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Dopamine: the salient issue

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There is general agreement that midbrain dopamine neurons play key roles in reward processing. What is more controversial is the role they play in processing salient stimuli that are not rewarding. This controversy has arisen for three main reasons. First, salient sensory stimuli such as tones and lights, which are assumed not to be rewarding, increase dopamine neuron activity. Second, aversive stimuli increase firing in a minority of putative dopamine neurons. Third, dopamine release is increased following aversive stimuli. Consequently, it has been suggested that these midbrain dopamine neurons are activated by all salient stimuli, rather than specifically by rewards. However, reconsideration of these issues, in light of new findings, suggests this controversy can be resolved in favour of reward theories.

Midbrain dopamine neurons of the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc), hereafter referred to as dopamine neurons, send projections to many regions including the striatum and prefrontal cortex. It is widely agreed that these dopamine neurons play key roles in the processing of rewarding stimuli, such as food, sex or money (i.e. stimuli that are positively reinforcing and can elicit positive hedonic reactions) [1]. There is strong evidence to support the idea that when dopamine is released it plays a dual role, modulating learning and ongoing behaviour. For example, dopamine release in the striatum facilitates synaptic plasticity and can directly modulate reward-seeking behaviour [1–3]. Dopamine also plays a key role in the reorganization of receptive fields in the primary auditory cortex [4], and in the prefrontal cortex it is involved in working memory [5]. The notion that dopamine is involved in reward processing has been captured by numerous specific hypotheses over the years [1]. Most recently, attention has focused on the ideas that dopamine signals a reward prediction-error rule and that it encodes reward incentive salience [6–11].

Unexpected rewards activate dopamine neurons

Electrophysiological studies show that dopamine neurons exhibit rapid and brief bursts of activity in response to unexpected rewarding stimuli or unexpected reward-predicting stimuli [8,9]. If an expected reward is presented, no response is observed in dopamine neurons. But if an expected reward fails to occur, then dopamine neurons are inhibited. On the basis of these and other studies [12,13], it has been suggested that dopamine neurons encode a reward prediction-error signal [6–9]. Studies of rapid dopamine release, using fast-scan cyclic voltammetry, agree with these results, showing that unexpected reward-predicting stimuli evoke rapid, phasic dopamine release in the nucleus accumbens and that expected rewards do not [14]. Taken together these studies provide a compelling view of how rewards and reward-related events change dopamine neuron activity.

Although it is widely accepted that dopamine neurons are activated by rewards, there is some disagreement over whether or not they are activated by non-rewarding stimuli. Schultz and colleagues [8,9,15] have argued that dopamine neurons are preferentially activated by rewarding stimuli. By contrast, others have argued that all salient stimuli (i.e. stimuli that are attention-grabbing or of motivational significance, but not necessarily rewarding) activate dopamine neurons, particularly those associated with behavioural switching [16–21]. This issue centers around three main findings. First, salient sensory stimuli that do not appear to be rewarding evoke activations of dopamine neurons. Second, aversive stimuli increase firing in a minority of putative dopamine neurons. Third, dopamine release is increased following aversive stimuli. I will now discuss these findings in detail and some recent evidence that helps resolve the issue.

Salient sensory stimuli increase dopamine neuron activity

Physically salient sensory stimuli, such as tones and lights, evoke rapid, phasic excitations in dopamine neurons [22,23]. In addition, novel stimuli of this type can evoke dopamine release, as measured using microdialysis over a timescale of minutes [24]. It is typically assumed that such stimuli are not rewarding, and consequently these findings appear to present a considerable problem for reward theories. However there are at least three reasons why this problem might be more apparent than real. First, these activations could represent generalizations to stimuli that are associated with reward [15]. The phasic dopamine response is so rapid (within 50–110 ms of stimulus presentation [8]) that there is little time for detailed processing of the stimuli, and under these circumstances one might expect errors of stimulus generalization to occur [8,25,26]. Second, under some circumstances, novelty itself can be rewarding, thereby encouraging exploration of novel environments [26]. For example, rats will often choose a novel environment over a familiar one [27]. It should be noted, however, that phasic activations in response to lights and tones often persist after many presentations, when the stimuli

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are clearly no longer novel [23]. Third, salient sensory stimuli could have rewarding properties, although not immediately obvious to the experimenter, that mean they are treated as rewards by the animal and lead to activation of dopamine neurons. For example, when given the choice between two levers that deliver food, rats prefer a lever that when pressed is followed by a visual stimulus [28]. By contrast, an auditory stimulus suppresses responses, suggesting that some sensory stimuli might have aversive properties [28]. It would be interesting to combine these subtle behavioural tests of reward with simultaneous recordings of dopamine neuron activity. Hence, the observation that salient sensory stimuli such as lights and tones activate dopamine neurons can be accommodated within reward theories in several ways.

Stimuli predicting reward omission decrease firing in dopamine neurons

When an expected reward fails to occur, dopamine neurons are inhibited [8,9]. This is a key prediction of the reward prediction-error hypothesis. It is important because an event such as reward omission is a motivationally significant, salient event that is not rewarding. This observation suggests that dopamine neurons are not activated by all salient stimuli, but just by those that are rewarding. Using a sophisticated conditioned inhibition procedure, Tobler, Dickinson and Schultz [25] provide further strong evidence that this is the case. Imagine the scenario where every time a light comes on reward is delivered, but when the light comes on and a tone sounds, no reward is delivered. In this case, the tone predicts reward omission (a stimulus traditionally referred to as a conditioned inhibitor) and is therefore, by definition, not rewarding, although it is attention grabbing. Consistent with the reward prediction-error hypothesis, a conditioned inhibitor stimulus inhibits firing in most dopamine neurons [25] (Figure 1). Taken together, these findings show that the unexpected omission of a reward, or the unexpected presentation of a stimulus that predicts reward omission, both lead to inhibition of dopamine neurons. Both of these types of event are salient in the sense that they are of motivational significance, but neither is rewarding. Consequently, it does not appear that dopamine neurons are activated in a non-specific manner by all generally salient stimuli. But are they selectively activated by rewards? Redgrave, Prescott and Gurney [17] have suggested that dopamine neurons are activated by stimuli that elicit behavioural and attentional switching. They argue that the omission of a reward should not evoke a change in behaviour but, rather, a perseverance of responding. Consequently, their hypothesis can be viewed as consistent with the observation that dopamine neurons are inhibited by reward omission. One class of stimuli that are both salient and induce behavioural and attentional switching, but are explicitly not rewarding, are aversive events, such as pinch, mild electric shock or air puff. How do dopamine neurons respond to such events?

Aversive stimuli increase firing in a minority of (putative) dopamine neurons

Aversive stimuli elicit mixed responses in dopamine neurons. The typical response is an inhibition of firing [29–33]. However, between 3% and 49% of dopamine neurons are activated by aversive stimuli (depending on the species and stimuli examined) [29–33]. These results are somewhat confusing and represent a major challenge to reward theories. It is important to note that in all of the electrophysiological studies discussed so far, dopamine neurons were identified using electrophysiological criteria alone (although the location of the recording electrode was confirmed to have been in the VTA or SNpc). These criteria include a broad, triphasic action potential and slow firing rate – properties that neurochemically identified dopamine neurons do indeed possess [34]. However, recent evidence suggests that there is a population of neurons in the VTA that is not dopaminergic but which nevertheless has electrophysiological properties similar to dopamine neurons [35]. My colleagues and I decided to directly examine this issue by recording responses to an aversive stimulus (a 15 s foot pinch) from individual putative dopamine neurons in anaesthetized rats [36]. Following electrophysiological recordings, we used the juxtacellular labelling technique to identify individual neurons neurochemically. We found that the putative dopamine neurons that are activated by an aversive stimulus are actually not dopaminergic (Figure 2). In addition, we found that neurochemically identified dopamine neurons were inhibited by the aversive stimulus (Figure 2), a finding that is consistent with the hypothesis that they are selectively activated by rewards.

Dopamine release and aversive stimuli

There is considerable evidence, originally from postmortem studies of dopamine metabolism but more recently using *in vivo* microdialysis, that extracellular levels of dopamine increase slowly (i.e. over a time course of minutes) following a variety of aversive stimuli [37–39]. At first sight, these findings present another major challenge to reward hypotheses. Moreover, how can these neurochemical findings be integrated with electrophysiological findings that show aversive stimuli inhibiting firing of dopamine neurons?

One plausible suggestion, discussed in detail by Daw, Kakade and Dayan [40], is that this slow increase in dopamine release is the consequence of an opponent process. Opponent process hypotheses of stimulus processing have been successfully used to explain a range of effects in the brain [41–43]. Briefly, opponent process theory states that stimuli activate two opposing processes: one process has a fast onset and offset, similar in timing to the actual stimulus; the second, opponent process is slow to begin and slow to end, typically outlasting the stimulus. For example, the offset of an aversive stimulus can cause relief and be rewarding. Opponent process theory suggests that an aversive stimulus will evoke a brief inhibition of dopamine release, followed by a slower increase. Because of the low time-resolution of microdialysis (typically, a sample is collected every 5–10 min), a brief decrease in dopamine release would be difficult to detect. In addition,

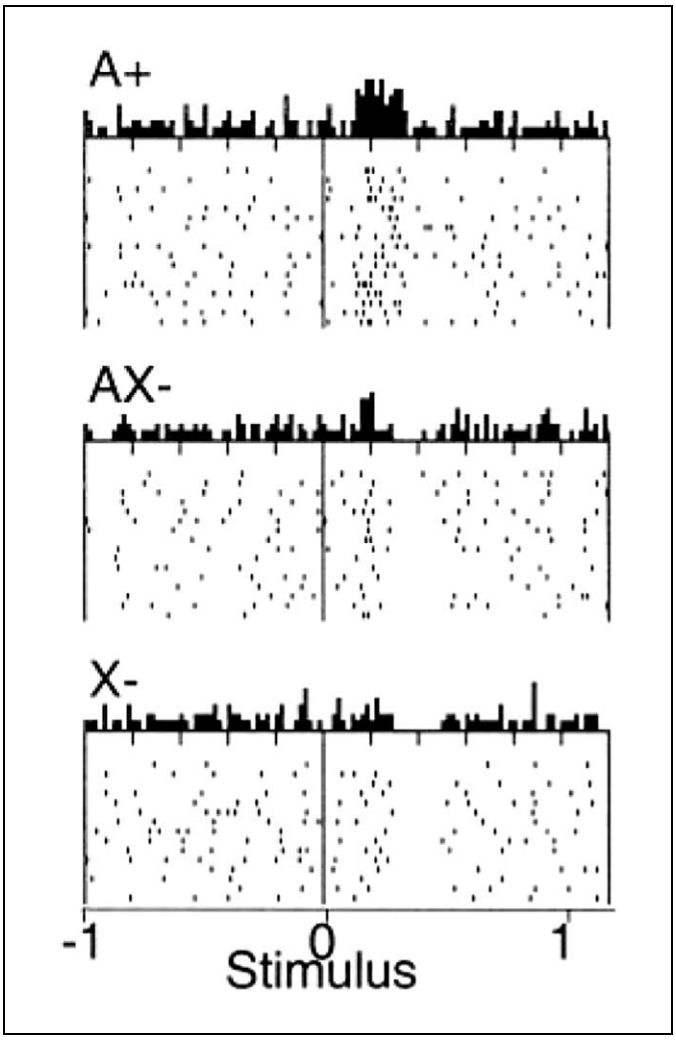

Figure 1. An example of an individual dopamine neuron that is inhibited by a stimulus predicting reward omission. At the top of each panel is a cumulative histogram of action potential number across time (each bar is 10 ms) for repeated presentations of the stimuli; below each histogram, the dashes represent individual action potentials occurring in each trial. Stimulus 'A' is paired with reward (A+) and excites the dopamine neuron. When 'A' is presented with 'X' no reward occurs (AX−), and therefore 'X' predicts reward omission. When 'X' is presented alone, the dopamine neuron is inhibited (X−). Other control stimuli were also presented but are not shown here. Reproduced, with permission, from [25] © (2003) the Society for Neuroscience.

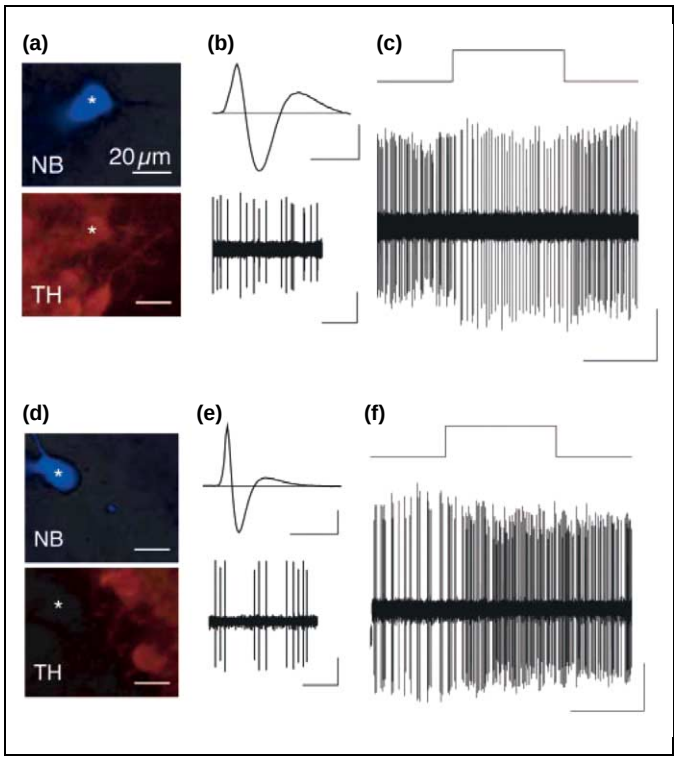

Figure 2. Neurochemically-identified dopamine neurons are inhibited by an aversive stimulus; the excited neurons are actually not dopaminergic. **(a)** A neuron labelled with neurobiotin (NB) that is tyrosine hydroxylase (TH)-positive and, therefore, dopaminergic (tyrosine hydroxylase is the essential rate-limiting enzyme in dopamine synthesis). **(b)** The broad action potential (upper trace) and slow firing rate (lower trace) typically used to identify putative dopamine neurons. **(c)** Firing of the dopamine neuron is decreased during the aversive stimulus. **(d)** A neuron labelled with neurobiotin that is tyrosine-hydroxylase-negative and, therefore, non-dopaminergic. This non-dopaminergic neuron also has a broad action potential and slow firing rate typically used to identify putative dopamine neurons **(e)**, but it was excited by the aversive stimulus **(f)**. Vertical scale bars: all 0.5 mV. Horizontal scale bars: (b) and (e) upper panels, 2 ms; (b) and (e) lower panels, 1 s; (c) and (f), 10 s. Reproduced, with permission, from [36].

the opponent process will be more strongly activated by repeated, intense stimuli [40]; this leads to the further prediction that following weaker, brief aversive stimuli, release might be inhibited in the absence of the opponent process and as a result might be easier to detect under these conditions. Di Chiara and colleagues [44,45] have provided some evidence using microdialysis that dopamine release in the nucleus accumbens shell is indeed inhibited by brief and relatively weak aversive stimuli. It will be interesting and important to examine this issue using more rapid sampling methods, such as fast-scan cyclic voltammetry.

At least two objections that can be made against the opponent process hypothesis. First, it has been argued that the opponent process account fails to explain why dopamine levels often rise before stimulus offset, during prolonged aversive stimuli [20]. However, most opponent process theories suggest that the opponent process begins during the stimulus. Second, and more challenging for the theory, it fails to explain why microdialysis studies report an increase in dopamine release following rewarding, appetitive stimuli [45]. Opponent process theory would predict a slow decrease in dopamine release following rewards. However, this again could be an issue of temporal resolution, particularly if one takes account of the asymmetry of positive and negative changes in the activity of dopamine neurons (Figure 3). When dopamine neurons are phasically activated, they can transiently increase their firing rates from a baseline of ~4 Hz to bursts of up to 25 Hz, which is estimated to cause a peak extracellular dopamine concentration of at least 100 nM from a baseline of ~5–10 nM [8]. By contrast, inhibitions of dopamine neurons typically reduce firing from 4 Hz to 1–3 Hz [29–33,36], and the consequent reduction in dopamine release will be limited by the low baseline concentration. Consequently, the initial, rapid reward-related release can be extremely large, and could mask smaller inhibitions of dopamine release (the effect of the opponent process) even if they are longer lasting. By contrast, the initial inhibitory signal during aversive stimuli is likely to be relatively small [36], and so might be easily masked by a prolonged opponent process (Figure 3).

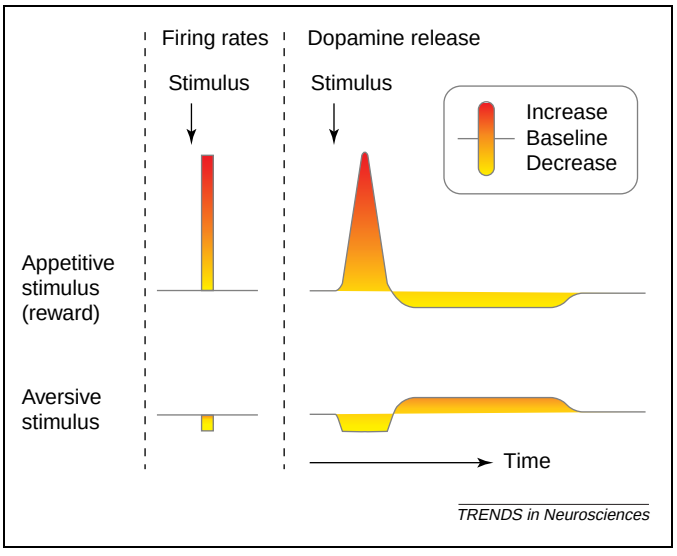

Figure 3. A qualitative illustration of dopamine neuron firing and proposed dopamine release in response to appetitive and aversive stimuli. Following a brief excitation, there is a longer duration but smaller magnitude reduction of release; following a brief inhibition of firing, there is a longer duration but smaller magnitude increase in dopamine release. Note that the asymmetry of excitation versus inhibition could lead to a net increase in dopamine detected by microdialysis following both types of stimulus.

How is the slow opponent process generated?

It is not clear how this slow opponent process is related to firing rates in dopamine neurons. Electrophysiological studies have reported that stimulus-evoked changes in firing (either excitations for rewards [8,9] or inhibitions for aversive stimuli [29–33,36]) occur with rapid onset and offset; following stimulus offset, firing rates return to baseline and do not appear to increase slowly, thus dissociating firing from the opponent process [36]. By apparent contrast, directly interfering with dopamine neuron firing (either by infusing tetrodotoxin into the medial forebrain bundle [46,47] or by infusing various glutamate, GABA and neuropeptide receptor antagonists into the VTA [48–52]) attenuates the augmenting effects of aversive stimuli on dopamine release in target areas. How can these findings be reconciled?

Montague and colleagues [53] have developed a simple yet powerful model of dopamine release. They have found that evoked, phasic dopamine release can be effectively modeled by taking into account just three short-term adaptations: short-lasting depression, short-lasting facilitation and longer-lasting depression. The longer-lasting depression persists for several minutes and they speculate that it could relate to dopamine biosynthesis and vesicular repackaging [54]. This effect might also be the result of presynaptic D2 dopamine autoreceptor stimulation, which directly inhibits dopamine release and synthesis [55]. It could be that the opposite occurs when dopamine neuron firing is inhibited, as for example during an aversive stimulus, and that a build up of synthesized dopamine and vesicular packaging could result in increased release when firing returns to baseline levels. This suggestion leads to the important prediction that brief inhibition of firing is necessary for the rebound increase in release, but that this increase in release is not the direct result of increased firing above baseline. This is in agreement with both the electrophysiological observations and the effects of interfering with dopamine neuron firing already discussed.

In summary, the observation that dialysate concentration of dopamine is increased by aversive stimuli could reflect an opponent process; this observation therefore can be readily accommodated by reward theories. This account makes the clear prediction that dopamine release will be transiently inhibited during aversive stimuli; it will be important to test this in the future.

Concluding remarks and future directions

Dopamine neurons have long been associated with processing appetitive, rewarding events. What has been more controversial is whether dopamine neurons are activated specifically by reward or more generally by all salient events. However, reconsideration of these issues in light of recent findings provides strong support for the hypothesis that dopamine neurons are specifically activated by rewards.

These new studies suggest several important directions for future work. First, a more detailed understanding is needed regarding the modulation of dopamine neuron activity by aversive stimuli. For example, it will be important to determine whether dopamine release in target areas is rapidly and transiently inhibited during aversive stimuli, as predicted by electrophysiological recordings of dopamine neurons. Second, a clearer understanding is needed of the conditions under which novel sensory stimuli activate dopamine neurons; in particular, the hypotheses that novelty itself can be rewarding and that some of these stimuli might actually have rewarding properties should be tested. Finally, perhaps the greatest challenges facing the field are to integrate studies of dopamine neuron firing with studies of dopamine release, and to establish how both relate to behaviour.

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