12 Reward-related Signals Carried by Dopamine Neurons

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Impaired neurotransmission of dopamine neurons projecting from the ventroanterior midbrain to the striatum and frontal cortex results in a multitude of severe behavioral impairments comprising motor, cognitive, and motivational processes. However, several lines of anatomical, physiological, and behavioral evidence suggest that dopamine neurons are not able to encode all details of the behaviors in which they are apparently involved. In order to assess more closely their function, we investigated the activity of dopamine neurons in monkeys during the performance of various behaviors.

SELECTIVE RESPONSES TO A LIMITED RANGE OF STIMULI

Primary Rewards

The optimal stimulus for activating dopamine neurons consists of a phasically occurring unpredicted food and liquid reward. Responses occur when animals touch a small morsel of hidden food during exploratory movements or when receiving a drop of liquid at the mouth outside of any behavioral task or while learning a task (figure 12.1 top) (Romo and Schultz, 1990; Ljungberg et al., 1992; Mirenowicz et al. unpublished observation). The responses do not occur when similarly shaped nonfood objects are touched or when a fluid valve is operated without actually delivering liquid.

Reward responses are abolished when the time of reward delivery is predicted by conditioned phasic stimuli, whereas the general reward prediction provided by known behavioral contexts alone does not abolish them. Thus, responses to reward encountered during spontaneous movements disappear when the same movement is performed in response to a conditioned stimulus. In a learning situation, reward responses disappear when a stimulus has become a valid reward predictor. Learning of a more complex delayed response task via several subtasks is accordingly accompanied by reward responses during the learning phase of each subtask which disappear when each learning curve reaches an asymptote.

The neurophysiological reasons for the disappearance of the response to predicted reward are unclear but might consist in an active inhibition. Omission of expected reward following an error of the animal or experimenter interaction phasically depresses the activity of dopamine neurons exactly at the time where reward would have occurred (Romo and Schultz, 1990; Ljungberg et al., 1991), even with a reward normally delivered 0.5 second after the last external stimulus (Schultz et al., 1993).

Conditioned Stimuli

Dopamine neurons are activated by conditioned visual or auditory stimuli that have become valid reward predictors (figure 12.1, middle) (Schultz, 1986; Schultz and Romo, 1990; Ljungberg et al., 1992). These stimuli are generally less effective than primary rewards, both in terms of response magnitude in individual neurons and in terms of fractions of neurons activated. Instruction and discriminative cues, which are primarily occasion-setting stimuli rather than predictors of reward, are less effective for activating dopamine neurons. Responses of dopamine neurons to a conditioned light have also been observed in haloperidol-treated rats (Miller et al., 1981). Dopamine neurons show minor or no activations prior to and during the execution of movements and are not activated during the delays of typical frontal cognitive tasks (De Long et al., 1983; Schultz et al. 1983, 1993; Romo and Schultz, 1990).

The large majority of responses specifically occur to appetitive stimuli, and only a few neurons are also activated by a conditioned aversive light or sound stimulus in an air puff or a saline avoidance task, and in response to other arousing stimuli (Mirenowicz and Schultz, unpublished observation).

As dopamine neurons respond to a conditioned, reward-predicting stimulus, they stop responding to the reward which is now predicted by the stimulus (see figure 12.1, middle). This response transfer occurs in single dopamine neurons tested both with unpredicted rewards and with reward-predicting conditioned visual or auditory stimuli in stable behavioral situations (Romo and Schultz, 1990). Likewise, the learning of an instrumental lever-pressing task is accompanied by a transfer of the response from the unpredicted reward to the reward-predicting conditioned stimulus (Ljungberg et al., 1992). The transfer is not always complete; the conditioned stimulus is usually somewhat less effective in activating dopamine neurons than the unpredicted primary reward, whereas the primary reward response is virtually always abolished in these situations.

Responses to conditioned stimuli also depend on whether that stimulus itself is unpredicted and are reduced when it is signaled by a preceding cue, to which dopamine neurons then may respond (figure 12.1, bottom) (Schultz et al., 1993). Extensive overtraining also atten-

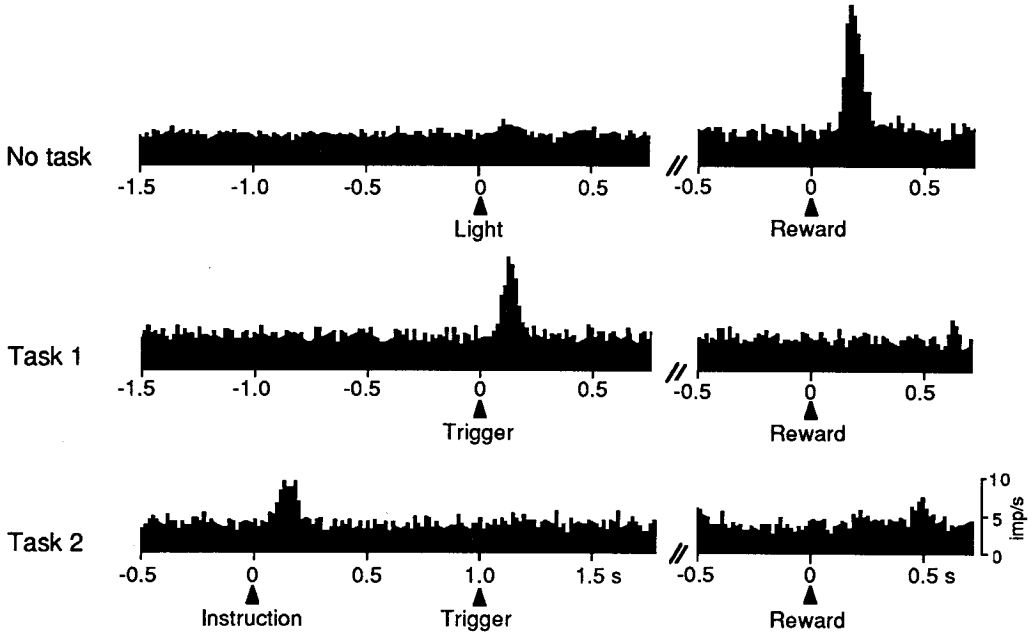

Figure 12.1 Responses of dopamine neurons to unpredicted primary reward and the transfer of this response to progressively earlier reward-predicting stimuli. All displays show population histograms obtained by averaging the normalized perievent time histograms of all dopamine neurons recorded in the indicated behavioral situations, independent of the presence of a response. (*Top*) In the absence of any behavioral task, there was no population response in 44 neurons tested with a small light (data from Ljungberg et al., 1992), but an average response in 35 neurons to a drop of liquid delivered at a spout in front of the animal's mouth (unpublished data). (*Middle*) Response to a reward-predicting trigger stimulus in a spatial choice reaching task, but absence of response to reward delivered during established task performance (23 neurons; data from Schultz et al,. 1993).(*Bottom*) Response to an instruction cue preceding by a fixed interval of 1 second the reward-predicting trigger stimulus in an instructed spatial reaching task (19 neurons; data from Schultz et al., 1993). The time base is interrupted because of varying intervals between the conditioned stimuli and the reward.

uates responses to conditioned stimuli (Ljungberg et al., 1992), probably because the animal comes to anticipate the stimulus on the basis of the events in the preceding trial in the highly stereotyped and automated task. Moreover, the conditioned stimulus may lose some of its reward-predicting incentive properties when the performance is established as an overtrained habit, where each response is no longer explicitly executed in order to receive an individual reward (Dickinson, 1980).

Dopamine neurons discriminate between reward-predicting and nonpredictive stimuli as long as the stimuli are sufficiently dissimilar (Ljungberg et al., 1992), in particular when different modalities are used (Mirenowicz and Schultz, unpublished observation). By contrast, dopamine neurons respond to both rewarded and unrewarded stimuli

when they are physically very similar. A small box that opens rapidly in front of the animal does not by itself activate dopamine neurons. However, responses occur to every opening if the box on some trials contains a visible morsel of food (Ljungberg et al., 1992). Also, responses occur indiscriminately to two identical boxes placed side by side despite the fact that only one of them contains food (Schultz and Romo, 1990). Animals perform an indiscriminate ocular orienting response to each opening, but approach only the baited box with their hand. Similarly, dopamine neurons continue to respond to conditioned stimuli even when these stimuli are used in a different task and thus have lost their original reward prediction property (Schultz et al., 1993).

Novel Stimuli

Unexpected novel stimuli are effective in activating dopamine neurons as long as they elicit behavioral orienting reactions (e.g., ocular saccades). Neuronal responses subside together with orienting reactions after several stimulus repetitions (Ljungberg et al., 1992). Similar responses of dopamine neurons to unconditioned high-intensity or novel stimuli in parallel with whole-body orienting reactions have been described in cats (Steinfels et al., 1983).

Common Response Characteristics

The responses of dopamine neurons to these different stimuli are remarkably similar. They are phasic and occur with latencies of 50 to 120 ms, last less than 200 ms, and are composed of occasionally a single impulse or, more often, a short burst of a few impulses. They are polysensory and independent of the side of visual, auditory, or somatosensory stimulus presentation relative to the body axis. Effective stimuli in most situations activate the majority of the population of dopamine neurons, and different dopamine neurons in groups A8, A9, and A10 respond to the same stimuli in a similar manner, such that clearly separate response types cannot be associated with different populations of neurons. This homogeneity of neuronal responses suggests that dopamine neurons respond in parallel as a population rather than displaying differential response profiles.

NATURE OF STIMULI EFFECTIVE FOR ACTIVATING DOPAMINE NEURONS

Predominance of Reward

The major stimuli for dopamine neurons are reward-related events, both primary rewards and conditioned, reward-predicting stimuli. Ex-

ceptions to this are novel or arousing stimuli and conditioned aversive stimuli. Novel stimuli are potential rewards or reward predictors and might be included in the class of reward-related events. Aversive responses are found in relatively few dopamine neurons (<20%) which apparently belong to a less specific subpopulation responding to a larger spectrum of behaviorally important stimuli.

Salient Stimuli

The events to which dopamine neurons respond belong to the most important, salient external stimuli to which a subject needs to react in order to not miss an important object. Salient stimuli are unconditioned rewards and aversive stimuli, conditioned stimuli predicting rewards or punishment, and high-intensity, surprising, novel stimuli. These stimuli alert the subject, which interrupts its ongoing behavior, orients to the stimulus, and processes it with high priority (Schultz, 1992). However, most dopamine neurons respond best to only a subset of salient stimuli, namely primary rewards and conditioned reward-predicting stimuli. This stimulus repertoire suggests a more circumscript coding of reward-related stimulus properties.

Characteristics of Reward-related Stimuli

In summary, the most potent stimuli for activating dopamine neurons are primary rewards and conditioned stimuli that signal such rewards. The maintenance of the dopamine response depends, however, upon ensuring that the occurrence of the reward or conditioned stimulus is not itself predicted by another phasic stimulus. With increasing experience of a signaling relation between a predictive stimulus and a primary reward, the dopamine response to reward is attenuated as that to the conditioned stimulus develops. In order for this conditioned attenuation to occur, it appears to be necessary that the stimulus itself provide information about the time of occurrence of reward, for in its absence the dopamine response to the reward is maintained across repetitive presentations in a constant, tonic environmental context. Furthermore, establishing a predictive relation between a stimulus and reward does not produce a general depression of the dopamine response to rewards for, if after such training, the reward is presented unexpectedly in the absence of the stimulus, a full dopamine response is elicited. Finally, it should be noted that the dopamine responses do not encode the particular physical properties of the eliciting event; both primary rewards and conditioned stimuli with differing sensory characteristics elicit a common dopamine response.

This characterization of the responses of dopamine neurons to primary rewards suggests that their activity may be related to the rein-

forcing function of rewards. In general terms, rewards appear to play two roles in the process of conditioning. The first is their function in bringing about the learning of a new behavioral response, whereas the second reflects the capacity of a reward to maintain an established behavioral response. In the absence of an effective reward, an established conditioned response will undergo extinction. Given this distinction, the response characteristics of dopamine neurons to rewards suggest a relationship to *learning* of new behavior rather than to *maintaining* an established behavior. Contemporary learning theories in general assume that only unexpected or surprising rewards bring about the acquisition of a new conditioned response (Dickinson, 1980). Thus, the critical feature of dopamine neurons that suggests a role in learning is their sensitivity to unexpected rewards. Dopamine neurons do not respond to fully predicted rewards, just as such rewards, although capable of maintaining already established conditioned behavior, are not effective in bringing about the acquisition of a new behavioral response. The finding that stimuli predicting primary rewards also activate dopamine neurons is compatible with this parallel for it is well established that such stimuli can act themselves as conditioned reinforcers in the acquisition of a new behavioral response.

In contrast to the responses of dopamine neurons to unexpected rewards, neurons in the striatum and in structures projecting to the striatum, such as the amygdala and orbitofrontal and anterior cingulate cortex, respond to primary rewards in well-established behavioral tasks and are not affected by the uncertainty of reward (Niki and Watanabe, 1979; Thorpe et al, 1983; Nishijo et al., 1988; Apicella et al., 1991). This suggests that different aspects of the reward signal are distributed over different neuronal systems in the brain and that the function of reward signals accordingly may vary among these systems. The neuronal response to reward in striatal, amygdalar, and cortical neurons during well-established behaviors suggests a function in maintaining rather than bringing about learning. Other neurons in the striatum are activated for several seconds during the expectation of reward following a well-established conditioned stimulus (Apicella et al., 1992), a further argument for a role of the striatum in the maintenance of learned behaviors.

Error Signals

The hypothesis that dopamine neurons may mediate the role of unexpected rewards to bring about learning can be refined by reference to the concept of an *error* signal. Contemporary learning theories characterize learning as acquisition of associative strength by a conditioned stimulus (Dickinson, 1980). The increment in associative strength in each learning episode in which the conditioned stimulus is paired with

a reward is determined by the discrepancy Δ which equals $(\lambda - V)$ where V is the current associative strength of the conditioned stimulus on that episode and λ is the maximum associative strength that could be sustained by the reward (Rescorla and Wagner, 1972; Mackintosh, 1975; Pearce and Hall, 1980). Thus, this discrepancy reflects the extent to which the conditioned stimulus has already been established as a predictor of reward. When Δ is zero, $V = \lambda$ which reflects the fact that the associative strength of the conditioned stimulus is sufficient to predict the occurrence of the reward, and little or no further learning (i.e., no increments in V) will occur. By contrast, when $\lambda > V$, the associative strength of the stimulus does not fully predict the reward and the Δ term is positive and leads to further increments in associative strength. In this sense, the Δ term represents the extent to which the animal has failed as yet to learn the full predictive relation between the conditioned stimulus and the reward, and for this reason it is referred to as an error signal. Learning algorithms that serve to minimize the Δ term can be considered as error correcting. Recent work has suggested that this learning rule is formally equivalent to the delta rule (Widrow and Hoff, 1960) of artificial neuronal networks (Sutton and Barto, 1981), thus allowing single neuronal elements, at least theoretically, to implement this learning rule. That temporal aspects in the unpredictedness of events are important for learning is suggested by the fact that the temporal variation in reinforcer occurrence constitutes an element of unpredictedness that allows learning (Dickinson et al., 1976).

Within this analysis of learning, the activity of dopamine neurons would appear to be a good candidate for representing the error signal or Δ term and also possibly applying it as a teaching signal controlling the changes in neuronal structures representing the associative strength of a conditioned stimulus or response. The error signal should be large on a learning episode when the reward is unexpected and a corresponding dopamine response is observed. By contrast, the error signal should be small when a predicted reward is presented and, in accord with the hypothesis, little or no activity is recorded in dopamine neurons in response to this event. Moreover, the depressant response of dopamine neurons to the unexpected omission of a reward following a well-established reward-predicting stimulus suggests a mechanism by which the Δ term may be computed at a neuronal level. Thus, it may well be that a predictive stimulus for a reward serves to inhibit the dopamine response that would otherwise be elicited by the reward.

In stressing another parallel between dopamine activity and the error signals governing learning, it should be noted that any error signal represented by the dopamine response can only relate to the salient, affective, or hedonic properties of the reward and not to any particulars of the reward objects, for, as we have noted, the same neuronal response is elicited by a variety of different rewards, as well as by con-

ditioned, reward-predicting stimuli of various sensory modalities. This assumption is, however, in accord with accounts of behavioral deficits observed following interference with dopamine neurotransmission (Wise et al., 1978; Robbins and Everitt, 1992; Robinson and Berridge, 1993).

IMPACT OF THE DOPAMINE MESSAGE ON POSTSYNAPTIC PROCESSING

Further clues to the function of phasic dopamine responses to reward-related stimuli can be obtained by comparing them with task-related activities in the target structures, and by taking into account the circuitry and neuronal mechanisms influenced by dopamine neurons. There could hardly be a greater difference of behavior-related activity than that seen between dopamine and striatal or cortical neurons. In contrast to the rather homogeneous responses of dopamine neurons to a narrow range of stimuli, striatal neurons show highly differentiated activity related to various stimuli; to the preparation, initiation, and execution of limb and eye movements; to the expectation of known behavioral events; and to the expectation and reception of reward.

Large Circuits

Dopamine neurons innervate basically the dorsal striatum, the ventral striatum (the nucleus accumbens of rodents), and the frontal cortex. These structures globally subserve the organization of behavioral output. The striatum is a part of loops involving the frontal cortex and in addition receives input from postcentral sensory and association cortex and from limbic cortical and subcortical structures (figure 12.2). Besides the loops with the cortex, basal ganglia output is directed to limbic structures and to the superior colliculus, which are involved in affective behavioral components, memory, and simple motor output. Thus, dopamine neurons are in a position to influence the control of behavioral output by their widespread projections to structures involved in highly differentiated information processing. The limited spectrum of their largely homogeneous activity suggests that dopamine neurons contribute a particular component of neuronal processing that is commonly important for their target structures.

Local Circuitry in Target Structures

The basic arrangement of synaptic influences of dopamine neurons on striatal and frontal cortex neurons of rats and monkeys consists of three elements: the dendritic spine of the postsynaptic neuron, the dopamine presynaptic varicosity contacting the stem of the dendritic spine, and

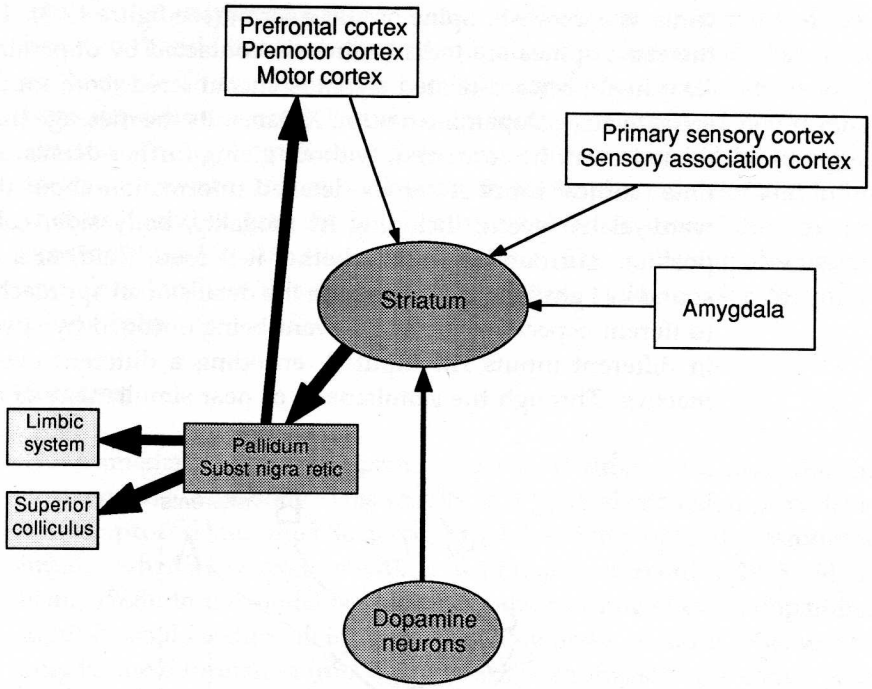

Figure 12.2 Highly simplified schema showing how dopamine neurons act on the striatum, which is linked through major circuits to other brain centers controlling behavioral output. The striatum denotes both the dorsal caudate and putamen and the ventral striatum including the nucleus accumbens. For reasons of simplicity, the dopamine innervation to the frontal lobe (*upper left: prefrontal cortex, premotor cortex, motor cortex)* has been omitted.

an excitatory cortical terminal at the tip of the dendritic spine (figure 12.3) (Freund et al., 1984; Goldman-Rakic et al., 1989; Smith et al., 1993). Every medium-sized striatal neuron receives about 500 to 5000 dopaminergic synapses at its dendritic spines and about 5000 to 10,000 cortical synapses (Doucet et al. 1986; for more details, see chapters 3 and 4). It is unclear whether all cortical inputs to a single striatal neuron could come from the same cortical column and rather unlikely that they originate from the same cortical neuron. It would be interesting to know which cortical areas may possibly converge onto striatal neurons. Although current schemes of basal ganglia connections suggest a maintained segregation of cortical inputs into the striatum (Alexander et al., 1986), it is conceivable that some functionally related, homotopical somatosensory and motor cortical areas project into common regions of the striatum (Flaherty and Graybiel, 1993). Such specific patterns of convergence would allow dopamine neurons to select the synaptic effects of cortical inputs at individual striatal neurons.

In a reduced model of such an anatomical arrangement, let *A* and *B* be two inputs converging on a single striatal neuron *I*, each of which

contacts a dendritic spine of that neuron (see figure 12.3). The stems of the same spines are indiscriminately contacted by dopaminergic input *X*. When a reward-related signal is encountered, both inputs *X* and *A* are activated. Dopamine neuron *X* transmits the message that a reward-related event has occurred, without giving further details. At the same time, cortical input *A* carries detailed information about the same reward-related event, including its modality, body side, color, texture, position, surrounding, and whether it is food, fluid, or a conditioned sound or light, and may also code the details of an approach movement (different aspects of the same event being encoded by specific activity in different inputs *A*). Input *B*, encoding a different event, remains inactive. Through the simultaneity or near simultaneity of activity in *A*

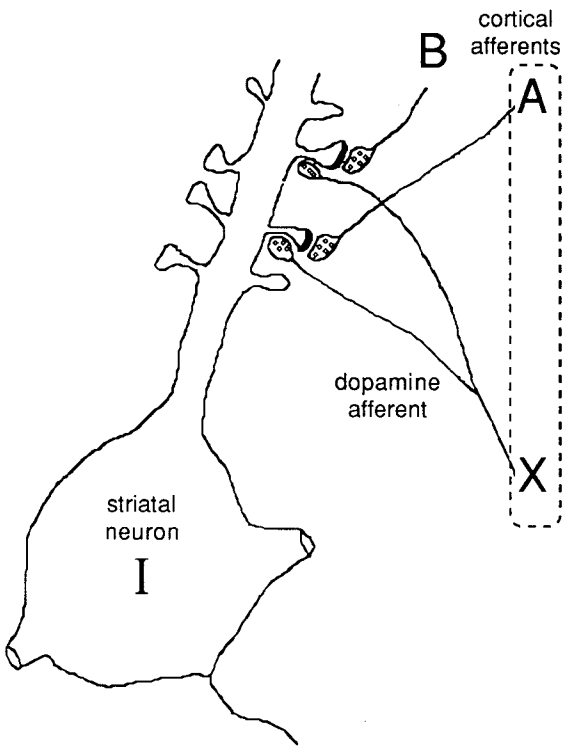

Figure 12.3 Synaptic arrangement of inputs from cortex and dopamine neurons to medium-sized spiny striatal neurons. The dendritic spine is contacted at its tip by a cortical axon and at its stem by a dopamine axon. In the basic design of hypothetical dopamine-dependent heterosynaptic plasticity induced by a reward-related event, cortical neurons A and B converge at the tip of dendritic spines on a single striatal neuron I. These connections might be modifiable by increased use, e.g., long-term facilitation. However, the modification occurs only when dopamine input X coming indiscriminately to the stems of the same dendritic spines is active at the same time. In the present example, cortical input A, but not B, is active at the same time as dopamine neuron X, as during the occurrence of a reward-related event. This leads to modification of the *A*→*I* transmission, but leaves the B→I transmission unaltered. (Anatomical drawing modified from Smith and Bolam, 1990.)

and X, the activity of neuron X may influence synaptic transmission between A and I but leave the transmission at the inactive $B \rightarrow I$ synapse unchanged. Thus, the message about a reward-related event coming from dopamine neuron X specifically influences the $A \rightarrow I$ neurotransmission. The key function of dopamine neuron X would be to signal the event (reward) that is particularly important for behavior and influence as a kind of gate the highly structured activity circulating in corticostriatal and limbic-striatal connections. The following discussion speculates on how this synaptic constellation could be used for influencing behavior.

Focusing

The immediate effect of dopamine release is probably a reduction in postsynaptic excitability. This results in a general reduction of corticostriatal processing, thus focusing striatal activity onto the strongest inputs, whereas weaker activity is lost (Toan and Schultz, 1985; Filion et al., 1988). In the model of figure 12.3, the focusing effect of dopamine input X would reduce all input activity of neurons A and B. This would only let the information from input A, as the strongest of the convergent inputs, pass beyond the impulse-generating mechanism at the cell body, whereas weaker activity would be lost. Figure 12.4 illustrates the focusing effect in a more complex network where several presynaptic (e.g., cortical) neurons converge in an ordered fashion onto postsynaptic (e.g., striatal) neurons, corresponding to convergence from somatosensory and motor cortex inputs to striatal regions (Flaherty and Graybiel, 1993). A contrast-enhancing nonlinear element would be the threshold phenomenon in the opening of voltage-dependent sodium channels at the excitable membrane. Thus, the phasic release of dopamine induced by a reward-related event would give higher impact to all information pertaining to the currently present reward event. The immediate result could be a reorientation of behavior towards salient appetitive stimuli.

Learning

Although the evidence from behavioral deficits arising from impaired dopamine neurotransmission does not unequivocally support a specific role of dopamine in learning and memory,it is tempting to suggest a hypothetical model according to which the reward-related responses of dopamine neurons could influence neuronal plasticity in the striatum and frontal cortex.

In our model of figure 12.3, let us make the synaptic weights of cortical inputs A and B to striatal neuron I hebbian-modifiable, and assume that this plasticity depends on dopamine input X. Neurons A and X would be simultaneously active when a reward-related stimulus occurs, whereas neuron B does not modify its activity. This would

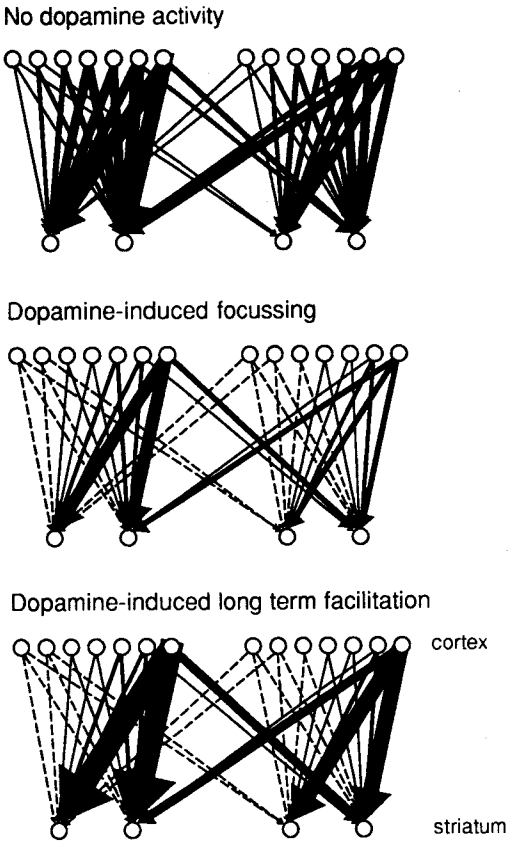

Figure 12.4 A possible influence of a phasic dopamine signal on the selection of striatal information processing based on convergent inputs. Suppose that inputs from different cortical origins converge in an ordered manner on single striatal neurons. The different strengths of these inputs reflect the differential activation of cortical neurons by the current behavioral situation. In the example, neurons could be activated by the physical stimuli emanating from the reward and its surroundings, by reaching movements of the arm toward the reward, and by event-related memory and expectation activity. (*Top*) In the absence of dopamine, cortical inputs would influence striatal neurons in a poorly contrasted manner. (*Middle*) Dopamine has an immediate focusing effect which nonlinearly enhances the strongest inputs occurring at the time of the dopamine signal relative to weaker inputs which are suppressed. (*Bottom*) In a hypothetical learning mechanism, dopamine facilitates long-term changes at hebbian-modifiable synapses. Arrow width represents the relative synaptic influences on postsynaptic impulse activity, consisting in a combination of presynaptic influence and synaptic strength.

increase the synaptic weight at the active synapse $A \rightarrow I$, but leave the weight at the inactive $B \rightarrow I$ synapse unchanged. If neuron A is subsequently activated again by a stimulus that shares some features with the stimulus having activated both neurons A and X before, but without necessarily also activating neuron X, the response in neuron I would be increased, whereas any input from neuron B leads to an unchanged postsynaptic response. Thus, neuron X need only be active in a subset of situations in which neuron A is active. In this model a reward-related event coming from dopamine neuron X would heterosynaptically facilitate plasticity of the $A \rightarrow I$ synapse. Or, the synaptic plasticity of $A \rightarrow I$ and $B \rightarrow I$ neurotransmission is conditional of X being conjointly active with A or B. In the more elaborate network of figure 12.4, the dopamine input would induce a long-term increase in transmission in those connections that were active when a reward-related event occurred. This selection of anatomically convergent inputs would in the future favor the processing of the inputs present at the striatal neurons when dopamine neuron X discharged, such as sensory responses from the rewarding event, short-term memory and expectation-related activity surrounding the event, and activity related to the particular movements leading to the event.

This model assumes that dopamine neurons may participate in learning by signaling an unpredicted reward. This signal might well code the most attracting aspects of the reward and be particularly important during the learning phase. However, dopamine neurons do not convey a message about the reinforcer once the reward contingencies are established and reward is predicted by phasic stimuli, although this reinforcer signal is important for the performance of learned behavior and for avoiding extinction. A neuronal network model using the dopamine signal for learning may take these characteristics into account and include a separate reinforcer signal for maintaining established behavior. Such a reinforcer signal during established task performance exists in striatal neurons (Apicella et al., 1991). Because of the difference against the reward response of dopamine neurons, the signal may enter the striatum from elsewhere, possibly from the amygdala. It would be interesting to see how the striatum and artificial networks would profit from different neuronal messages signaling the physically same reinforcing event during learning and performance, respectively. Taken together, this suggests that the dopamine signal could be an important substrate for reinforcement learning which appears to be appropriate for the basal ganglia, in contrast to postulated learning mechanisms in the cerebellum using error or deviation signals.

Recent biological findings appear to suggest a role of dopamine in neuronal plasticity. Dopamine neurotransmission may not operate in the same time range of milliseconds as cortically induced excitations. The association of dopamine receptors with G proteins, and particularly

the involvement of a second messenger in the case of the D1 receptor, suggests onsets and durations of postsynaptic membrane effects in the range of seconds. Thus, the dopamine signal appears to influence postsynaptic neurons in a different manner than most other striatal and cortical neurotransmitters (for further details see chapter 4). In addition, inputs to the striatum and nucleus accumbens are subject to posttetanic potentiation and depression (Calabresi et al. 1992b; Pennartz et al. 1993), some of which depend on intact dopamine transmission (Calabresi et al., 1992a). The slower time course of dopamine membrane action may leave a trace of the reward event and influence all subsequent activity. The possibility of dopamine-dependent striatal plasticity and the central importance of unpredicted reward for learning suggest that the observed responses of dopamine neurons may contribute to changes in postsynaptic neuronal circuits underlying reward-directed learning. The reward-related input to dopamine neurons could be the decisive signal upon whose reception the striatal synapses concurrently activated by the events leading to the obtention of reward would be strengthened.

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