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Is the Short Latency Dopamine Burst Too Short to Signal Reward Error ?

Peter Redgrave, Tony J. Prescott and Kevin Gurney

Department of Psychology, University of Sheffield, Sheffield, S10 2TP, U.K.

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Corresponding Author: Dr. Peter Redgrave, Dept. Psychology, University of Sheffield, Sheffield, S10 2TP, U.K. e-mail: P.Redgrave@sheffield.ac.uk.

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Unexpected stimuli which are behaviourally significant have the capacity to evoke a short latency, short duration burst of firing in mesencephalic dopamine neurones. An influential interpretation of the experimental data characterising this response proposes that dopamine neurones play a critical role in reinforcement learning by signalling errors in the prediction of future reward. In the present viewpoint we propose a different functional role for the short latency dopamine response in the mechanisms of associative learning. We suggest that the initial burst of dopaminergic firing may represent an essential component in the process of switching attentional and behavioural selections to unexpected, behaviourally important stimuli. This switching response could be a critical prerequisite for associative learning and may be part of a general short latency reaction, mediated by catecholamines, which prepares the organism to react appropriately to biologically significant events.

Introduction: "Any act which in a given situation produces satisfaction becomes associated with that situation so that when the situation recurs the act is more likely than before to recur also". Although the effects of positive and negative reinforcement on behaviour have been known for centuries, Thorndike [1] in this statement formalised the linking of action to situation on the basis of outcome. It also emphasises two of the principal functions of rewarding or appetitive stimuli: to produce satisfaction (hedonia) and to adjust the probabilities of selecting immediately preceding actions. A third, often recognised function of rewarding stimuli is to elicit approach and consummatory behaviour [2]. While the neural mechanisms mediating any of these processes have yet to be identified in detail, much evidence points to the vertebrate basal ganglia playing a central role [3]. Numerous investigations of this system using a wide range of experimental techniques suggest that ascending dopaminergic projections from the ventral midbrain (substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA)) to the striatum (caudate, putamen and nucleus accumbens) provide essential signals for reinforcement learning [2, 4, 5]. Currently, a popular view is that dopaminergic input to the striatum provides the reinforcement signal required to adjust the probabilities of subsequent action selection [4-7]. A particularly important and influential part of the evidence supporting this view concerns the short latency, short duration response of dopamine cells observed after the unexpected presentation of a behaviourally significant stimulus [2, 8]. This response has been widely interpreted as providing the system with a reinforcement prediction error signal [5, 9]. We will, however, argue that the short latency burst of dopamine activity could have a rather different functional role. Specifically, we suggest that the short latency response may represent an important component of the processes responsible for re-allocating attentional and behavioural resources in favour of unexpected salient events. From this point in our discussion we will use this restricted sense of the term "switching" to denote re-allocation processes, and the word "salient" to refer to stimuli with special biological significance.

The short latency dopamine response: The essential characteristics of the dopamine response have been considered in several recent reviews [2, 5, 8, 10, 11] so we will provide only a brief summary of them here. Typically, dopamine neurones in several species

exhibit a burst of impulses immediately following unexpected (salient) events including sudden novel stimuli, intense sensory stimuli, primary rewards, and arbitrary stimuli classically conditioned by association with primary rewards (Figure 1). The response comprises a characteristic short latency (50-110 ms), short duration (<200 ms) burst of 3-6 spikes which is superimposed on spontaneous, low level single spike activity (1-9 spikes/s). The latency and duration of this initial burst of firing are comparatively stereotyped and are similar for all eliciting stimuli. A synchronised burst of activity is evoked in a significant proportion of dopamine cells throughout both the VTA and SNc on both sides of the brain. Electrotonic coupling between dopamine neurones is thought, in part, to contribute to this population response [10]. Given the divergent nature of the nigrostriatal projection it is presumed that the short latency burst produces a relatively non-differentiated wave of dopamine input to wide areas of the striatum.

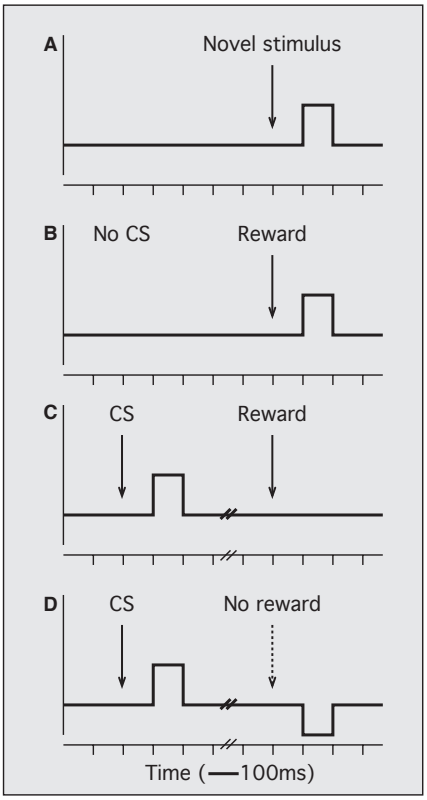

Fig. 1. A schematic illustration of dopamine cell responses to salient stimuli in different experimental conditions described by Schultz et al.[5, 8] A. The unexpected presentation of a novel stimulus evokes a burst of firing in a significant proportion of dopamine cells with a latency and duration of approximately 100ms. B. A similar response is elicited by unexpected primary rewards. C. When a conditioned stimulus (CS) reliably predicts a primary reward the burst of activity in dopamine cells transfers to the conditioned stimulus. D. After conditioning, if an anticipated (predicted) reward is not delivered there is a short pause (~100 ms) in the baseline activity approximately 100 ms after the anticipated time of delivery.

Short latency dopamine and learning: A particularly arresting feature of the short latency dopamine reaction is its propensity to change over time with repeated stimulus presentation and with changes in experimental context (for references see reviews by Schultz et al.[2, 8, 12]). For example, the response elicited by a novel event habituates rapidly when the stimulus is repeated in the absence of behaviourally relevant consequences (reward or punishment). In this case, habituation of the neuronal response appears to correlate with the diminishing capacity of the stimulus to elicit behavioural orienting. If the presentation of a primary reward is repeated in a predictable manner, the rewarding stimulus also loses its ability to evoke a dopamine response. The burst of dopamine activity will, however, gradually transfer to a predicting stimulus, such as a

light or tone, that reliably precedes the primary reward (Figure 1C). If, once a conditioned response has been established, the predicting stimuli is *not* followed by the expected reward, a reliable depression in the spontaneous activity of the dopamine neurones has been observed 50-100 ms after the time of expected reward delivery (Figure 1D). Finally, extensive overtraining in these experimental tasks produces a gradual attenuation of neuronal responses to conditioned stimuli as performance becomes highly stable and automatised.

The dopamine response to non-reward stimuli: The response of dopamine neurones to non-reward stimuli is related to precise experimental conditions. On the one hand it has been shown that the dopamine neurones react with a short burst of pulses when a monkey's hand touches a hidden morsel of food, but not when it touches similarly shaped non-food objects [8, 12]. It is also claimed that non-noxious, primary aversive stimuli, such as air puffs to the hand or drops of saline to the mouth, together with conditioned visual and auditory stimuli in active avoidance tasks, are largely ineffective in stimulating dopamine neurones [13]. On the other hand, the conditioned dopamine response can generalise to physically similar but non-rewarded stimuli. For instance, opening the door of an adjacent, but never baited, goal box reliably elicited both an orienting movement from the animal and a bursting response from the dopamine neurones [8].

Dopamine as an 'effective reinforcement signal': Largely on the basis of these characteristics Schultz and his colleagues [2, 5, 8, 12] propose that the short latency dopamine response is related to the reinforcing function of rewards. It is important to note that only unexpected rewards (or punishments) lead to the acquisition of new conditioned responses [14]—predicted reinforcement serves to maintain already established conditioned behaviour but is unable to promote the learning of new conditioned responses. The finding that dopaminergic activity is associated with unexpected rewards (or with stimuli previously associated with reward), and is suppressed when expected rewards fail to materialise, suggests it could indicate the difference (or error) between the predicted and actual reward and thereby provide the 'effective reinforcement signal' to a neural mechanism capable of associative learning. The short latency dopamine response has therefore inspired comparisons with artificial reinforcement learning techniques developed by researchers in machine learning [15], and several computational models of the basal ganglia viewed as a reinforcement learning system have been constructed on this basis [5, 9].

An alternative hypothesis: We, however, would like to consider an alternative interpretation of the data summarised above. Our view is based on a rather different assumption about the basic function of the short latency dopamine response. Recently we made a general proposal that vertebrate basal ganglia have evolved as a centralised selection device, specialised to resolve conflicts between multiple sub-systems competing for access to limited motor or cognitive resources [16, 17]. Within this framework selection operations implemented within the basal ganglia [3, 18] specifically disinhibit the sensorimotor connections of 'winning' competitors, while at the same time maintaining or increasing the inhibitory control over 'losing' competitors. This model extends the work of others [3, 18-23] who have also considered selection to be one of the core functions

of the basal ganglia. Within this framework an additional, often overlooked function of rewarding events can be distinguished. Before a rewarding stimulus can be approached and consumed it is first necessary to interrupt ongoing behaviour and switch attentional and behavioural resources to deal with the rewarding event. A plausible alternative function for the short latency dopamine response could therefore be to provide a signal that facilitates the re-allocation of limited behavioural and cognitive processing capacity towards *any* unexpected event of behavioural significance, including reward. The suggestion that dopamine may promote behavioural switching has previously been made with respect to the general effect of dopamine modulation on basal ganglia function (see below and [19, 24-26] for review).

It is our view that in most of the experimental paradigms concerned with the short-latency dopamine response, the presumed reward error function of the response is confounded with the animal switching attentional and/or behavioural strategy . In the specific case of reward-related stimuli, the animal invariably is required to stop whatever it is doing and switch, first to localise the reward, then to acquire and consume it.

The response to novel stimuli: The finding that unexpected novel or intense stimuli always elicit a robust dopamine response (Figure 1A) is consistent with the idea that this signal could play a role in the processes of terminating current selections and opening new ones. In contrast, the response to novel stimuli causes some difficulty for the 'effective reinforcement' hypothesis[5]. Presumably, a sudden novel event could be 'good' (directly or indirectly linked with reward), 'bad' (directly or indirectly linked with punishment) or 'indifferent' (no reinforcement consequences). If the dopamine neurones signal effective reward, it is not easy to see why they should classify *all* novel stimuli as "better-than-expected" thereby reinforcing or maintaining the behaviour which happens currently to be selected.

It is also particularly odd that this positive classification is made prior to, or at best, during the saccadic response designed to bring 'whatever the event is' on to the fovea for analysis (Figure 2). To appreciate this point it is necessary to recall that unexpected visual events normally elicit two distinct responses in units of the intermediate and deep layers of the superior colliculus (Figure 2A). Initially there is a short latency (~50ms) visual response (which is also present in the superficial sensory layers) followed by a longer latency (>150ms) pre-saccadic motor burst [27]. The latter response plays an important role in the initiation of saccadic eye movements which have even longer latencies, normally in the range of 180-200 ms (80-110 ms for express saccades)[28] . The function of the saccadic response is to bring the location of an unexpected event onto the fovea for more detailed analyses involving feature extraction and object recognition. In the light of our suggestion it is interesting to note that the short latency dopamine response seems to fit neatly between the sensory and pre-saccadic motor burst recorded in the primate superior colliculus (c.f. Figures 2A&2B). It may also be significant that it precedes the disinhibitory output signal from substantia nigra which is instrumental in facilitating the pre-saccadic burst recorded from tectal target neurones [29](Figure 2C). Why are these observations important? Because, if the dopamine neurones signal reward prediction error, the computations required to generate this signal would have to be

conducted *before* the animal switches it gaze to see what the stimulus was. In other words reward would have to be signalled before the identity of the stimulus is fully known. In the light of these considerations we suggest that the short latency dopamine reaction may be more plausibly associated with processes involved in diverting attention and behavioural resources to deal with unexpected salient stimuli.

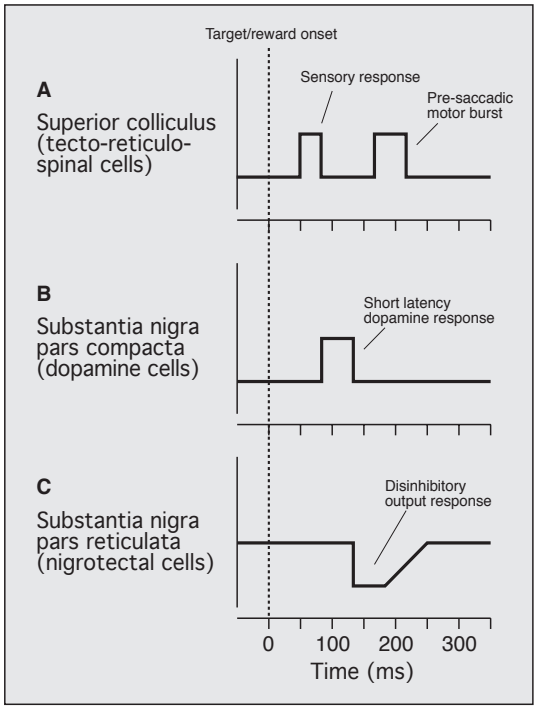

Fig. 2. Short latency dopamine responses occur prior to saccadic eye movements which bring unexpected events onto the fovea. **A.** An unexpected visual event typically elicits a short latency sensory reaction (~50ms) and a longer latency (>150ms) pre-saccadic motor burst in primate superior colliculus [27, 31]. **B.** The typical latency of dopamine cells to unexpected stimuli is 70-100 ms [2]. **C.** A significant visual stimulus elicits a disinhibitory output response from the basal ganglia which generally coincides with the pre-saccadic motor burst in collicular target neurones [29] i.e. >150 ms.

Response transfer to conditioned stimuli: So why do the dopamine cells appear able to distinguish stimuli that predict reward? It has been known for many years that evoked responses in primary sensory areas of the brain are influenced by reinforcement outcome [30]. For example, Wurtz and Goldberg[31] showed that non-reinforced presentation of light spots to a monkey quickly lead to habituation of the neuronal responses within collicular sensory receptive fields. However, by associating a stimulus with reward the previously habituated sensory response was greatly enhanced. Furthermore, it was shown that this enhancement was restricted to reward-related stimuli presented only within a cell's receptive field. Such observations rule out the possibility that the reward-related sensory enhancement was associated with a general effect of reward on arousal. Thus, if the magnitude of the representation of a stimulus in primary sensory networks can be influenced by association with reinforcing stimuli, then (assuming this parameter is available for extraction prior to object recognition) it could provide the required input to dopamine neurones to explain their responses to reward-predicting stimuli. In other words, the activity of dopamine neurones could simply reflect the habituation and reinforcement-related enhancement of stimulus-evoked activity in primary sensory networks. This suggestion precludes the need for the dopamine cells to extract the specific reinforcement value of a stimulus.

However, the question then arises, why then do the dopamine cells not respond to the delivery of signalled reward (Figure 1C)? One explanation might be that, where a classically conditioned stimulus predicts the reward, this predictor will itself initiate the selection of functional channels devoted to reward localisation, acquisition and consumption. If the function of the short latency dopamine response is to promote resource switching, the further facilitation of switching on reward delivery would be unnecessary, even counterproductive. This view would therefore predict that the normal activation of dopamine cells by signalled reward is suppressed as part of the conditioning process.

Response generalisation: It has been reported that a monkey will reliably interrupt on-going behaviour and orient to the opening of a never-baited box immediately adjacent to one providing reward [32]. The dopamine neurones also respond consistently to the 'never-rewarded' stimulus. The generalisation of classically conditioned activity evoked in primary sensory networks which relay input to the dopamine neurones may underlie these observations. On the other hand, if the function of dopamine neurones is to signal a reward prediction, it is difficult to see how the classification of consistently unrewarded stimuli as "better-than-expected" could be anything other than confusing to the learning system. It is interesting to note that, in fact, the system is not confused. Although the dopamine neurones respond, current behaviour is interrupted, and the animal orients, the monkey does not reach towards the never-baited goal box [32]. These results also suggest that the mechanisms used to assess the salience of an unexpected sensory event have insufficient resolution to distinguish the two similar boxes at predictably different locations. This could be seen as further evidence supporting our suggestion that short latency dopamine responses are initiated prior to object recognition.

Suppression of dopamine activity by reward omission: The brief pause in dopaminergic activity when an anticipated reward is not delivered is one of the important pieces of evidence used to support the 'effective reinforcement' hypothesis [5] (Figure 1D). However, there are also problems both with the generality of this suggestion and with its likely mechanism. First, an action can have a negative outcome not only if an expected reward fails to materialise, but also if it leads to an unexpected aversive or punishing stimulus. In both cases the future probability of selecting the action in similar circumstances should be reduced. It is, however, interesting that a corresponding dip in dopamine activity is not reliably observed when primary or conditioned aversive stimuli are presented [13]. If dopamine neurones signal effective reinforcement in a general model of conditioning, should their activity not also be depressed by aversive events? On the other hand, if the dopamine signal is used to facilitate behavioural switching, the dip in dopamine activity when expected reward is not delivered might have a different explanation. If the firing of dopamine neurones facilitates switching[24], reduced activity could suppress switching. When an expected outcome of an action unexpectedly fails to materialise the neural substrate for action selection must determine an appropriate response. However, immediately to suppress the previously selected actions may not be adaptive and certainly does not accord with experimental observations. For example, when continuous reinforcement delivery systems are suddenly disabled conditioned animals typically emit a vigorous burst of operant activity [33]. It is only later, after a

period of persistent non-reinforcement, that responses begin to extinguish. Both common sense and experimental data suggest, therefore, that the immediate response to the omission of expected reward is, in most circumstances, to "try it again". Viewed in the context of the present argument the initial persistence of operant responding in the absence of reward implies a reduced tendency to switch attention and behaviour. One possibility, therefore, is that the dip in dopamine activity following reward omission promotes a temporary increase in focus on currently selected channels. This suggestion is certainly consistent with evidence that animals with dopamine-depleting lesions show a marked tendency to persist in unrewarded operant behaviour [34].

Do dopamine neurones respond to aversive stimuli?: This is a critical issue which can separate the reinforcement-error hypothesis and the most general version of the switching hypotheses (that *all* stimuli with biological significance facilitate the re-allocation of limited processing resources by a mechanism which involves the short latency dopamine response). Since primary and conditioned aversive stimuli are particularly effective in terminating current behaviour and attracting attentional and behavioural resources, the general switching hypothesis would certainly predict that such stimuli would activate dopamine neurones. On this issue, however, there is much confusion. On the one hand, an extensive literature shows both that aversive and stressful events can increase the release of dopamine, and also that behaviour motivated by these stimuli is impaired by dopamine depletions [35]. On the other hand, electrophysiological observations in monkeys suggest that dopamine neurones are relatively insensitive to aversive stimuli [13]. There are, however, reasons to be cautious about the generality of the latter finding. First, as has been pointed out by Horvitz et al. [36], it may be unwise to draw general conclusions concerning the short latency reaction of dopamine neurones to aversive events on the basis of their response to a mild puff of air to the hand or a drop of saline to the tongue. It may therefore be important to test the sensitivity of dopamine cells to noxious stimuli that have a greater potential to interrupt and redirect ongoing behaviour. For example, the response of dopamine neurones to the repeated presentation of a stimulus which is initially novel, but is also noxious/aversive has yet to be tested. However, it has been noted that in anaesthetised animals dopamine cells often respond to frankly noxious stimuli with a long latency generally depressive reaction [37]. Unfortunately it is difficult to know how to interpret these observations since short latency excitatory responses to non-noxious stimuli were absent in the anaesthetised preparation.

A second reason for caution is that in published accounts of comparative tests of dopaminergic sensitivity to appetitive and aversive events [13], different responses were required for the two classes of stimuli. To avoid the mild aversive stimuli the monkey had only to break contact with a resting key. However, in the case of the appetitive stimuli the animal was required to release the resting key, then make an additional reaching movement to a lever which they had to touch to receive reward. Although it is known that dopamine neurones are relatively insensitive to movement [32], it is possible that a greater diversion of computational resources was required to complete the more demanding task used in the reward condition.

It is, however, important to note that if the comparative insensitivity of dopamine cells to aversive stimuli were to be confirmed by future investigations, we would then have to entertain the possibility that appetitive and aversive stimuli act via separate parallel mechanisms to influence attentional and behavioural selections. This position would be similar to that currently adopted by Schultz and his colleagues vis-à-vis unexpected stimuli representing negative reinforcement error[5]. It is important to recognise, however, that although the response of dopamine cells to aversive stimuli has important implications for our general switching hypothesis, is not strictly relevant to the restricted question of the response of dopamine cells to reward, and the general thesis that in current experimental paradigms reward is invariably confounded with a requirement for the animal to switch attention.

Switching: a consistent theme in dopamine research: The current proposal links well to experimental literature which, over several decades, has suggested that dopamine plays an important role in behavioural switching. It has been shown that a range of treatments which alter levels of dopamine neurotransmission affect various aspects of selection and behavioural switching in a variety of experimental paradigms [19, 24-26]. Depending on the site and nature of the intervention, these effects include changes in the dominance relations between behaviours, reductions or increases in switching relative to controls, changes in the variability of behaviour, and failure to complete behaviours. From such data Robbins and Sahakian [24] drew the general conclusion that mild to moderate increases in dopaminergic activity tend to facilitate switching while comparable reductions in transmission can suppress switching. It is possible that striatal dopaminergic neurotransmission could therefore play a general role in regulation of the frequency and timing of behavioural selections [20].

The short latency dopamine response and associative learning: The switching hypothesis outlined above raises the possibility that the short latency dopamine signal plays a more general role in associative learning than that proposed by the 'effective reinforcement' model [5]. The disruption of processes linking salient events with resource selection could explain why experimental manipulations of dopamine transmission can effect both positively and negatively reinforced associative learning [33], and associative learning in the absence of reinforcement [38]. For example, consider the phenomenon of latent inhibition where non-reinforced exposure to a stimulus reduces the 'associability' of that stimulus when it is later paired with a primary reward [39]. The slowing of conditioning that occurs in these circumstances may, in part, arise from the inability of the pre-habituated stimulus to evoke a short latency dopamine response[2]. The fact that latent inhibition is disrupted by dopamine agonists such as amphetamine and enhanced by dopamine blockers [39] supports this view. In terms of the current hypothesis, latent inhibition would occur because the 'to-be-conditioned' stimulus fails to attract a diversion of resources, which consequently impairs the processes by which the stimulus is linked both with specific cognitive and behavioural selections, and with primary reinforcement. In other words, it may be difficult to learn much about a stimulus without first interrupting current behaviour and attending to it. In this context, a specific role of dopamine in the re-allocation process could be to 'bind' the representation of a significant biological event to the selection of a particular action . It is this link which

may later be strengthened or weakened by subsequent signals indicating outcome – a reinforcement signal.

A general catecholamine response to salient stimuli?: The current proposal that short latency dopamine reactions contribute to behavioural switching initiated by salient events has several features in common with suggestions concerning the function of the noradrenergic neurones of locus coeruleus [40]. Dopamine and noradrenergic neurones show strikingly similar responses to salient events (see reviews by Schultz et al.[8] and Aston-Jones et al. [40]), both having a slow spontaneous rate of discharge (1-8 spikes/s) which is interrupted by a short latency (~50-100ms), short duration (~100ms) burst of pulses in response to unexpected novel stimuli (of all modalities), or to primary reinforcers. In both classes of neurone the reaction to such stimuli involves a significant proportion of the cell population, whilst neither class responds in a reliable fashion to consummatory movements or to stimuli in highly automatised tasks. Furthermore, in both classes, repeated non-reinforced presentation of a neutral stimulus leads to response habituation which can be reinstated by association with primary reward. In summary, both dopamine and noradrenalin neurones are maximally activated by unexpected stimuli made salient by virtue of their novelty, or their status as primary reinforcers or by their association with primary reinforcers. In the case of noradrenalin neurones, it has been argued by Aston-Jones and his colleagues [40] that this response profile is indicative of a functional system primarily involved in regulating attention to the external environment and readiness to respond to unexpected events. Our current proposal is that the short latency dopamine response performs an analogous function within the basal ganglia. If the supposition that selection is a core function of the basal ganglia is correct [16, 17], the dopamine signal could assist in preparing the animal to deal with the unexpected by promoting the switching of attentional and behavioural resources toward biologically significant stimuli.

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Selected references

1 **Thorndike, E. L.** (1911) *Animal intelligence*., Macmillan
2 **Schultz, W.** (1998) *J Neurophysiol* 80, 1-27
3 **Wickens, J.** (1993) *A theory of the striatum*., Pergamon
4 **Wickens, J.** (1997) *Comput. Neural Syst.* 8, R77-R109
5 **Schultz, W., et al.** (1997) *Science* 275, 1593-1599
6 **Kimura, M. and Matsumoto, N.** (1997) *Eur. Neurol.* 38, 11-17
7 **Beninger, R. J. and Miller, R.** (1998) *Neurosci. Biobehav. Rev.* 22, 335-345
8 **Schultz, W., et al.** (1995) in *Models of information processing in the basal ganglia*. (Houk, J. C., Davis, J. L. and Beiser, D. G., eds.), pp. 233-248, MIT Press

9 **Beiser, D. G., et al.** (1997) *Current Opinion in Neurobiology* 7, 185-190

10 **Bunney, B. S., et al.** (1991) *Synapse* 9, 79-94

11 **Overton, P. G. and Clark, D.** (1997) *Brain Res Rev* 25, 312-334

12 **Schultz, W.** (1997) *Current Opinion in Neurobiology* 7, 191-197

13 **Mirenowicz, J. and Schultz, W.** (1996) *Nature* 379, 449-451

14 **Dickinson, A.** (1980) *Contemporary animal learning theory*., Cambridge University Press

15 **Barto, A. G.** (1995) in *Models of information processing in the basal ganglia*. (Houk, J. C., Davis, J. L. and Beiser, D. G., eds.), pp. 215-232, MIT Press

16 **Redgrave, P., et al.** (1998) *Neuroscience* in press

17 **Prescott, T. J., et al.** (1998) *Adaptive Behavior* (in press)

18 **Mink, J. W.** (1996) *Prog. Neurobiol.* 50, 381-425

19 **Cools, A. R.** (1980) *Behav. Brain Res.* 1, 361-378

20 **Robbins, T. W. and Brown, V. J.** (1990) *Rev. Neurosci.* 2, 181-213

21 **Hikosaka, O.** (1994) in *The basal ganglia IV: New ideas and data on structure and function*. (Percheron, G., McKenzie, J. S. and Feger, J., eds.), pp. 589-596, Plenum Press

22 **Rolls, E. T.** (1994) *Revue Neurologique* 150, 648-660

23 **Marsden, C. D. and Obeso, J. A.** (1994) *Brain* 117, 877-897

24 **Robbins, T. W. and Sahakian, B. J.** (1983) in *Stimulants: Neurochemical, behavioural and clinical perspectives*. (Creese, I., ed.), pp. 301-338, Raven Press

25 **Oades, R. D.** (1985) *Neurosci. Biobehav. Rev.* 9, 261-282

26 **Salamone, J. D.** (1991) in *The mesolimbic dopamine system: From motivation to action*. (Willner, P. and Scheel-Kruger, J., eds.), pp. 599-613, John Wiley & Sons

27 **Jay, M. F. and Sparks, D. L.** (1987) *J. Neurophysiol.* 57, 22-34

28 **Moschovakis, A. K.** (1996) *Curr Opin Neurobiol* 6, 811-816

29 **Hikosaka, O. and Wurtz, R. H.** (1983) *J. Neurophysiol.* 49, 1230-1253

30 **Hernandez-Peon, R.** (1961) in *Sensory communication*. (Rosenblith, W. A., ed.), pp. 497-520, MIT Press

31 **Wurtz, R. H. and Goldberg, M. E.** (1972) *Invest. Ophthalmol.* 11, 441-50

32 **Schultz, W. and Romo, R.** (1990) *J. Neurophysiol.* 63, 607-624

33 **Salamone, J. D., et al.** (1997) *Neurosci. Biobehav. Rev.* 21, 341-359

34 **Koob, G. F., et al.** (1978) *J. Comp. Physiol. Psychol.* 92, 917-927

35 **Salamone, J. D.** (1994) *Behav. Brain Res.* 61, 117-133

36 **Horvitz, J. C., et al.** (1997) *Brain Res.* 759, 251-258

37 **Schultz, W. and Romo, R.** (1987) *J Neurophysiol* 57, 201-17

38 **Young, A. M. J., et al.** (1998) *Neuroscience* 83, 1175-1183

39 **Weiner, I.** (1990) *Psychological Bulletin* 108, 442-461

40 **Aston-Jones, G., et al.** (1991) *Progress In Brain Research* 88, 501-520