Review TRENDS in Neurosciences Vol.30 No.5

Behavioral dopamine signals

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Lesioning and psychopharmacological studies suggest a wide range of behavioral functions for ascending midbrain dopaminergic systems. However, electrophysiological and neurochemical studies during specific behavioral tasks demonstrate a more restricted spectrum of dopamine-mediated changes. Substantial increases in dopamine-mediated activity, as measured by electrophysiology or voltammetry, are related to rewards and reward-predicting stimuli. A somewhat slower, distinct electrophysiological response encodes the uncertainty associated with rewards. Aversive events produce different, mostly slower, electrophysiological dopamine responses that consist predominantly of depressions. Additionally, more modest dopamine concentration fluctuations, related to punishment and movement, are seen at 200–18 000 times longer time courses using voltammetry and microdialysis *in vivo*. Using these responses, dopamine neurotransmission provides differential and heterogeneous information to subcortical and cortical brain structures about essential outcome components for approach behavior, learning and economic decision-making.

Introduction

The description of the function of dopamine has been dominated for many decades by two basic observations: the severe movement deficits after dopamine-depleting lesions in patients with Parkinson's disease, and the reduced behavioral responses to motivating stimuli after interference with dopamine neurotransmission in experimental rats. Because relating all brain activity to the functioning of single neurons (as the basic unitary elements for neural processing) is preferred, the question arises as to which of the many functions deficient after dopamine-depleting lesions could actually be attributed to the impulse activity of single dopaminergic neurons projecting to postsynaptic targets, such as the striatum, nucleus accumbens and frontal cortex. A review of the past 50 years of dopamine research might be the appropriate time for reviewing the current data concerning the relation of dopamine-impulse activity to specific behavioral functions. Here, we review not only the electrophysiological response of dopaminergic neurons to reward- and uncertainty-related events, but we also set them in a larger context by describing data from other techniques measuring dopamine-mediated changes, such as voltammetry and microdialysis. These physiological dopamine-mediated changes are compared with the effects of dopamine-depleting lesions to obtain a more coherent view of the function of dopamine.

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Available online 2 April 2007.

Reward

Although it is essential for survival of both individuals and genes, reward information does not affect the brain through specific, dedicated, sensory receptors. By contrast, the function of rewards is defined by their action on behavior. Neural decision-making systems, dealing with the pursuit of essential objects for survival, would benefit from explicit neuronal signals for reward, just as visual perception is derived from specific information provided by retinal responses to visual stimuli. The search for reward neurons as a 'retina of the reward system' has identified midbrain dopamine-mediated signals that signify the pure reward value of objects, irrespective of their sensory components or the behavioral functions necessary to obtain them.

Reward-prediction error

Rewards occur after reward-predicting stimuli and behavioral actions. They generate approach and consummatory behavior, constitute outcomes of the preceding stimuli and actions, serve as positively reinforcing feedbacks ('come back for more') and produce reward predictions through associative conditioning. The reward-prediction error reflects the difference between predicted and obtained rewards and constitutes the essential term for reward-driven learning, according to the Rescorla–Wagner learning rule.

Most midbrain dopaminergic neurons exhibit burst activity, also known as 'phasic activation', following primary food and liquid rewards. The response to reward does not occur unconditionally but seems to code the prediction error, such that an unpredicted reward elicits activation (positive-prediction error), a fully predicted reward elicits no response and the omission of a predicted reward induces a depression (negative-prediction error; Figure 1a) [1].

The dopamine-mediated coding of the reward-prediction error fulfills formal criteria postulated by animal learning theory. In the blocking paradigm, a stimulus is not learned (instead, it is 'blocked') as a valid reward-predicting, conditioned stimulus if it is paired with an already fully predicted reward, indicating the importance of prediction errors for learning [2]. The absence of a reward following the blocked stimulus does not produce a prediction error and, accordingly, does not produce a dopamine-mediated response, whereas the delivery of a subsequent reward produces a positive-prediction error and hence an activating dopamine-mediated response [3] (Figure 1b). By contrast, after a well-trained, reward-predicting control stimulus, reward omission produces a negative-prediction error, and hence a depressed neural response, and reward delivery does not lead to a dopamine-mediated response.

 0166-2236/$ – see front matter doi:10.1016/j.tins.2007.03.007

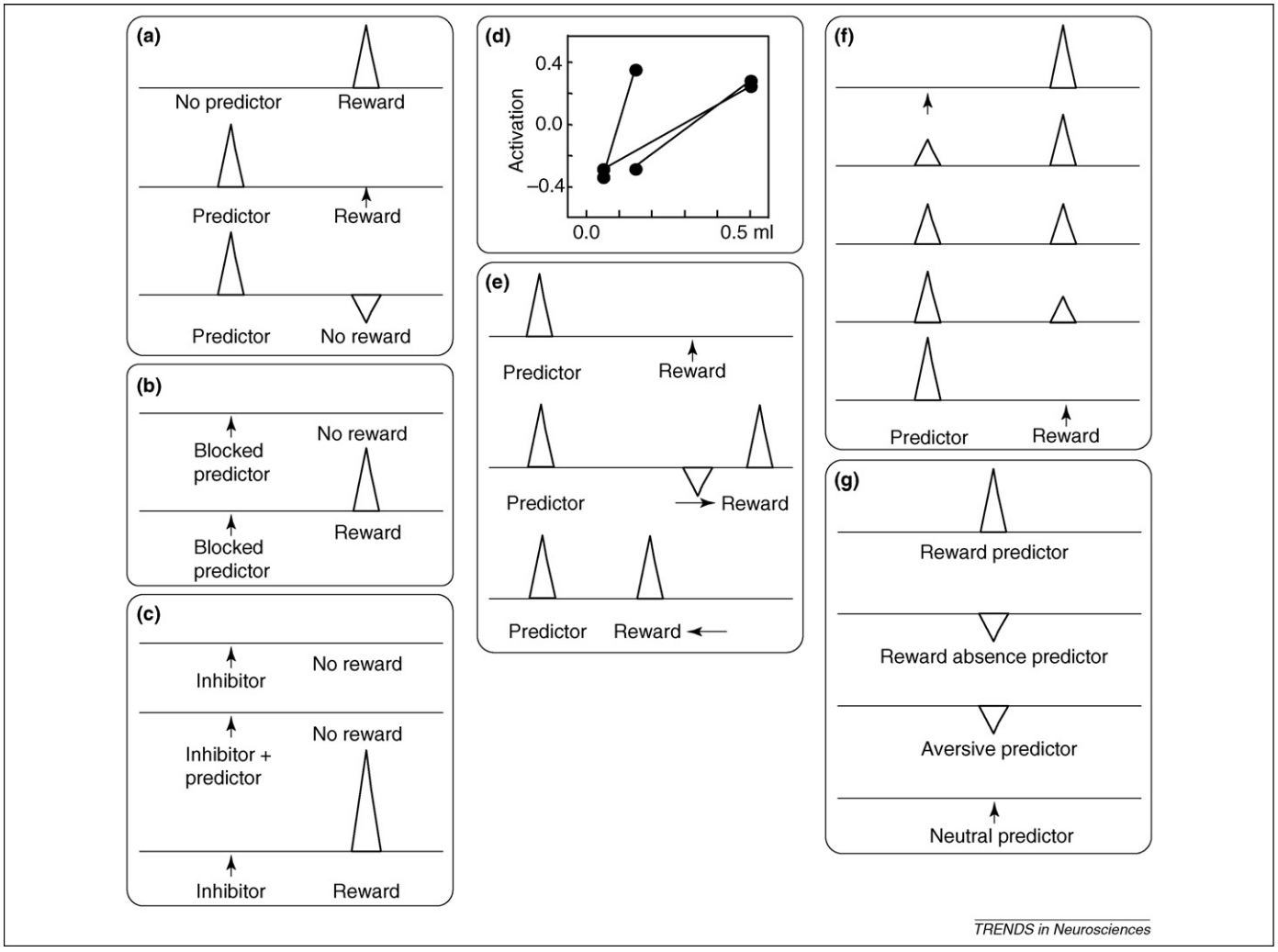

Figure 1. Schematics of electrophysiological responses of single dopaminergic neurons to reward-related stimuli. **(a)** Prediction-error coding at the time of the reward: activation following an unpredicted reward (positive-prediction error; top), no response to a fully expected reward (no prediction error; middle), and depression following omission of a predicted reward (negative-prediction error; bottom). **(b)** Reward-prediction-error coding in a blocking paradigm: absence of a reward following a blocked stimulus does not induce a neuronal response (no prediction error; top), and neuronal activation following delivery of a reward after a blocked stimulus (positive-prediction error; bottom). **(c)** Reward-prediction-error coding in a conditioned-inhibition paradigm: absence of a reward following a conditioned inhibitor does not induce a neuronal response (no prediction error; top), absence of a reward following a conditioned inhibitor paired with a usually reward-predicting stimulus does not induce a neuronal response (no prediction error in summation test; middle), and strong activation following a reward delivered after a conditioned inhibitor (strong positive-prediction error; bottom). **(d)** Adaptive coding of the reward-prediction error to employed probability distributions. Neuronal responses are similar despite a tenfold difference in reward magnitude predicted by the specific conditioned stimuli. **(e)** Temporal-reward-prediction error. Displacement of a reward by 500 ms leads to activation at the new reward time and depression at the habitual reward time, unless the reward occurs before the habitual time (cancellation of reward prediction; bottom). **(f)** Reward-prediction-error coding during learning. Successive steps of learning (top to bottom) lead to gradual reduction of reward-prediction error in successive trials, according to the Rescorla–Wagner learning function, reduction of dopamine-mediated activation in response to reward (right) and build-up of dopamine-mediated activation in response to reward-predicting stimuli (left). **(g)** Differential responses to conditioned stimuli. From top to bottom: activation following a reward-predicting stimulus, depression following a conditioned inhibitor that predicts the absence of reward, depression following a conditioned aversive stimulus, and no response to a nonpredictive stimulus.

In the conditioned inhibition paradigm, a test stimulus is presented simultaneously with an established reward-predicting stimulus but no reward is given afterwards, making the test stimulus a conditioned inhibitor that predicts the explicit absence of reward. Reward omission after a well-learned, conditioned inhibitor does not produce a prediction error or a response in dopaminergic neurons, even if a well-learned, reward-predicting stimulus is added [4] (Figure 1c). By contrast, the occurrence of reward after the inhibitor produces a strong positive-prediction error and hence enhanced activation of dopaminergic neurons, because the prediction error represents the difference between the actual reward and the negative prediction from the inhibitor.

In combination, the data from these formal tests suggest that dopaminergic neurons show bidirectional coding of reward-prediction errors, according to Equation 1:

$$\text{Dopamine response} = \text{reward occurred} - \text{reward predicted}. \quad \text{(Equation 1)}$$

Thus, the dopamine-mediated response to rewards might constitute a neural basis of prediction error because it seems to convey the crucial learning term ($\lambda - V$) of the Rescorla–Wagner learning rule and complies with the principal characteristics of teaching signals of efficient reinforcement models using temporal-difference learning [5,6]. Neuronal models using dopamine-like reward-prediction errors can

efficiently learn foraging behavior and delayed response tasks [7,8]. The influence of dopamine-mediated signals on postsynaptic neurons might consist of short- and long-term modifications of corticostriatal synaptic transmission [9–11].

In general terms, prediction errors might contribute to the self-organization of behavior. Brain mechanisms establish predictions, compare current inputs with predictions from previous experience and emit a prediction-error signal if a mismatch is detected. The error signal might function as an impulse for synaptic modifications that lead to subsequent changes in predictions and behavioral reactions. The process is reiterated until behavioral outcomes match the predictions and the prediction error becomes nil. In the absence of a prediction error, there is no signal for modifying synapses and synaptic transmission is unchanged and stable.

The responses to positive- and negative-prediction errors are graded, such that a partial-prediction error induces a smaller error response. Prediction-error responses co-vary in a monotonic fashion with both magnitude and probability of reward [12,13]. Formally, they reflect the expected value of the probability distribution of reward magnitudes relative to the prediction [12,13]. Thus, dopaminergic neurons have access to information about probability distributions of rewards contained in predictions. However, the dopamine-mediated response does not reflect the absolute value of the prediction error but adapts to the mean and variance of the predicted probability distribution of reward magnitudes within the 2s stimulus–reward intervals. For example, if different visual stimuli predict specific binary distributions of equiprobable reward magnitudes with different means and variances, the larger magnitude in each distribution always elicits the same positive response, even if there is a tenfold difference in the reward magnitude, although responses to unpredicted rewards co-vary with magnitudes in these neurons [13] (Figure 1d). As a result of this adaptation, the neural response discriminates between the two probable outcomes equally, regardless of the absolute difference in magnitude.

The dopamine-mediated prediction-error response is not only sensitive to the expected value of the reward relative to its prediction, but is also sensitive to the time of the predicted reward. A reward that is shifted backwards or forwards in time by 500 ms induces activation at its new time. Depression occurs at the original reward time if the reward has not occurred yet [14] (Figure 1e). The dopamine-mediated prediction-error response also co-varies with reward predictions that change systematically in subsequent trials [14]. Thus, dopaminergic neurons have access to temporal information on reward predictions contained in explicit stimuli and environmental contexts.

Although the dopamine-mediated coding of reward-prediction errors has been studied during established performance with well-trained, reward-predicting stimuli, dopaminergic neurons also emit the reward-prediction error signal during learning. The positive and negative signals reflect the occurrence of rewards relative to the current degree of prediction and dissipate slowly in successive learning trials [15] (Figure 1f).

Reward-predicting stimuli

Reward-predicting stimuli occur before rewards, predict the outcomes of actions, provide essential advance information for decision-making in choice behavior, generate overt approach behavior and serve as positive, conditioned reinforcers for earlier stimuli and actions in higher-order associative learning.

Most midbrain dopaminergic neurons show phasic activation following conditioned visual, auditory and somatosensory reward-predicting stimuli [16] (Figure 1a, e–g). The activity of the neurons is briefly depressed by stimuli predicting the explicit absence of reward [4]. The neurons show little activation and some depression following conditioned aversive stimuli and no response to inedible objects or known neutral stimuli, unless the stimuli are physically intense [17]. However, dopaminergic neurons show generalized activation–depression responses to neutral and aversive stimuli if these stimuli are not distinctively different from reward predictors.

The dopamine-mediated responses to reward-predicting stimuli occur irrespective of spatial position, sensory stimulus attributes and parameters of arm, mouth and eye movements [16]. The responses co-vary with the expected values of the probability distributions of reward magnitudes, irrespective of the underlying probability and magnitude components [13]. The responses are modulated by the motivation of the animal [18] and the choice of reward that the animal makes among rewards of different values [19].

Dopaminergic neurons are not activated by reward-predicting conditioned stimuli that are predicted by another stimulus with a time course in the range of seconds [16,20] and are depressed if a predicted conditioned stimulus fails to occur [8]. These responses conform to the hypotheses of temporal-difference learning models that conceptualize prediction errors irrespective of primary or conditioned reinforcers and consider a response to a conditioned stimulus as reflecting an error in the prediction of the conditioned stimulus [6].

Physically intense stimuli induce activation of dopaminergic neurons, which is enhanced by stimulus novelty, whereas inconspicuous novel stimuli are ineffective [20,21]. However, other strongly attention-inducing stimuli are ineffective in producing the characteristic, short-latency, reward-related activation of dopaminergic neurons, including primary and conditioned aversive events [17], reward omission [1] and conditioned inhibitors [4]. Thus, the activation of dopaminergic neurons does not seem to be owing to the general alerting or attention-generating functions of reward-related stimuli but might reflect the known rewarding and approach-generating functions of intense stimuli. The combined data suggest that activation of dopaminergic neurons might reflect a combined sensitivity to rewarding and physically salient events or might be related to less well-known forms of attention attached commonly to rewards and physically salient stimuli but not punishers, negative surprises and conditioned inhibitors.

Reward uncertainty

In the natural world, rewards usually occur with some degree of uncertainty. Uncertainty is conceptualized by

probability theory, which defines the degree of uncertainty within a given distribution of probable outcomes. Conventional measures of uncertainty include the statistical term 'variance' and the information-theoretic term 'entropy'. Uncertainty has a substantial influence on the subjective reward value, reducing it in risk-averse individuals and increasing it in risk seekers, as conceptualized by the microeconomic expected-utility theory [22,23].

Reward uncertainty is easily tested by different binary, all-or-none probability distributions of magnitudes, which enables separation of the expected value (linearly increasing from $P = 0$ to $P = 1$) from uncertainty, expressed as variance or entropy (inverted U function, with a peak at $P = 0.5$). More than one-third of dopaminergic neurons show a relatively slow, sustained and moderate activation between the reward-predicting stimulus and reward. This activation is highest for conditioned stimuli predicting reward at $P = 0.5$, and it is progressively lower for probabilities farther away from $P = 0.5$ in either direction [12]. Activation occurs in single trials of single neurons and does not propagate backwards during learning, from reward to the conditioned stimulus (Figure 1f), as has been assumed by several implementations of temporal-difference reinforcement models [1]. Activation does not occur if a reward is substituted with a visual stimulus. Uncertainty-related activation is distinct from, and uncorrelated to, the dopamine-mediated responses to rewards and reward-predicting stimuli (Figure 2). A similar activation occurs if conditioned stimuli predict two equiprobable rewards with different magnitudes and co-varies with variance (entropy is constant at 1 bit), suggesting that variance is a viable measure of uncertainty for dopaminergic neurons.

The neuronal uncertainty signal about rewards could provide essential information if dealing with uncertain outcomes. The distinct neural coding of reward value and uncertainty is consistent with the separation of expected utility into these two components, as suggested by the financial-decision theory [23] and found in human brain imaging studies [24,25]. However, the separation contradicts the combined coding as a scalar variable generally assumed by the classic expected-utility theory [22]. At the postsynaptic neuronal level, a distinction between uncertainty and reward signals could be made according to the differential stimulation of dopamine receptors. The uncertainty signal evokes low dopamine concentrations appropriate for stimulating high-affinity dopamine D2 receptors, whereas the reward signals induce much higher dopamine concentrations appropriate for stimulating low-affinity dopamine D1 receptors [26–31].

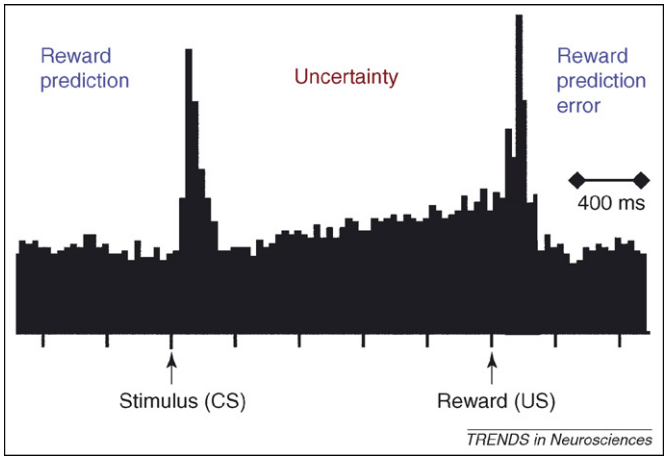

Figure 2. Coding of reward uncertainty, distinct from the reward-prediction error, by dopaminergic neurons. The sustained response during the stimulus–reward interval co-varies with uncertainty (variance of binary probability distribution), whereas the more phasic prediction-error response co-varies with the expected value of experienced minus predicted rewards. The graph shows the average activity of a population of 44 dopaminergic neurons (all three activations are also seen in individual trials of individual neurons). The vertical axis shows the impulse activity (gray baseline activity is ~2 impulses/s). Abbreviations: CS, conditioned stimulus; US, unconditioned stimulus.

Aversive events

Punishers have motivationally opposite effects to rewards, produce withdrawal behavior, constitute negative outcomes, serve as negative reinforcers in aversive conditioning by reducing the behavior leading to punishment and increasing the behavior leading to its avoidance, and produce aversive predictions for decision-making in choice behavior.

Dopaminergic neurons from monkeys, rabbits and rats respond, mostly with depressions, to electrical stimulation of peripheral nerves, air puffs, painful pinches, hypertonic saline, or conditioned visual or auditory stimuli associated with an inescapable electric shock to the ear, air puff or saline in active avoidance trials [17,32–34]. Depending on the nature of the stimulus, the responses usually start slowly and last for several seconds, with the exception of rapid depressions after electrical nerve stimulation, which show time courses similar to the depressions seen after negative-prediction errors in awake animals. Some dopamine-mediated responses in anesthetized animals consist of initial activations or rebound activations after depressions, starting slowly after stimulus onset and lasting for several seconds, often beyond stimulus offset [32,35]. The responses are usually five to ten times slower than the short-latency, phasic activations induced by reward-related stimuli and have a disproportionately stronger effect on the average impulse activity than shorter depressions. Only neurons responding with depressions, but not activations, to pain-pinch immunopositively stain for a dopamine marker, suggesting that some neurons activated by aversive stimuli under anesthesia might not be dopaminergic [34]. Only a few aversive responses resemble the short-latency, phasic activations typical of reward-related stimuli [17,36].

In responding to aversive stimuli, dopaminergic neurons have few direct activations, several rebound activations and frequent depressions, and, as such, the neurons distinguish quite clearly between aversive and reward-related stimuli (Figure 3a–c), even with their propensity for generalizing activation–depression responses. In particular, the phasic, unidirectional, activation impulse response typical of rewards occurs only rarely after aversive stimuli in both awake and anesthetized animals. These differences, with time courses in the subsecond range, should be easily detectable by postsynaptic striatal and cortical neurons operating with the precision of tens of milliseconds but are unlikely to be detectable in dopamine-release studies, with time courses of minutes.

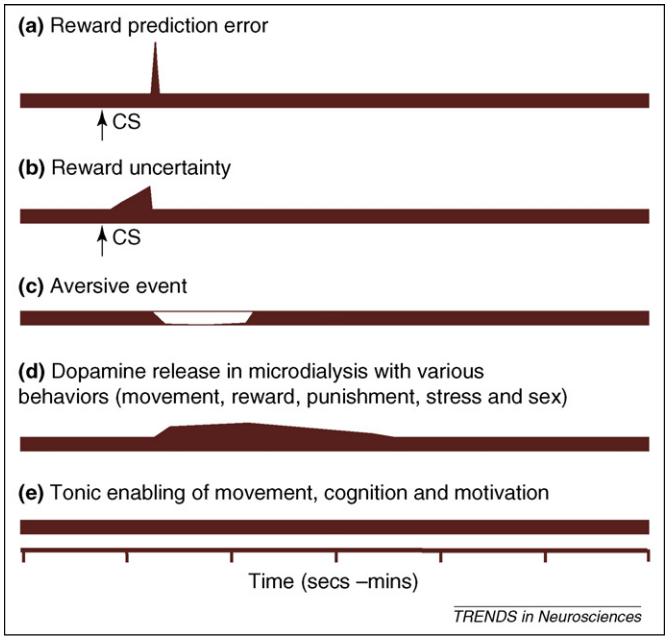

Figure 3. Dopamine-mediated responses, measured by different methods, with different time courses and related to different kinds of information. **(a)** Reward-prediction-error response. **(b)** Uncertainty-related response. Uncertainty is measured by statistical variance. **(c)** Slower depression following aversive stimuli, such as pain pinch under anesthesia. **(d)** Slow dopamine concentration change following a variety of behavior-related events, as measured by microdialysis *in vivo*. **(e)** Tonic dopamine concentration influence, enabling a large variety of behavioral functions of postsynaptic neurons in the striatum and cortex. These functions are deficient after dopamine-depleting lesions in patients with Parkinson's disease and experimental animals. Abbreviation: CS, conditioned stimulus.

Voltammetry

Rapid changes in dopamine concentrations, with time courses of a few seconds, are detected in the nucleus accumbens, striatum and frontal cortex by electrochemical methods using microelectrodes that measure the currents related to oxidation and reduction of dopamine. The changes occur in relation to various behaviorally relevant events, including exposure to novel environments, unpredicted primary liquid rewards, sexual stimuli, conditioned visual and olfactory stimuli predicting food or drug rewards and approach behavior during reward expectation that precedes lever pressing for food or drug rewards [26,27,37–39]. Whereas earlier voltammetric studies also detected electrochemical changes with unrewarded movements and primary and conditioned aversive stimuli, such as tail pinch, ice bath, restraint stress, restraining objects and social intruders [40–42], the specific chemical species responsible for these changes during behavior has not been established.

Thus, voltammetric measurements detect changes in dopamine release with behaviours similar to the electrophysiological responses of dopaminergic neurons, namely reward-related and novel stimuli. The two techniques reveal changes with approximately comparable time courses, although the voltammetric changes are somewhat slower. Furthermore, the voltammetric technique involves adsorption and desorption of dopamine to the electrode and is slow compared with the rapid time changes in extracellular dopamine concentration [43]. These comparisons suggest that the electrophysiologically measured behavior-related activity translates to dopamine release in terminal regions. However, the behavioral events effective for voltammetric changes show a somewhat larger spectrum, including rewarded movements and possibly aversive events.

Microdialysis *in vivo*

Insertion of tubes of submillimeter thickness, with semipermeable membranes, into specific brain structures can be used to collect molecules diffusing from the surrounding tissue into the perfusate. The dialyzate is subsequently analyzed for dopamine using highly sensitive biochemical and electrochemical methods.

A considerable number of behavioral events lead to 20–100% increases in the dopamine concentration in the nucleus accumbens, striatum and frontal cortex. These increases last up to tens of minutes and often beyond the studied behavior. Effective events include a considerable range of behavioral events, including novel environments, primary food and liquid rewards, visual and auditory stimuli that predict food, liquid or drug rewards, sexual activity, aversive electric foot shock, tail shock, ice bath, handling and restraint stress, visual, auditory and taste stimuli associated with foot shock or lithium-induced malaise, lever pressing for food, performance of delayed alternation, and active electric foot shock avoidance [44–55] (Figure 3d).

A single dialysis measure of dopamine for 1 min or several minutes covers a much longer period than many sensory, motor, motivational and cognitive events, which occur in a time course of seconds or fractions of seconds. It is possible that the observed changes in dopamine concentration are related to rather slow processes, including appetite, hunger, satiation, behavioral excitation, aggression, mood, fatigue, desperation, sleepiness and neuronal functions, such as maintenance of hippocampal plasticity or memory consolidation [56,57]. Microdialysis-measured changes in dopamine concentration in the range of 10–60 min are ~200–1800 times slower than the fastest behavior-related voltammetric changes of 2–3 s and 3000–18 000 times slower than electrophysiological responses to reward-related stimuli lasting 200 ms. Changes in dopamine concentration occurring within a single 1 min sample are still 300 times slower than the 200 ms dopamine-mediated reward signal. Whereas fast-scan voltammetry can detect rapid transients in dopamine concentration, the dopamine-mediated signal measured by dialysis might partly reflect the temporal integration of transient changes. Thus, the temporal differences between microdialysis and other measures of dopamine activity are substantial and make the relationships to individual behavioral processes more difficult to assess and interpret.

Some of the behavior-related dopamine-mediated changes measured by voltammetry have not been confirmed to be dopamine-mediated, which would explain the lack of agreement with dopamine-impulse activity. Furthermore, some changes reported by microdialysis are rarely reported with dopamine-impulse activity. The dopamine concentration increases during microdialysis related to punishers and movements could derive from rebound impulse activations following aversive-induced depressions [26,28]. Other possible sources of dopamine

are the presynaptic influences of glutamatergic cortical inputs on striatal dopamine release [58]. Corticostriatal fibers from different origins, carrying activities related to punishment, could induce dopamine release through local presynaptic influences on dopamine varicosities, without involving changes in impulse activity at dopamine cell bodies. Indeed, release of dopamine from the accumbens following aversive stimuli diminishes after differential blockade of striatal glutamate receptors [59], although another study emphasizes the necessary role of dopamine impulses [60]. Presynaptic influences on dopamine release might also explain the regional differences in primary and conditioned punisher-induced dopamine release in the nucleus accumbens and frontal cortex [51,57,61]. Movement-related inputs from motor and premotor cortical areas to the striatum might mediate the movement-related dopamine-mediated changes observed using voltammetry and dialysis.

Processes deficient in parkinsonism

Dopamine depletion in patients with Parkinson's disease and experimental animals produces severe, well-documented deficits in movement, motivation and cognition. Externally administered dopamine precursors and receptor-stimulating agents encourage restitution of many motor, motivational and cognitive functions, although some deficits in discrimination, learning and appetitive behavior remain [62–66]. Although treatment using dopamine precursors might restore dopamine concentrations and enable effective phasic signals in the remaining dopaminergic neurons, the therapeutic efficacy of direct dopamine receptor agonists cannot be owing to restored dopamine-impulse activity, with specific temporal changes. Thus, dopamine neurotransmission is crucially involved in several behavioral processes for which it does not seem to show temporal changes; for example, arm and eye movements are not associated with major dopamine-impulse changes [67,68].

It seems that the mere presence of dopamine receptor stimulation without temporal changes assures the proper functioning of the large number of behavioral processes deficient after dopamine depletion. These processes are probably carried by the postsynaptic striatal and prefrontal neurons. Apparently, a large variety of behavior-related changes in postsynaptic striatal and prefrontal neurons depend on tonic, rather than phasically changing, stimulation of dopamine receptors. Thus, dopamine seems to have a predominantly enabling, modulatory role on postsynaptic neurons involved in these functions (Figure 3e).

The required level of dopamine receptor stimulation depends on tonic dopamine-impulse activity maintaining an ambient, sustained, extracellular dopamine concentration that is further regulated locally by processes such as dopamine reuptake, end-product control of synthesis and release, and presynaptic influences from other neurotransmitters [31,69]. The basal striatal dopamine concentration of 5–10 nM is part of an extracellular 'soup of neurotransmitters' and sufficient to tonically stimulate D2 receptors in their, mostly, high-affinity state [30]. Accordingly, the tonic, enabling dopamine concentration might be derived from the same impulse-dependent or presynaptically-controlled release of dopamine that changes phasically in relation to behavior-related events.

Concluding remarks

The reviewed data demonstrate that a neurotransmitter system can have two distinct properties that, amazingly, are operational at the same time. It can be involved in the transmission of time-specific information about a restricted spectrum of external events. Concurrently, it can have a crucial, apparently sustained, influence on postsynaptic neural processes without temporal modulation. Although other neurotransmitter systems are also known to contribute to the chemical mix of the extracellular liquid in the brain, the crucial functions of the 'soup of neurotransmitters' has rarely been shown so clearly as in the case of dopamine. The phasic responses to reward-related events, notably reward-prediction errors, seem to lead to chemically measurable dopamine release, although the current limitations of voltammetry do not enable us to make close comparisons between time courses in the subsecond range. By contrast, the behavioral relationships of dopamine release measured by dialysis *in vivo* occur over a much longer timescale, which might suggest that they belong partly to different behavioral processes than those involved in immediate, subsecond reactions to external events.

Acknowledgements

The author's work is supported by the Wellcome Trust, Swiss National Science Foundation, Human Frontiers Science Program and several other grant and fellowship agencies.

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