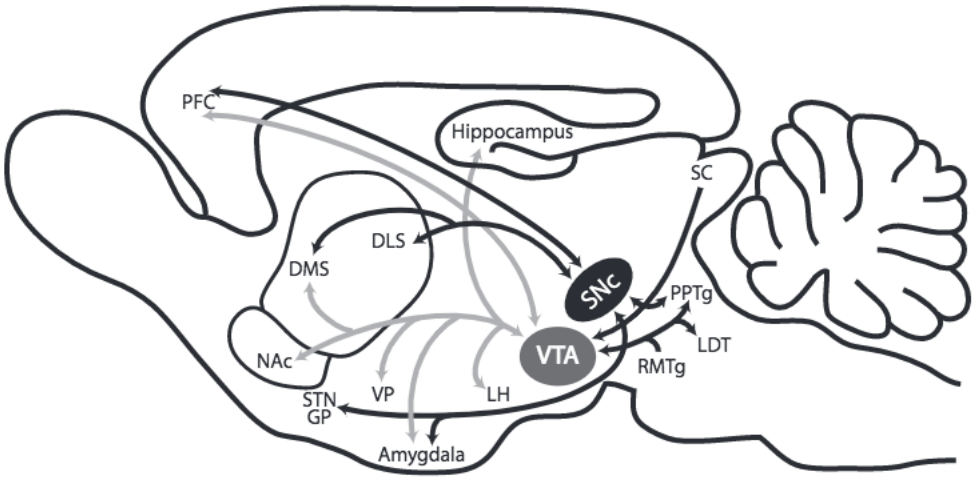


Figure 10.1
Schematic of the primary afferents and efferents of the midbrain dopaminergic nuclei depicted on a rodent brain. Although the correspondence between the midbrain dopamine pathways in rodents and primates is large, there are some important differences in both the putative definitions of the VTA and SNc and the density of projections to regions such as mediodorsal nucleus of the thalamus and non-prefrontal cortex; for example, see ref. 30 for a more detailed discussion of these differences. As the focus of this chapter is on rodent studies, the anatomy and physiology where described will be consistent with the rodent dopamine system.

mirrors a functional differentiation demonstrated by both recording and interference studies across mammalian species: while dorsolateral striatum is implicated in a range of sensorimotor functions, ventromedial striatum has a more direct connection with rewards and motivated behavior. For the purposes of this chapter, we largely concentrate on control of behavior by phasic changes in dopamine in mesolimbic pathways, although a number of the principles may well be common to both systems.

Dopamine, Drives, and Reward

One of the earliest sets of experiments to investigate how motivations might be translated into actions in the brain came from the accidental discovery that electrical stimulation delivered to parts of the limbic forebrain when an animal made a particular response would cause an animal to repeat that action.[74] These responses might be as simple as pressing a lever or positioning in a box or may involve navigating correctly in a complex maze. In some situations, the intracranial self-stimulation (ICSS) would act as such a potent positive reinforcer that animals would overcome electric shocks or even forgo food when starving to achieve the

stimulation.[73] More recently, it has been argued that stimulation parameters can be titrated so that animals will trade off stimulation for other positive reinforcers such as sucrose or saline dependent on their internal state, suggesting that ICSS might be acting as a "payoff" signal in a computation of the overall subjective utility of the available options.[99] ICSS sites included parts of the cortex, hippocampus, lateral hypothalamus, NAc, and "as far back as the tegmentum."[74]

Although the relationship between ICSS and natural rewards and the anatomical basis for ICSS is not fully resolved, the coincidence between some of the potent sites for electrical stimulation and the location of either the cell bodies, axons, or major terminal regions of mesolimbic dopamine neurons suggested a possible connection between dopamine and control of motivated behavior. However, it should be noted that characterization of threshold and optimal electrical-stimulation parameters favors the primary activation of small myelinated fibers, rather than dopamine axons, which are large and unmyelinated.[98] Nonetheless, support for an important role of dopamine transmission in ICSS-mediated reinforcement comes from pharmacological and lesion studies that showed injections of dopamine antagonists into the median forebrain bundle, which carries mesolimbic dopamine fibers, or large dopaminergic lesions could attenuate ICSS with electrodes placed around the VTA, whereas amphetamine, an indirect dopaminergic agonist, caused a reduction in the stimulation threshold required to sustain responding.[33] Microdialysis studies in the NAc have reported persistent raised dopamine tone during repeated VTA-centered ICSS, and there is also separate evidence that animals would acquire ICSS only if electrical stimulation resulted in this phasic elevation of extracellular dopamine concentrations as detected by fast-scan cyclic voltammetry.[40] At a cellular level, it has been shown that the rate of learning of ICSS correlates with the dopamine-dependent potentiation of corticostriatal synapses.[84] Although it is likely that ICSS can occur in certain circumstances without direct activation of dopaminergic neurons or phasic increases in dopamine concentration,[40,61] the persistent impression nonetheless remains of a role for subcortical dopamine in providing a component of a reward signal that can motivate or even entirely control current behavior.

A second line of evidence implicating dopamine in the translation of drives into actions comes from research into a situation paradigmatic of the loss of control, namely, addiction. Addiction is defined as a loss of control over some aspect of behavior accompanied by a compulsive drive to continue with such behavior in spite of negative consequences.[32] As mentioned earlier, psychostimulants such as amphetamine are known to enhance ICSS, suggesting a link between the drugs, reward, and dopamine.[33] Many drugs of abuse increase dopamine levels in NAc and in other parts of the striatum,[28,78,107] and the direct effects of these drugs on motor function can be attenuated by low levels of dopamine antagonists.[26] More recently, several

lines of evidence have implicated striatal dopamine release and dopamine receptor availability in NAc in aspects of vulnerability to addiction, which in turn seems connected with aspects of impulse control.[23,27,68] It is not just drugs of abuse that are associated changes in dopamine function. Other compulsive behaviors such as pathological levels of gambling, shopping, or binge eating have been observed in patients taking dopamine agonists.[21,108] Although the complex functional and neurobiological facets of addiction and compulsion are beyond the scope of this chapter, and certainly extend beyond NAc dopamine, the preceding findings nonetheless again underline an indelible link between subcortical dopamine and aspects of behavioral control.

A third indication of the role subcortical dopamine might play in aiding the translation from motivation to action comes from studies of Parkinson's disease. Although Parkinson's disease primarily causes the progressive loss of dopamine neurons in SNc, there is also some depletion of dopamine within mesolimbic pathways, particularly at later stages of the disease.[52] Though this disorder is usually associated with a variety of motor disturbances such as akinesia, rigidity, and tremor, another extremely common symptom is apathy, believed to occur in as many as 70% of patients.[56] The degree of apathy has been correlated with catecholamine levels in the ventral striatum,[83] and levodopa can help increase levels of motivation in at least a proportion of patients with Parkinson's disease.[20] More recently, it has been suggested that some symptoms classified as problems with general motor function, such as bradykinesia, might be partly based on changes in motivation to act.[60] In a speed-accuracy trade-off task, patients with Parkinson's disease were found to be just as able as controls to make the appropriate movements accurately within the required speed range. However, these patients were shown to make significantly more slow movements when the task was made more difficult, as if they had become more sensitive to the energetic demands of the movement. Therefore, a deficit that had been previously classified as a pure motor impairment was instead shown to be a problem with correctly integrating the costs and benefits of a response, implying that dopamine may be critical not just for making movements, but also for motivating a desire to act.[70]

Dopamine, Cue Control, and Prediction

The preceding lines of evidence strongly implicate mesolimbic dopamine as playing a critical role in motivating actions and the control of behavior. Nonetheless, taking evidence from ICSS, addiction, and Parkinson's disease in isolation—each of which provides a heterogenous model of behavior and is underpinned by a complex underlying neurobiology—does not easily allow us to specify what that role might be. This is partly because dopamine transmission and the effects of dopamine disruption

vary substantially in different parts of the striatum (and cortex) based on both ascending and descending anatomical projections,[2,5,91,103] even though many electrophysiological studies have tended to report largely similar responses across their sampled putative dopamine neurons during behavior, whether recording from the VTA or SNc.[93]

Up until now, we have treated both the terms "motivation" and "action" as unitary concepts. However, it has been long appreciated that the former can be divided behaviorally and neurobiologically into a preparatory, anticipation phase prior to the receipt of a reward and a consummatory phase once reward has been obtained.[47,85] This partially overlaps with the psychological idea that an animal might be motivated by incentive properties to "want" to gain a particular reward separate from the degree to which the reward may cause any pleasure or "liking" when received.[11] Equally, appetitive actions can be guided by associations with stimuli or with particular instrumental responses, each of which may either evoke a rich representation of the predicted contingent outcome (i.e., when behavior is "goal-directed"), or may instead control either automatic responses that are largely impervious to changes in current motivational state ("habit"-like behavior).[4,25]

Therefore, to try to understand how dopamine might modulate the control of behavior, it is necessary to probe further the types of situation where dopamine transmission is elicited and necessary for appropriate responses to be selected. Although it has been shown that feeding or the presentation of appetitive rewards, as well as a variety of other positive reinforcers such as companionship or drugs of abuse, can cause increased dopamine cell firing and release in various areas of the striatum,[5,78,87,90,95,115] mesolimbic dopamine does not appear to be required for feeding behavior. Lesions to the mesolimbic dopamine pathways to NAc do not cause deficits, whereas lesions to the pathways going to dorsal striatum do.[118] Indeed, feeding remains impaired in genetically targeted dopamine-deficient mice following restored dopamine production only in NAc,[102] but is rescued by selective restoration of dopamine function in the nigrostriatal pathway. Moreover, if facial expressions are taken as an indicator of the hedonic pleasure associated with food, neither dopamine agonists nor antagonists appear to alter the degree to which animals like or dislike the taste of foods,[11,104] a finding supported by more direct measures of subjective pleasantness in patients with Parkinson's disease.[100] Dopamine-deficient mice can also develop preferences for one reward type over another (e.g., sucrose versus water) to a degree similar to wild-type littermates.[16]

Instead, several lines of evidence suggest that the mesolimbic dopamine pathways are involved with signaling the potential availability of positive reinforcers, particularly when this is predicted by some external cue. Dopamine lesions or antagonism of NAc attenuate the usual increases in locomotor activity in the presence of food and profoundly reduce levels of operant responding for reward guided by predictive

cues.[54,120] Stimuli associated with primary rewards reliably cause rapid increases in activity in dopamine neurons and in dopamine transmission in NAc.[6,19,57] Though such changes in dopamine activity in response to the presentation of cues known to predict reward can occur before any movement takes place,[57,62] there is also evidence that NAc dopamine transmission is permissive, and arguably causally related, to allowing motivated responses to be directed by these cues. In well-trained animals, Roitman and colleagues found that a rewarded lever-press response tended to occur at the peak of the phasic rise in dopamine transmission in NAc, even on trials where animals failed to respond for some time after cue onset.[90] More directly, Phillips and colleagues not only showed increases in dopamine concentration in this region just as an animal chooses to approach a lever to obtain infusions of cocaine in the presence of a cue indicating the drug's availability, but also demonstrated that briefly electrically evoking dopamine release by stimulating the VTA significantly increased the likelihood of drug-seeking response being initiated.[78]

It is notable that in both of the preceding studies, presentation of cues that had explicitly not previously been paired with reward and/or where there was no possibility to respond failed to elicit any detectable increase in NAc dopamine concentration. It has been clearly established that the timing of putative midbrain dopamine cell activity is adaptive, as exemplified during acquisition of an auditory reaction-time task where initial phasic increases in activity of dopamine neurons to the presentation of liquid reward progressively diminish as the task is learned while the activity at the time of an earlier predictive auditory cue simultaneously develops.[62] Comparably, in a Pavlovian conditioning experiment, increased phasic changes in dopamine transmission in NAc has been shown within a single animal across several sessions to move from being triggered by the presentation of a reward to being elicited by a predictive cue,[19] and NAc dopamine depletion or antagonism receptor activation disrupts the expression and later consolidation of new appetitive learning.[22,24,29]

Such findings have led to suggestions that dopamine might be crucial to facilitating associations between a conditioned stimulus (CS) and reward or an unconditioned stimulus (UCS)[5,117] or to enhance the CS-UCS relationship in order to form habits.[31] An influential, formal computational theory has proposed that dopamine activity and release relays reward prediction errors—the difference between the predicted future reward in the current state and the actual experience reward—that are important in learning.[95] In trained animals, if the amount of reward is in compliance with the CS-predicted value, there is no phasic dopaminergic activity at the UCS. However, in situations where greater-than-predicted reward is delivered, the UCS causes a phasic increase in firing in dopamine neuron activity, whereas situations where less-than-predicted reward is delivered are marked with a brief cessation of dopaminergic cell firing at the time of the UCS.

These findings suggest that a primary role of mesolimbic dopamine transmission in control of behavior is simply to use discrepancies in these reward predictions to improve performance. However, it is important to note that animals in which mesolimbic dopamine transmission is disrupted either pharmacologically or genetically can still display evidence of learning. Dopamine-deficit mice, if activated by caffeine (acting via extra-dopaminergic mechanisms), are able to learn a T-maze spatial discrimination.[88] Moreover, NAc-dopamine lesioned animals can acquire Pavlovian conditioned approach responses, although at a retarded rate compared to controls, and it has recently been shown that mice lacking NMDA receptors on midbrain dopamine neurons, which attenuate phasic dopamine transmission in NAc, also learn certain cue-reward associations at a similar rate to normal animals.[19,76] There are likely multiple ways to learn associations between stimuli and outcomes,[25,110] and therefore likely multiple influences even on the performance of a simple action in response to a cue. The preceding evidence indicates that dopamine in NAc may be particularly important early in training for learning about and representing predictions of future reward states based on cues at times when the structure of the task environment is not fully known.

Dopamine and the Representation of the Benefits of a Goal

The majority of studies investigating the role of dopamine in motivated appetitive behavior have examined situations where there is only a single appropriate, externally rewarded response to learn about. However, in more natural settings, animals are faced with multiple possible options, each of which may be associated with different likelihoods of success and different potential outcomes, and the appropriate choice may depend on the animal's current motivational state as well as on any externally determined task rules. Parameters such as reward size, quality, and hunger have measurable effects on motivation and the choices that animals make.[17,46]

Internal states, such as hunger, thirst, sexual arousal, or stress, have been shown to affect dopamine activation. Tonic changes in NAc dopamine levels, as measured by microdialysis, are modulated by levels of food deprivation and also by the sensory properties of consumed food such that, after an initial meal of one foodstuff, a second meal of the same palatable food would hardly be eaten and there would be little increase in dopamine levels, whereas animals given a different type of food that was readily consumed did cause significant dopamine efflux.[1,115] Several peptides that regulate food intake are known to affect dopamine signaling. Leptin, a satiety signal released by nondepleted adipose cells, inhibits feeding-evoked dopamine release in NAc,[55] while ghrelin and orexin, which promote feeding, enhance dopamine signaling.[12,50] To date, few studies have investigated how such changes in state affect dopamine firing rates or fast release properties, which will be important

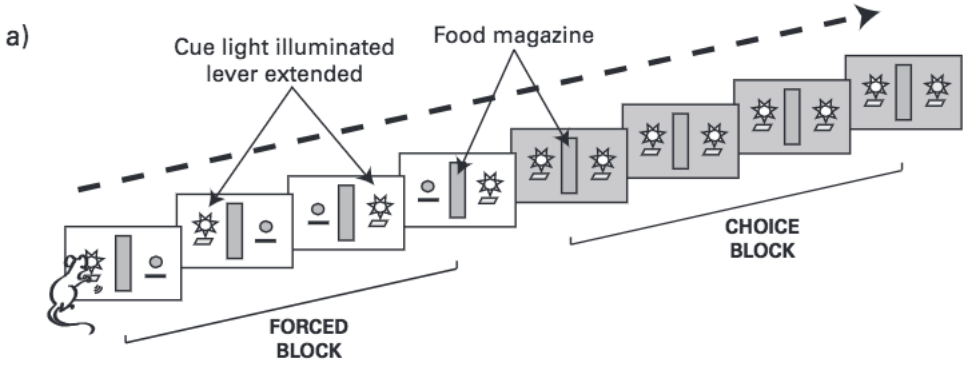
for addressing the degree to which current motivation is related to modulations in phasic dopaminergic signaling and, if so, how rapidly any changes in motivation are transmitted to the mesolimbic dopamine system.

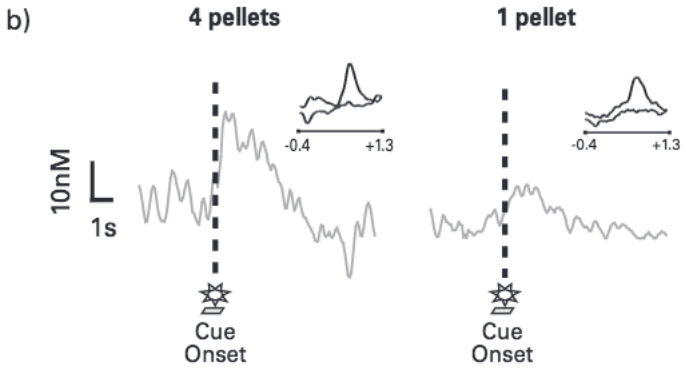
However, several studies have demonstrated that the firing rates of putative midbrain dopamine neurons in response to sensory stimuli correlate with fundamental economic parameters relating to future rewards such as reward magnitude and probability.[36,65,89,105] To test whether this would be translated into terms of NAc dopamine release, Gan and colleagues used fast-scan cyclic voltammetry during a two-option decision-making task where animals were trained to select between a "reference" option, which gained them a single food pellet after a certain number of responses, and an alternative where the same response requirement would result in a greater reward in one condition or a lesser reward in another.[39] Blocks of trials were divided into "forced" trials, where only one option was available, and "choice" trials, where both options were presented (figure 10.2a). In keeping with the electrophysiological findings, once the reward contingencies were learned and animals were consistently choosing the high reward option, the size of phasic dopamine release in NAc on forced trials scaled with anticipated reward magnitude in response to predictive cues (figure 10.2b and c). Such reporting of reward size remained after extended experience with the reward contingencies (figure 10.2c).

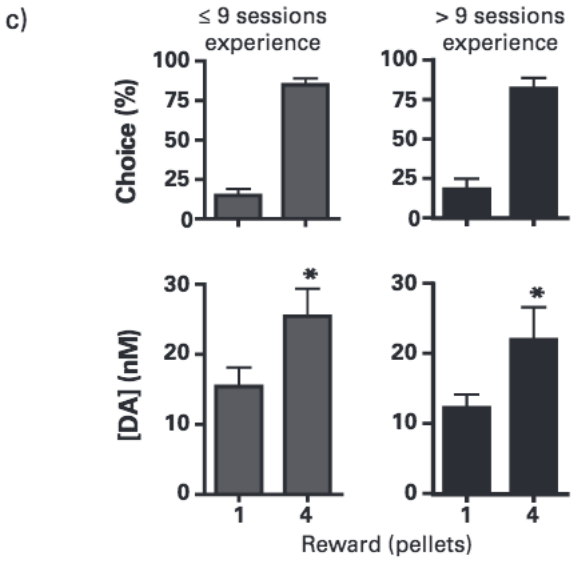
Some data also that suggest dopamine neurons change their activity as a function of the timing of future rewards, with cues indicating sooner reward delivery having slightly higher or more persistent increases in firing rates.[35,53,89] However, it is not yet clear to what degree this modulation of activity represents a temporally discounted reward value signal or the increased uncertainty about future reward timing and contingency between the cue and the reward as delays increase.

To have a controlling effect on behavior, dopamine would be expected to play an important role in guiding trial-by-trial decisions between different rewarding options. To date, the evidence speaking to this issue is sparse and somewhat contradictory. In a two-option decision-making task where visual stimuli were associated with different probabilities of reward delivery, the firing rate of putative SNc

Figure 10.2
Dopaminergic signaling to the NAc in a two-option reward-based decision-making task.[39] (a) Schematic of a set of eight trials comprising the behavioral task. Animals were presented with either "forced trials" (white background) or "choice trials" (gray background). Forced and choice trials occurred in blocks of four trials (two forced trials for each lever in the forced blocks, pseudorandomly presented). (b) Representative dopaminergic recordings from two forced trials, one where a cue predicts four food pellets (top left-hand panel) and the other where the alternative cue predicts one food pellet (top right-hand panel). Color plots represent cyclic voltammograms across time with the oxidation potential of dopamine indicated by a red arrow. Bottom panels represent extracted dopamine traces for those trials. (c) Postbehavioral criterion choices (upper panels) and average peak dopaminergic transmission to cues (lower panels) in animals that had either ≤ 9 or > 9 sessions experience with the four-pellet versus one-pellet condition. Data redrawn from Gan et al.,[39] with permission.


a)
Cue light illuminated
lever extended
Food magazine
CHOICE
BLOCK
FORCED
BLOCK


b)
4 pellets
1 pellet
-0.4
+1.3
-0.4
+1.3
10nM
1s
Cue
Onset
Cue
Onset


c)
≤ 9 sessions
experience
> 9 sessions
experience
Choice (%)
100
75
50
25
0
[DA] (nM)
30
20
10
0
*
*
1
4
1
4
Reward (pellets)

dopamine neurons in monkeys correlated with the average reward associated with the subsequently chosen option, even if the animal chose the lower value of the two available options.[65] By contrast, in another two-option decision-making study in rats where a particular odor was associated with a choice between options that differed either in the delay to reward (short versus long delay) or in reward magnitude (large versus small reward), the activity of putative dopamine neurons in VTA instead encoded the value of the best of the two options, regardless of which was subsequently chosen.[89]

Whether these differences are indicative of functional separation within the VTA and SNc or are caused by the different paradigms (one in which firing rates are correlated to the appearance of two cues, the other where a separate cue is associated with both options being available) remains to be seen. Using a task where choice trials were indicated by presentation of both response options, Gan and colleagues showed that NAc dopamine release on trials when the animal subsequently chose the high-value option was comparable to release on forced trials when only the high-value option was available,[39] and preliminary evidence suggests that signals prior to low reward choices are similar to those on low-reward forced trials (Walton, Gan, and Phillips, unpublished observations). In all these tasks to date, however, the questions as to why animals might choose a lower-value option and whether the factors that might promote such behavior—such as exploration bonuses or, in changeable paradigms, representations of previous task contingencies—are influencing dopamine firing patterns and release remain. Ideally, these questions should be investigated using a task where more than one factor could influence a choice and where these factors might have differing weightings on the mesolimbic dopamine system.

Although behavioral preferences are strongly influenced by rewards and reward-predictive cues and, in at least some situations, the firing rates of dopamine neurons and dopamine release seem to reflect the choices being made, this does not necessarily imply that mesolimbic dopamine has a primary role in setting behavioral policy. In the study by Gan et al., the assignment of the high- and low-utility options reversed in each session, meaning animals were required to relearn the cost-benefit contingencies. As can be observed in figure 10.3a, cue-evoked NAc dopamine release on forced trials developed rapidly within a testing session to reflect the magnitude of future reward delivery as the animals learned the reward contingencies associated with each option.[39] If these data are time-locked to the point in the session when animals reached a behavioral criterion of making more than 75% of high-value option choices, it becomes evident that dopamine often scales with pending reward size several blocks of trials before they have learned to display a consistent preference for the high-reward option (figure 10.3b). Even when an animal failed to reach the behavioral criterion during a single session, it was nonetheless apparent

that the differential reward magnitudes were being reflected by dopamine release (figure 10.3c).

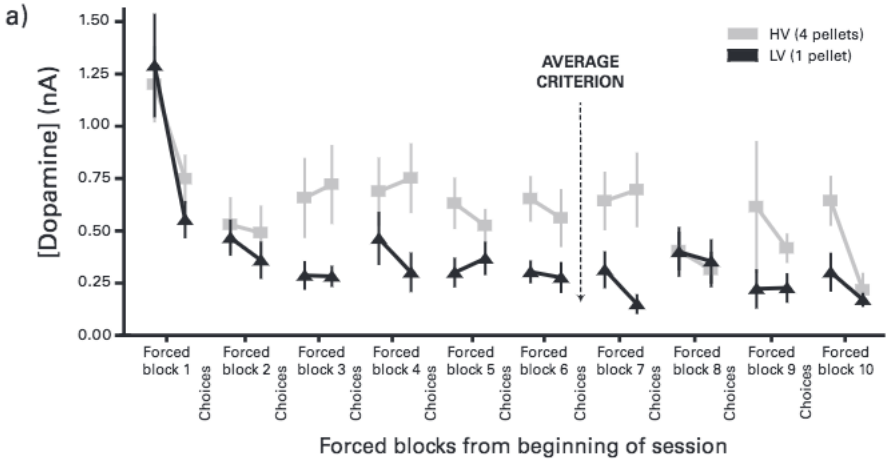
These data are comparable to those in a saccade timing task where monkeys had to use trial-and-error feedback to determine when to make an eye movement.[8] Even though the firing rate of dopamine neurons accurately relayed errors in reward prediction, these signals only weakly correlated with subsequent changes in reaction time following receipt of some magnitude of reward, suggesting that decisions about when to move were being mainly controlled via a different mechanism. Therefore, although mesolimbic dopamine might rapidly adapt to represent current predictions of future outcomes, this may be providing only one motivating influence on the actions that are taken at any particular moment.

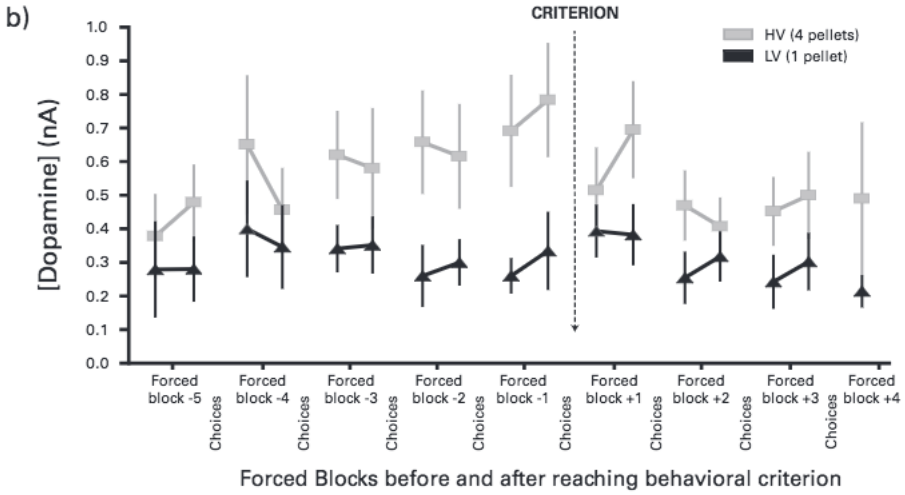
Dopamine, Utility, and the Intersection of Reward and Action

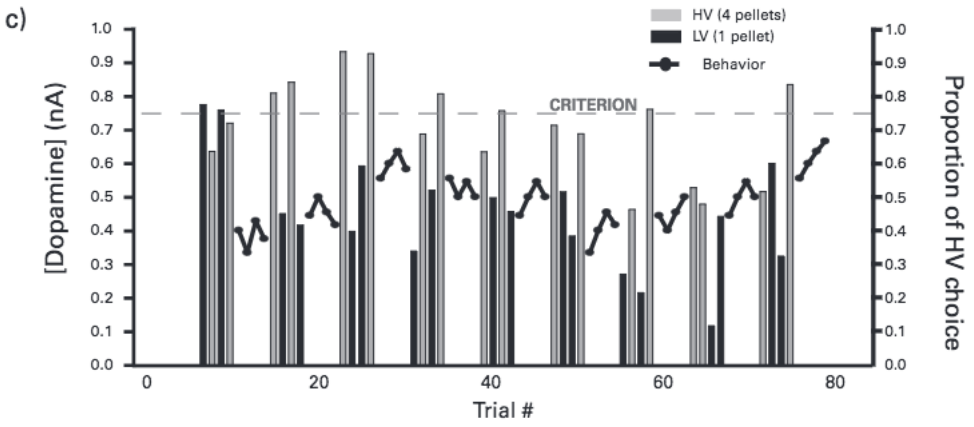
Given the large literature implicating dopamine as critical to enabling a large number of rewarded behaviors, this disconnection between NAc dopamine release and decision making raises the question of what role it does play in the control of behavior, particularly in instrumental settings. Up until here, the discussion of how motivation is translated to action has concentrated on how rewards help guide response selection, with little regard for how the reward is obtained. However, in order to make appropriate decisions, it is important to evaluate not only the potential benefits of a course of action, but also the costs, such as the anticipated amount of work that will be required to obtain such payoffs. All other factors being equal, animals will usually prefer to pursue goals that require less effort to achieve,[101] and several lines of evidence demonstrate that animals' choices are weighted by both the costs and benefits of the available options, with animals tolerating increasing costs for higher-value rewards.[7,38,111] Moreover, such decisions are influenced by the current motivational state of the animal, with food-deprived animals being more willing to put in work to achieve reward than those who have recently been given access to a meal.[37]

Importantly, lesion and pharmacology studies have implicated dopamine specifically in the NAc as being important to enabling cues to energize behavior and, in particular circumstances, to allowing animals to overcome effort constraints to obtain larger or more palatable reward.[91] This is particularly prominent in tasks where the less beneficial outcome is a readily available primary reward (for instance, laboratory chow freely available in an operant box) whereas the availability of the larger reward at greater response cost is signaled by a conditioned stimulus (e.g., the presence of the lever in the operant box).

To address how response costs are represented by phasic NAc dopamine release, Gan and colleagues tested animals on the two-option decision-making task described


a)
[Dopamine] (nA)
1.50
1.25
1.00
0.75
0.50
0.25
0.00
HV (4 pellets)
LV (1 pellet)
AVERAGE CRITERION
Forced block 1
Choices
Forced block 2
Choices
Forced block 3
Choices
Forced block 4
Choices
Forced block 5
Choices
Forced block 6
Choices
Forced block 7
Choices
Forced block 8
Choices
Forced block 9
Choices
Forced block 10
Forced blocks from beginning of session


b)
[Dopamine] (nA)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
CRITERION
HV (4 pellets)
LV (1 pellet)
Forced block -5
Choices
Forced block -4
Choices
Forced block -3
Choices
Forced block -2
Choices
Forced block -1
Choices
Forced block +1
Choices
Forced block +2
Choices
Forced block +3
Choices
Forced block +4
Forced Blocks before and after reaching behavioral criterion


c)
[Dopamine] (nA)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
HV (4 pellets)
LV (1 pellet)
Behavior
CRITERION
0
20
40
60
80
Trial #
Proportion of HV choice

earlier (figure 10.2a), except that now the reward magnitude associated with each option was the same and value was instead manipulated by altering the number of lever presses required to obtain the reward.[39] The cost parameters were set such that they had comparable motivating effects on choice behavior as the reward manipulation had, with animals rapidly learning to prefer the low-cost option. Nonetheless, in spite of this preference, in most cases, dopamine did not encode an effort-discounted value signal (figure 10.4). One exception was in situations where the response cost was unexpectedly lower than the reference cost, where dopamine release preferentially encoded the low-cost option; however, after repeated experience of these contingencies, even this scaling with net value disappeared. This lack of encoding of upcoming response costs by NAc phasic dopamine was also recently observed in a more dynamic, progressive ratio paradigm where responses costs escalate as a function of the animals' past choices.[112]

These findings may initially seem surprising given that disruption of dopamine affects allocation of effortful actions. However, they can be reconciled by considering such cost-benefit trade-offs in terms of utility curves depicting the amount of effort expenditure an animal would put in to obtain an expected future payoff given its current motivational state.[79] In such a framework, mesolimbic dopamine might participate in encoding the availability of particular sizes of future payoffs with reference to the work required to reach these goals such that appropriate cost expenditures can be set. Somewhat paradoxically, to provide useful input to such a computation, the phasic dopamine signal elicited by a predictive cue would itself have to be impartial to movement-related response costs. Moreover, this would allow for separate updating of predictions about the costs and benefits of a course of action when discrepancies are detected, something that would not be possible if dopamine signaled the overall net utility of a course of action.

Dopamine, Salience, and a Motivation to Learn?

Under this model, the mesolimbic dopamine system plays an important but limited role in translating motivation into action. Specifically, phasic dopamine release

Figure 10.3
Dopamine, learning, and choices. (a) Average dopamine release in forced trials from the beginning of the session (signals on choice trials are not depicted). On average, animals reached the ≥75% high-reward choices between forced blocks 6 and 7. (b) Average dopamine release in forced trials centered on the point at which each animal reached the behavioral criterion in each session. As signals were, on average, 1.5 to 2 times as large on the first of the forced trials as on any other trial in a session, data from these first high- and low-reward forced trials have been removed. (c) Behavioral choice and dopamine release for an example animal that never reached the behavioral criterion in one particular session. Smoothed choice performance is depicted by the black dots, peak forced trial dopamine by the red and blue bars.

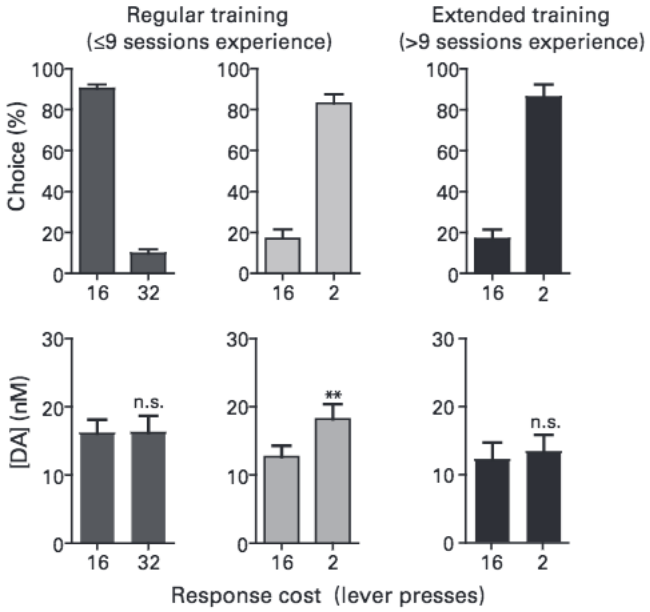


Figure 10.4
Post-behavioral criterion choices (upper panels) and average dopamine release (lower panels) to cues predicting different effort requirements (lever presses) to gain the reward in the two-option decision-making task of Gan et al.,[39] redrawn with permission. Animals were tested after having either ≤ 9 (left-hand and center panels) or > 9 sessions experience (right-hand panel) of the effort contingencies prior to recording session.

enables environmental stimuli to promote, but not control, responses as a function of their anticipated benefits in allowing animals to seek potentially costly rewards. This naturally raises the question of what in a natural environment might be considered "beneficial" to an animal? Moreover, how does this fit in with the abundant evidence suggesting an important role for dopamine in learning?

It has been known for some time that novel, salient stimuli cause rapid increases in the firing rates of putative dopamine neurons, sometimes even in the absence of appetitive consequences.[15,49,57] Redgrave and colleagues have pointed out that the latency of firing of dopamine neurons to the presentation of a simple visual stimulus is sufficiently fast to normally occur prior to any orienting response to that stimulus,[82] suggesting that dopamine serves as a marker for unpredictable events rather than as an indicator of upcoming reward value.[81]

Even in situations where the task rules are known, there is still evidence that the initial presentation of cues can cause increased levels of phasic dopamine activity, if the task contingencies (for example, the reward sizes or response costs) are not known. Analyzing NAc dopamine release from interleaved sessions of discrete trial

fixed and progressive ratio tasks, Wanat and colleagues found that phasic signals to the first cue signaling the opportunity to response evoked on average about 50 to 100% more dopamine than that in all other trials.[112] As there was only one available response option, such increased release could be caused either by the unpredictable timing of the start of the session or by a prediction error for the incentive properties of the entire session.

However, neither of these explanations easily accounts for the patterns of release observed early in a session during the two-option decision-making task of Gan and colleagues.[39] In each session, the first four trials of each session were forced (two presentations of either the left or right option in pseudorandom order). As can be observed in figure 10.3a, phasic changes in dopamine transmission elicited by the first presentation of cues to be associated with high reward or low reward was substantially larger than anything else in the session. This was not dependent on the cost-benefit contingencies in the previous session or the order of presentation of the forced trials, demonstrating that it does not simply reflect previous associations or anticipation of all the rewards to be obtained in the coming session. Moreover, when the same option was presented on both of the first two forced trials of a session, the dopamine signal on the next trial to the alternative cue was significantly larger than release to the second presentation on the previous trial of the other cue (Walton, Gan, and Phillips, unpublished observations).

While the general setup did not change from session to session in this paradigm, the assignment cost-benefit contingencies consistently reversed between sessions, meaning that animals were required to learn new cue-outcome associations to guide appropriate behavior. In a separate study, dopamine neuron activity was modulated by the requirement to learn about an outcome in a multistep-decision task where animals had to learn using positive and negative reinforcement a three-target sequence and then repeat it twice.[92] Firing rates were lower on the first repeat trial than on the second or third search trial despite the expected value of the repeat trial (i.e., the reward probability) being higher than either of the search trials. Moreover, here, as in the earlier studies of Pavlovian conditioning, dopamine also seemed permissive of responding, with responses to cues of identical value being larger when reaction times were shorter. The size of cue-evoked responses also correlated positively with activity at the time of reward delivery, suggesting that moment-by-moment fluctuations in drive to learn about cues might have influenced the effectiveness of reinforcers update predictions. In a separate study, the responses of dopamine neurons correlated with a strong bias that monkeys exhibited to seek advanced information about future rewards.[13]

In the wild, the future benefits of a course of action are frequently not fully known. Yet in spite of this uncertainty, which should logically reduce the expected value of an outcome, all foraging species are believed to have a drive to explore

unknown elements of their surroundings.[75] It is known that, as well as the connection between dopamine and novelty, NAc dopamine lesions can disrupt the long-lasting potentiation of so-called adjunctive motivated behaviors such as drinking, gnawing, or wheel running evoked by cues following receipt of a food reward.[86] The preceding evidence suggests that one function of phasic mesolimbic dopamine may be to provide an opportunistic drive in response to environmental stimuli to motivate animals to seek out potential future rewards to satisfy their current needs. Simultaneously, dopamine release might in turn facilitate learning about predictors of the structure of their environment by changing synaptic plasticity and modulating the excitability of output neurons within the targets of the mesolimbic dopamine system. This might explain why phasic dopamine release in the study by Gan and colleagues did represent the net utility of effort when the cost contingency was unexpectedly low compared to the standard response cost, yet after extended training reflected only the pending reward magnitude of the benefit and not the associated costs. Collectively, such a system would provide what Horwitz and colleagues have called a "good parent,"[48] promoting appropriate behaviors to help reduce uncertainty and gain benefits even when costs have to be overcome. Future experiments comparing changeable versus static environments will be important to further elucidate these functions.

Caveats and Conclusions

It is worth noting that several important issues concerning the role of dopamine in translating motivation to action have largely been sidestepped in this chapter. First, what role does dopamine release at different time scales play in these functions? We have concentrated here on phasic changes in dopamine-mediated activity and release. However, modulations in background tonic dopamine levels can be detected across minutes. Even within the phasic range, alterations in the firing rate of midbrain dopamine cells can happen as rapidly as 70 to 100 msec following the presentation of a salient visual stimulus, yet can also occur across several seconds during states such as uncertainty.[94] Moreover, it has recently been suggested that the dynamics of firing rates within hundreds of seconds may convey different types of information, including salience, timing, and value.[13,71] It will be important to determine how these different modes of transmission affect control of behavior.

Second, all the studies discussed have investigated how dopamine modulates animals' responses to positive reinforcers. However, it is evident that aversive events may also be strongly motivating. While it had been thought for a long time that dopamine neurons mainly coded positive prediction errors and were uniformly

inhibited by negative prediction errors or aversive events,[94,106] new evidence indicates that this may have been a simplification, as dopamine cells, particularly those more dorsolateral within SNc, have been found to be excited by stimuli associated with aversive consequences as well as the aversive air puff itself.[59]

This also relates to a third important area requiring consideration, namely, how the modulatory role ascribed to the mesolimbic dopamine system relates to the functions of the nigrostriatal dopamine projection to dorsal parts of the striatum and to the mesocortical projection to thalamus and cortex. Do the same computational principles apply to each set of pathways, with the specific function of each being determined by the connectivity and local circuits of the terminal regions, or is the information conveyed by each system markedly distinct? Does this separation relate in any way to the nature of the representations, in terms of stimulus versus action values and goal-directed versus habitual response selection? Though the answers to these questions are far from clear, it is apparent that the different dopamine systems interact during learning and choice behavior to promote appropriate adaptive behavior.[3,10]

Manipulations of the mesolimbic dopamine pathways affect the motivation of humans and animals to act and the decisions they ultimately take. The firing patterns of midbrain dopamine neurons and dopamine release in the NAc reflect predictions of future benefits evoked by environmental stimuli. This appears to be important for prompting animals to seek rewards to satisfy their internal needs, particularly in situations where the structure of the environment remains unknown. Nonetheless, phasic dopamine release appears to be only indirectly related to the choices made by an animal in instrumental situations. Instead, by signaling the benefits of pending payoffs separate to response costs, dopamine may provide a positive component to computations of the overall utility of a course of action in enabling animals to overcome response costs. This may be crucial in uncertain environments to allowing animals to explore novel options and motivating animals to learn. However, in situations where the dopamine system fails to be appropriately regulated, such as certain neuropsychiatric disorders or through the effects of pharmacological agents, this may cause loss of control over behavior and an increase in impulsive choices.[14,23]

Acknowledgments

The preparation of this manuscript was supported by a Wellcome Trust Research Career Development Fellowship to MEW. The work depicted in figures 10.2 through 10.4 was funded by the National Institutes of Health (R01-MH079292, R21-AG030775, P.E.M.P.). The authors have no competing interests.

Outstanding Questions

• What role does dopamine release in different striatal (and cortical) regions play in the control of behavior? Are the dynamics of phasic dopamine release different in these regions? If so, what factors control when, where, and how much dopamine is released within restricted regions?

• There are multiple influences on behavior and multiple representations of value in the brain. Theoretically, phasic dopamine cell firing and release seem to correlate better with predictions of a "habitlike" system. However, little work has been done to date probe how dopamine might represent richer "goal" values. The presence of anatomical connections allowing midbrain dopamine cells to receive information and to influence hypothalamic motivational state signals makes this a pressing question.

• Dopamine is clearly involved in learning and representing the predicted state of the world. But what factors are included in such a representation: simply the mean expected benefits in a particular context, or a complex set of factors such as the mean and known variance of reward, uncertainty in these estimates, and learning rates?

Further Reading

Special issue of the journal *Psychopharmacology* (2007, 191; 3). Many detailed and differing perspectives on dopamine can be found within this special issue, including a paper by two of this chapter's authors that sets out the theoretical framework behind many of the ideas contained here.

Kehagia AA, Murray GK, Robbins TW. 2010. Learning and cognitive flexibility: frontostriatal function and monoaminergic modulation. *Curr Opin Neurobiol* 20: 199–204. An interesting recent review looking at dopamine, cognitive control, and behavioral flexibility, and also broadening out the question to include other monoamines and frontostriatal circuits.

References

1. Ahn S, Phillips AG. 1999. Dopaminergic correlates of sensory-specific satiety in the medial prefrontal cortex and nucleus accumbens of the rat. *J Neurosci* 19(RC29): 21–26.

2. Aragona BJ, Day JJ, Roitman MF, Cleaveland NA, Wightman RM, Carelli RM. 2009. Regional specificity in the real-time development of phasic dopamine transmission patterns during acquisition of a cue-cocaine association in rats. *Eur J Neurosci* 30: 1889–1899.

3. Ashby FG, Turner BO, Horvitz JC. 2010. Cortical and basal ganglia contributions to habit learning and automaticity. *Trends Cogn Sci* 14: 208–215.

4. Balleine BW, Dickinson A. 1998. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology* 37: 407–419.

5. Bassareo V, De Luca MA, Di Chiara G. 2002. Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. *J Neurosci* 22: 4709–4719.

6. Bassareo V, Di Chiara G. 1999. Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *Eur J Neurosci* 11: 4389–4397.

7. Bautista LM, Tinbergen J, Kacelnik A. 2001. To walk or to fly? How birds choose among foraging modes. *Proc Natl Acad Sci USA* 98: 1089–1094.

8. Bayer HM, Glimcher PW. 2005. Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron* 47: 129–141.

9. Beaulieu JM, Gainetdinov RR, Caron MG. 2007. The Akt-GSK-3 signaling cascade in the actions of dopamine. *Trends Pharmacol Sci* 28: 166–172.

10. Belin D, Jonkman S, Dickinson A, Robbins TW, Everitt BJ. 2009. Parallel and interactive learning processes within the basal ganglia: relevance for the understanding of addiction. *Behav Brain Res* 199: 89–102.

11. Berridge KC, Robinson TE. 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Behav Brain Res Rev* 28: 309–369.

12. Borgland SL, Taha SA, Sarti F, Fields HL, Bonci A. 2006. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. *Neuron* 49: 589–601.

13. Bromberg-Martin ES, Hikosaka O. 2009. Midbrain dopamine neurons signal preference for advance information about upcoming rewards. *Neuron* 63: 119–126.

14. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, et al. 2010. Dopaminergic network differences in human impulsivity. *Science* 329: 532.

15. Bunzeck N, Duzel E. 2006. Absolute coding of stimulus novelty in the human substantia nigra/VTA. *Neuron* 51: 369–379.

16. Cannon CM, Palmiter RD. 2003. Reward without dopamine. *J Neurosci* 23: 10827–10831.

17. Caraco T, Martindale S, Whittam T-S. 1980. An empirical demonstration of risk-sensitive foraging preferences. *Anim Behav* 28: 820–830.

18. Carlsson A, Lindqvist M, Magnusson T. 1957. 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature* 180: 1200.

19. Clark JJ, Sandberg SG, Wanat MJ, Gan JO, Horne EA, Hart AS, Akers CA, et al. 2010. Chronic microsensors for longitudinal, subsecond dopamine detection in behaving animals. *Nat Methods* 7: 126–129.

20. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. 2002. Motivation, reward, and Parkinson's disease: influence of dopatherapy. *Neuropsychologia* 40: 2257–2267.

21. Dagher A, Robbins TW. 2009. Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron* 61: 502–510.

22. Dalley JW, Chudasama Y, Theobald DE, Pettifer CL, Fletcher CM, Robbins TW. 2002. Nucleus accumbens dopamine and discriminated approach learning: interactive effects of 6-hydroxydopamine lesions and systemic apomorphine administration. *Psychopharmacology (Berl)* 161: 425–433.

23. Dalley JW, Fryer TD, Brichard L, Robinson ES, Theobald DE, Laane K, Pena Y, et al. 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. *Science* 315: 1267–1270.

24. Dalley JW, Laane K, Theobald DE, Armstrong HC, Corlett PR, Chudasama Y, Robbins TW. 2005. Time-limited modulation of appetitive Pavlovian memory by D1 and NMDA receptors in the nucleus accumbens. *Proc Natl Acad Sci USA* 102: 6189–6194.

25. Dayan P, Balleine BW. 2002. Reward, motivation, and reinforcement learning. *Neuron* 36: 285–298.

26. De Wit H, Wise RA. 1977. Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine. *Can J Psychol* 31: 195–203.

27. Deminiere JM, Piazza PV, Le Moal M, Simon H. 1989. Experimental approach to individual vulnerability to psychostimulant addiction. *Neurosci Biobehav Rev* 13: 141–147.

28. Di Chiara G, Imperato A. 1988. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc Natl Acad Sci USA* 85: 5274–5278.

29. Di Ciano P, Cardinal RN, Cowell RA, Little SJ, Everitt BJ. 2001. Differential involvement of NMDA, AMPA/kainate, and dopamine receptors in the nucleus accumbens core in the acquisition and performance of pavlovian approach behavior. *J Neurosci* 21: 9471–9477.

30. Duzel E, Bunzeck N, Guitart-Masip M, Wittmann B, Schott BH, Tobler PN. 2009. Functional imaging of the human dopaminergic midbrain. *Trends Neurosci* 32: 321–328.

31. Everitt BJ, Dickinson A, Robbins TW. 2001. The neuropsychological basis of addictive behaviour. *Brain Res Brain Res Rev* 36: 129–138.

32. Everitt BJ, Robbins TW. 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 8: 1481–1489.

33. Fibiger HC, LePiane FG, Jakubovic A, Phillips AG. 1987. The role of dopamine in intracranial self-stimulation of the ventral tegmental area. *J Neurosci* 7: 3888–3896.

34. Fields HL, Hjelmstad GO, Margolis EB, Nicola SM. 2007. Ventral tegmental area neurons in learned appetitive behavior and positive reinforcement. *Annu Rev Neurosci* 30: 289–316.

35. Fiorillo CD, Newsome WT, Schultz W. 2008. The temporal precision of reward prediction in dopamine neurons. *Nat Neurosci* 11: 966–973.

36. Fiorillo CD, Tobler PN, Schultz W. 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. *Science* 299: 1898–1902.

37. Floresco SB, Ghods-Sharifi S. 2007. Amygdala-prefrontal cortical circuitry regulates effort-based decision making. *Cereb Cortex* 17: 251–260.

38. Floresco SB, Onge JR, Ghods-Sharifi S, Winstanley CA. 2008. Cortico-limbic-striatal circuits subserving different forms of cost-benefit decision making. *Cogn Affect Behav Neurosci* 8: 375–389.

39. Gan JO, Walton ME, Phillips PE. 2010. Dissociable cost and benefit encoding of future rewards by mesolimbic dopamine. *Nat Neurosci* 13: 25–27.

40. Garris PA, Kilpatrick M, Bunin MA, Michael D, Walker QD, Wightman RM. 1999. Dissociation of dopamine release in the nucleus accumbens from intracranial self-stimulation. *Nature* 398: 67–69.

41. Geisler S, Derst C, Veh RW, Zahm DS. 2007. Glutamatergic afferents of the ventral tegmental area in the rat. *J Neurosci* 27: 5730–5743.

42. Grace AA, Bunney BS. 1983. Intracellular and extracellular electrophysiology of nigral dopaminergic neurons—2. Action potential generating mechanisms and morphological correlates. *Neuroscience* 10: 317–331.

43. Grace AA, Bunney BS. 1984. The control of firing pattern in nigral dopamine neurons: burst firing. *J Neurosci* 4: 2877–2890.

44. Grace AA, Bunney BS. 1984. The control of firing pattern in nigral dopamine neurons: single spike firing. *J Neurosci* 4: 2866–2876.

45. Hare TA, Camerer CF, Rangel A. 2009. Self-control in decision-making involves modulation of the vmPFC valuation system. *Science (New York, NY)* 324: 646–648.

46. Hodos W. 1961. Progressive ratio as a measure of reward strength. *Science* 134: 943–944.

47. Holland PC, Rescorla RA. 1975. Second-order conditioning with food unconditioned stimulus. *J Comp Physiol Psychol* 88: 459–467.

48. Horvitz JC, Choi WY, Morvan C, Eyny Y, Balsam PD. 2007. A "good parent" function of dopamine: transient modulation of learning and performance during early stages of training. *Ann N Y Acad Sci* 1104: 270–288.

49. Horvitz JC, Stewart T, Jacobs BL. 1997. Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat. *Brain Res* 759: 251–258.

50. Jiang H, Betancourt L, Smith RG. 2006. Ghrelin amplifies dopamine signaling by cross talk involving formation of growth hormone secretagogue receptor/dopamine receptor subtype 1 heterodimers. *Mol Endocrinol* 20: 1772–1785.

51. Joel D, Weiner I. 2000. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 96: 451–474.

52. Kish SJ, Shannak K, Hornykiewicz O. 1988. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med* 318: 876–880.

53. Kobayashi S, Schultz W. 2008. Influence of reward delays on responses of dopamine neurons. *J Neurosci* 28: 7837–7846.

54. Koob GF, Riley SJ, Smith SC, Robbins TW. 1978. Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. *J Comp Physiol Psychol* 92: 917–927.

55. Krugel U, Schraft T, Kittner H, Kiess W, Illes P. 2003. Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *Eur J Pharmacol* 482: 185–187.

56. Leentjens AF, Dujardin K, Marsh L, Martinez-Martin P, Richard IH, Starkstein SE, Weintraub D, et al. 2008. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. *Mov Disord* 23: 2004–2014.

57. Ljungberg T, Apicella P, Schultz W. 1992. Responses of monkey dopamine neurons during learning of behavioral reactions. *J Neurophysiol* 67: 145–163.

58. Martinelli M, Rudick CN, Hu XT, White FJ. 2006. Excitability of dopamine neurons: modulation and physiological consequences. *CNS Neurol Disord Drug Targets* 5: 79–97.

59. Matsumoto M, Hikosaka O. 2009. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459: 837–841.

60. Mazzoni P, Hristova A, Krakauer JW. 2007. Why don't we move faster? Parkinson's disease, movement vigor, and implicit motivation. *J Neurosci* 27: 7105–7116.

61. Miliaressis E, Emond C, Merali Z. 1991. Re-evaluation of the role of dopamine in intracranial self-stimulation using in vivo microdialysis. *Behav Brain Res* 46: 43–48.

62. Mirenowicz J, Schultz W. 1994. Importance of unpredictability for reward responses in primate dopamine neurons. *J Neurophysiol* 72: 1024–1027.

63. Misgeld U. 2004. Innervation of the substantia nigra. *Cell Tissue Res* 318: 107–114.

64. Mogenson GJ, Jones DL, Yim CY. 1980. From motivation to action: functional interface between the limbic system and the motor system. *Prog Neurobiol* 14: 69–97.

65. Morris G, Nevet A, Arkadir D, Vaadia E, Bergman H. 2006. Midbrain dopamine neurons encode decisions for future action. *Nat Neurosci* 9: 1057–1063.

66. Moss J, Bolam JP. 2010. The relationship between dopaminergic axons and glutamatergic synapses in the striatum: Structual considerations. In: Dopamine Handbook (Iversen LL, Iversen SD, Dunnett SB, Bjorklund A, eds), pp 49–59. New York: Oxford University Press.

67. Mountcastle VB. 1974. Medical Physiology, 13th Ed. St Louis: Mosby & Co.

68. Nader MA, Czoty PW, Gould RW, Riddick NV. 2008. Positron emission tomography imaging studies of dopamine receptors in primate models of addiction. *Philos Trans R Soc Lond B Biol Sci* 363: 3223–3232.

69. Neve KA, Seamans JK, Trantham-Davidson H. 2004. Dopamine receptor signaling. *J Recept Signal Transduct Res* 24: 165–205.

70. Niv Y, Rivlin-Etzion M. 2007. Parkinson's disease: fighting the will? *J Neurosci* 27: 11777–11779.

71. Nomoto K, Schultz W, Watanabe T, Sakagami M. 2010. Temporally extended dopamine responses to perceptually demanding reward-predictive stimuli. *J Neurosci* 30: 10692–10702.

72. Oakman SA, Faris PL, Kerr PE, Cozzari C, Hartman BK. 1995. Distribution of pontomesencephalic cholinergic neurons projecting to substantia nigra differs significantly from those projecting to ventral tegmental area. *J Neurosci* 15: 5859–5869.

73. Olds J. 1969. The central nervous system and the reinforcement of behavior. *Am Psychol* 24: 114–132.

74. Olds J, Milner P. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J Comp Physiol Psychol* 47: 419–427.

75. Panksepp J. 1998. Affective Neuroscience. New York: Oxford University Press.

76. Parkinson JA, Dalley JW, Cardinal RN, Bamford A, Fehnert B, Lachenal G, Rudarakanchana N, Halkerston KM, Robbins TW, Everitt BJ. 2002. Nucleus accumbens dopamine depletion impairs both acquisition and performance of appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. *Behav Brain Res* 137: 149–163.

77. Paus T. 2001. Primate anterior cingulate cortex: where motor control, drive and cognition interface. *Nat Rev Neurosci* 2: 417–424.

78. Phillips PE, Stuber GD, Heien ML, Wightman RM, Carelli RM. 2003. Subsecond dopamine release promotes cocaine seeking. *Nature* 422: 614–618.

79. Phillips PE, Walton ME, Jhou TC. 2007. Calculating utility: preclinical evidence for cost-benefit analysis by mesolimbic dopamine. *Psychopharmacology (Berl)* 191: 483–495.

80. Platt ML, Glimcher PW. 1999. Neural correlates of decision variables in parietal cortex. *Nature* 400: 233–238.

81. Redgrave P, Gurney K. 2006. The short-latency dopamine signal: a role in discovering novel actions? *Nat Rev Neurosci* 7: 967–975.

82. Redgrave P, Prescott TJ, Gurney K. 1999. Is the short-latency dopamine response too short to signal reward error? *Trends Neurosci* 22: 146–151.

83. Remy P, Doder M, Lees A, Turjanski N, Brooks D. 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain* 128: 1314–1322.

84. Reynolds JN, Hyland BI, Wickens JR. 2001. A cellular mechanism of reward-related learning. *Nature* 413: 67–70.

85. Robbins TW, Everitt BJ. 1992. Functions of dopamine in the dorsal and ventral striatum. *Semin Neurosci* 4: 119–127.

86. Robbins TW, Koob GF. 1980. Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. *Nature* 285: 409–412.

87. Robinson DL, Heien ML, Wightman RM. 2002. Frequency of dopamine concentration transients increases in dorsal and ventral striatum of male rats during introduction of conspecifics. *J Neurosci* 22: 10477–10486.

88. Robinson S, Sandstrom SM, Denenberg VH, Palmiter RD. 2005. Distinguishing whether dopamine regulates liking, wanting, and/or learning about rewards. *Behav Neurosci* 119: 5–15.

89. Roesch MR, Calu DJ, Schoenbaum G. 2007. Dopamine neurons encode the better option in rats deciding between differently delayed or sized rewards. *Nat Neurosci* 10: 1615–1624.

90. Roitman MF, Stuber GD, Phillips PE, Wightman RM, Carelli RM. 2004. Dopamine operates as a subsecond modulator of food seeking. *J Neurosci* 24: 1265–1271.

91. Salamone JD, Correa M, Farrar A, Mingote SM. 2007. Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology (Berl)* 191: 461–482.

92. Satoh T, Nakai S, Sato T, Kimura M. 2003. Correlated coding of motivation and outcome of decision by dopamine neurons. *J Neurosci* 23: 9913–9923.

93. Schultz W. 1998. Predictive reward signal of dopamine neurons. *J Neurophysiol* 80: 1–27.

94. Schultz W. 2007. Multiple dopamine functions at different time courses. *Annu Rev Neurosci* 30: 259–288.

95. Schultz W, Dayan P, Montague P. 1997. A neural substrate of prediction and reward. *Science* 275: 1593.

96. Semba K, Fibiger HC. 1992. Afferent connections of the laterodorsal and the pedunculopontine tegmental nuclei in the rat: a retro- and antero-grade transport and immunohistochemical study. *J Comp Neurol* 323: 387–410.

97. Shi WX. 2005. Slow oscillatory firing: a major firing pattern of dopamine neurons in the ventral tegmental area. *J Neurophysiol* 94: 3516–3522.

98. Shizgal P. 1989. Toward a cellular analysis of intracranial self-stimulation: contributions of collision studies. *Neurosci Biobehav Rev* 13: 81–90.

99. Shizgal P. 1997. Neural basis of utility estimation. *Curr Opin Neurobiol* 7: 198–208.

100. Sienkiewicz-Jarosz H, Scinska A, Kuran W, Ryglewicz D, Rogowski A, Wrobel E, Korkosz A, Kukwa A, Kostowski W, Bienkowski P. 2005. Taste responses in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 76: 40–46.

101. Solomon RL. 1948. The influence of work on behavior. *Psychol Bull* 45: 1–40.

102. Szczypka MS, Kwok K, Brot MD, Marck BT, Matsumoto AM, Donahue BA, Palmiter RD. 2001. Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice. *Neuron* 30: 819–828.

103. Takada M, Tokuno H, Hamada I, Inase M, Ito Y, Imanishi M, Hasegawa N, Akazawa T, Hatanaka N, Nambu A. 2001. Organization of inputs from cingulate motor areas to basal ganglia in macaque monkey. *Eur J Neurosci* 14: 1633–1650.

104. Tindell AJ, Berridge KC, Zhang J, Pecina S, Aldridge JW. 2005. Ventral pallidal neurons code incentive motivation: amplification by mesolimbic sensitization and amphetamine. *Eur J Neurosci* 22: 2617–2634.

105. Tobler PN, Fiorillo CD, Schultz W. 2005. Adaptive coding of reward value by dopamine neurons. *Science* 307: 1642–1645.

106. Ungless MA, Magill PJ, Bolam JP. 2004. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* 303: 2040–2042.

107. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. 2006. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. *J Neurosci* 26: 6583–6588.

108. Voon V, Fernagut PO, Wickens J, Baunez C, Rodriguez M, Pavon N, Juncos JL, Obeso JA, Bezard E. 2009. Chronic dopaminergic stimulation in Parkinson's disease: from dyskinesias to impulse control disorders. *Lancet Neurol* 8: 1140–1149.

109. Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM. 2004. Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci* 27: 468–474.

110. Walton ME, Behrens TE, Buckley MJ, Rudebeck PH, Rushworth MF. 2010. Separable learning systems in the macaque brain and the role of orbitofrontal cortex in contingent learning. *Neuron* 65: 927–939.

111. Walton ME, Kennerley SW, Bannerman DM, Phillips PE, Rushworth MF. 2006. Weighing up the benefits of work: behavioral and neural analyses of effort-related decision making. *Neural Netw* 19: 1302–1314.

112. Wanat MJ, Kuhnen CM, Phillips PE. 2010. Delays conferred by escalating costs modulate dopamine release to rewards but not their predictors. *J Neurosci* 30: 12020–12027.

113. Wanat MJ, Willuhn I, Clark JJ, Phillips PE. 2009. Phasic dopamine release in appetitive behaviors and drug addiction. *Curr Drug Abuse Rev* 2: 195–213.

114. Whalen PJ, Bush G, Shin LM, Rauch SL. 2006. The emotional counting Stroop: a task for assessing emotional interference during brain imaging. *Nat Protoc* 1: 293–296.

115. Wilson C, Nomikos GG, Collu M, Fibiger HC. 1995. Dopaminergic correlates of motivated behavior: importance of drive. *J Neurosci* 15: 5169–5178.

116. Wise RA. 1978. Catecholamine theories of reward: a critical review. *Brain Res* 152: 215–247.

117. Wise RA. 2004. Dopamine, learning and motivation. *Nat Rev Neurosci* 5: 483–494.

118. Wise RA. 2006. Role of brain dopamine in food reward and reinforcement. *Philos Trans R Soc Lond B Biol Sci* 361: 1149–1158.

119. Wise RA. 2009. Roles for nigrostriatal—not just mesocorticolimbic—dopamine in reward and addiction. *Trends Neurosci* 32: 517–524.

120. Yun IA, Wakabayashi KT, Fields HL, Nicola SM. 2004. The ventral tegmental area is required for the behavioral and nucleus accumbens neuronal firing responses to incentive cues. *J Neurosci* 24: 2923–2933.