

Multiple functions of dopamine neurons

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Abstract

Dopamine neurons carry phasic signals for a limited number of behavioural events. The events include, in descending order, reward, physically intense stimuli, risk and punishment. Recent neurophysiological studies have provided interesting details on these functions.

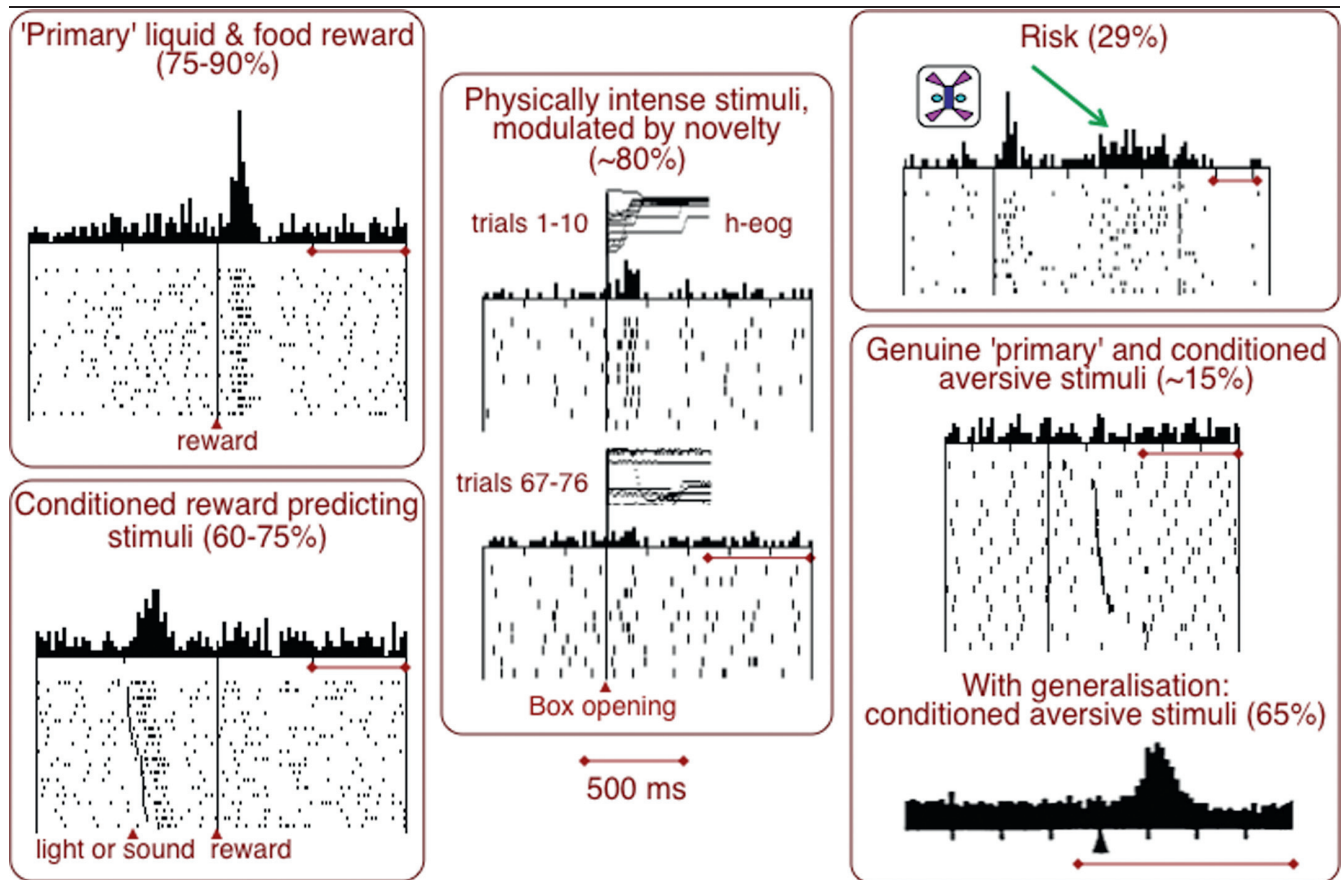
Introduction and context

Results from lesion and psychopharmacological studies suggested a wide range of behavioural functions for mid-brain dopaminergic systems. The key question is, which of these functions are actively encoded by impulse activity and dopamine release and thus give rise to a phasic dopamine signal suitable for rapid neuronal mechanisms? Promising leads come from drug addiction and electrical self-stimulation, suggesting that dopaminergic stimulation has rewarding and approach-generating effects [1,2]. The strongest dopamine signal is related to reward, as most dopamine neurons are phasically activated by reward-predicting stimuli and code bidirectional reward prediction errors in humans [3], monkeys (60-90% of dopamine neurons) [4] and rats [5]. However, dopamine neurons code more than reward (Figure 1) [6]. Substantial dopamine activations occur also with physically intense, salient stimuli (75-90% [4,7]), whereas novelty on its own fails to elicit activations [8] but enhances the response efficacy of stimuli [6]. Slightly slower activations code the predicted risk of future rewards in a fraction of dopamine neurons (29%) [9]. Only a small proportion of dopamine neurons in awake animals are activated by punishers and conditioned aversive stimuli such as air puffs, hypertonic saline or electric shock (<20% [10], 18-29% [11]), whereas depressions constitute the more frequent response. Aversive stimulation in anaesthetised animals produces varying but often low degrees of mostly slower, activating responses (50% [12], 18% [13], 17% [14], 14% [15]). Activating responses occur frequently to conditioned aversive stimuli

when these are presented in random alternation with conditioned, reward-predicting stimuli of the same sensory modality (65% [10]); the activations are much less frequent when the two types of stimuli have different sensory modalities.

The reasons for 'false' aversive activations [10] might lie in generalisation with rewarding stimuli, sensitisation or pseudoconditioning, or stimulus salience. Generalisation arises from similarities between conditioned stimuli, which might explain the influence of sensory modalities on neuronal responsiveness [10]. Sensitisation or pseudoconditioning arises when a primary reinforcer sets a contextual background and provokes unspecific behavioural responses to any events within this context [16]. As dopamine neurons are very sensitive to reward, a rewarding context might induce a 'default' unspecific response to stimuli set in this context. Salience can be derived from physically strong stimuli or from motivationally important events like rewards, punishers or novel stimuli. Physical salience seems to drive dopamine neurons [4,7] but would not explain aversive responses to the usually employed small visual stimuli. Motivational salience might explain activations in dopamine neurons if these occur indiscriminately with both appetitive and aversive events without confounding generalisation and sensitisation-pseudoconditioning, but this remains to be shown. There are several possible explanations for the observed aversive activating responses of dopamine

Figure 1. Multiple dopamine signals



Neurophysiological activations of dopamine neurons following primary rewards and conditioned, reward-predicting stimuli, physically intense stimuli, risk, and primary and conditioned aversive stimuli. Horizontal bars indicate 500 ms in all panels. Data are from [4,9,10,26]. h-eog, horizontal electro-oculogram.

neurons, of which sensitisation-pseudoconditioning might be the most important one. True aversive activations do not seem to involve more than 10-20% of dopamine neurons when these confounds are ruled out, and aversive experiments that are more definitive would need to completely eliminate all contextual reward associations with the laboratory in which an awake animal is being tested.

Major recent advances

Neurophysiological reinvestigations with better identification of dopamine neurons confirmed the overall low incidence of aversive dopamine activations in anaesthetised animals [17] and located such neurons in the ventromedial tegmental area [18]. Aversive air puffs in awake monkeys produced activations in some dopamine neurons (23% [19], 11% [20]), similar to air puff to the arm (14% [10]). Interestingly, the air puff failed to induce bidirectional prediction error responses typical for reward; prediction had only modulating effects on aversive responses [20].

Conditioned, air puff-predicting stimuli activated a few dopamine neurons in one study (13% [19]) but substantially more than the air puff itself in another study (37% [20]). Since a conditioned stimulus is less aversive than the air puff it predicts, the higher number of activations to the stimulus (37%) compared with the air puff (11%) suggests an inverse relationship between aversiveness and activation, leaving the proportion of truly aversively activated dopamine neurons closer to 11% than 37%. One possible explanation for the more frequent aversive stimulus activations might lie in sensitisation or pseudoconditioning by the reward, whereas generalisation would be less with block design [20]; motivational salience would be highest for primary air puff and thus explain activations in only about 11% of neurons responding to this event. Although the stimulus activations correlated positively with air puff probability in the population, they were not assessed in individual neurons [20]. A population correlation may arise from a relatively small number of positively correlated neurons within that population.

Studies using other techniques described further functional aspects of dopamine signalling. Fast-scan voltammetry in behaving rats revealed dopamine increases with rewards that shifted to reward-predicting stimuli after conditioning [21], suggesting that impulse responses of dopamine neurons lead to corresponding dopamine release from striatal varicosities. The dopamine increase was differential for rewards (sucrose) and failed to occur with punishers (quinine) [22]. Apparently, the impulse response to punishment was insufficient for producing a measurable voltammetric dopamine change. This result contrasts with an earlier reported dopamine increase following aversive stimuli detected by *in vivo* dialysis [23,24]. The time courses of *in vivo* dialysis, which are 200 to 1800 times longer than those of fast-scan voltammetry, might allow the detection of dopamine released from the relatively few dopamine neurons activated by punishers. Finally, neuron-specific optical stimulation of dopamine neurons via genetically inserted channelrhodopsin-2 induced Pavlovian place preference in behaving rats [25], indicating an overwhelming causal influence of the rewarding rather than the aversive dopamine signal on learning and approach behaviour.

Future directions

Although the prediction error response of dopamine neurons would make a good teaching signal, the bulk of available data are correlational. Methods allowing investigators to study the causal role of dopamine in learning were initially hampered by the uncertain identity of electrically stimulated neurons [1], but these issues might be overcome by the recently emerging optogenetic methods [25]. Future optogenetic work might delineate the contributions of the different components of the prediction error response to behavioural learning and identify the particular forms of learning sensitive to dopamine signals.

Rewards, and in particular conditioned stimuli predicting such rewards, serve for choices between differently valued options. Future work may address the role of dopamine reward responses in decision making in which they might provide both a teaching signal for value updating and a value prediction signal for the different objects and actions involved in the decision process.

Future studies may investigate the role of non-reward-related dopamine signals in behavioural reactions. Although the dopamine systems appear to be more homogeneous in function compared with most other brain structures, a certain functional heterogeneity might prove advantageous for its role in behaviour. The various dopamine signals might differentially influence specific brain processes, and fine-grained studies in neuronal

connectivity and receptor localisation should provide useful information.

Competing interests

The author declares that he has no competing interests.

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