Neural mechanisms of reward-related motor learning

Jeffery R Wickens*, John N J Reynolds and Brian I Hyland

The analysis of the neural mechanisms responsible for reward-related learning has benefited from recent studies of the effects of dopamine on synaptic plasticity. Dopamine-dependent synaptic plasticity may lead to strengthening of selected inputs on the basis of an activity-dependent conjunction of sensory afferent activity, motor output activity, and temporally related firing of dopamine cells. Such plasticity may provide a link between the reward-related firing of dopamine cells and the acquisition of changes in striatal cell activity during learning. This learning mechanism may play a special role in the translation of reward signals into context-dependent response probability or directional bias in movement responses.

Addresses
Department of Anatomy and Structural Biology, School of Medical Sciences, University of Otago, P.O. Box 913, Dunedin, New Zealand
*e-mail: jeff.wickens@otago.ac.nz

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Abbreviations
HFS high-frequency stimulation
ICSS intracranial self-stimulation
LTP long-term potentiation

Introduction

Reward is important in motor learning. The integration of reward into behavior occurs where reward-related neural signals meet circuits concerned with motor performance. The dopamine system has been identified as a major processor of reward. One of its major targets is the striatum, which is well known for its importance in motor control.

The striatum receives inputs from all regions of the cerebral cortex, and parts of the thalamus. These excitatory glutamatergic inputs converge with dopamine inputs from the substantia nigra in the striatum (Figure 1). The output of the striatum influences other basal ganglia nuclei, which through direct and indirect pathways reach the thalamus and thence motor regions of the cerebral cortex. This anatomical organization provides a favorable substrate in the striatum for integrating dopaminergic reward signals with sensory cues (from corticostriatal and thalamostriatal afferents) and generating motor commands (through direct and indirect output pathways).

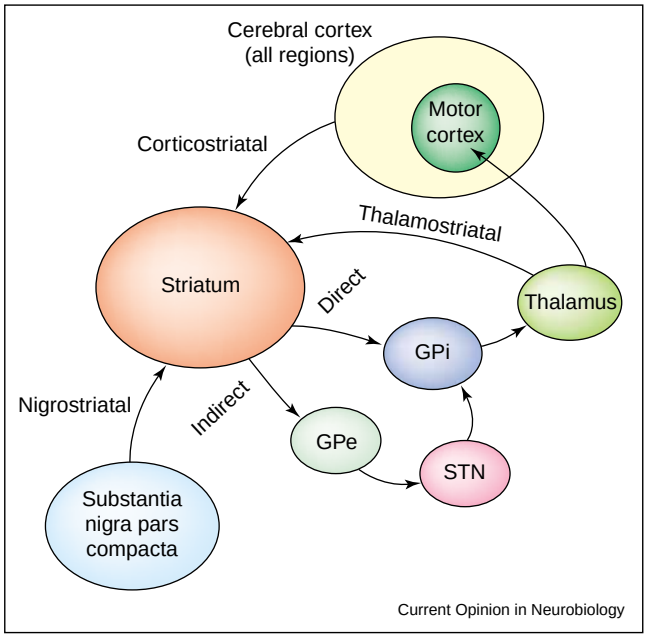
Recent advances in our understanding of the cellular mechanisms that perform this integration have been achieved using electrophysiological studies of synaptic plasticity in the corticostriatal and thalamostriatal afferents. Here, we discuss the involvement of the dorsal striatum in reward-related motor learning, together with recent data on changes in striatal cell firing that occur during such learning, and consider possible links between motor learning and underlying synaptic plasticity mechanisms.

Involvement of the dorsal striatum in reward-related motor learning

Although the striatum has been regarded as important in the control of movement for a long time, it is now recognized that it plays a key role in learning. For instance, extensive evidence indicates a role for the dorsal striatum in response selection and in learning simple stimulus discrimination. One prominent hypothesis is that this brain region mediates a form of learning in which stimulus-response associations [1] or habits [2] are acquired on the basis of positive reinforcement [3•]. Localized brain lesions and pharmacological approaches have been used to examine the role of the basal ganglia in stimulus-response learning. In rats, lesions of the dorsal striatum impair acquisition of tasks requiring a win-stay strategy, in which rewards are obtained by repeating the same action [4]. This is a behavioral measure of stimulus-response associative learning [5]. In humans with neurodegenerative diseases of the basal ganglia, behavioral [6,7] and brain neuroimaging techniques [8] also provide evidence of a role for the basal ganglia in habit learning.

Although lesion studies have suggested the striatum plays a key role in reward-related motor learning, other approaches are required to determine the neural mechanisms involved. The discovery of intracranial self-stimulation (ICSS) opened an important window on reinforcement mechanisms. In ICSS, animals learn to press a lever for electrical stimulation of their own brain. Moving-electrode mapping studies show that the highest response rates and lowest thresholds are in areas traversed by dopamine fibers or containing dopamine cell bodies [9]. Furthermore, dopamine antagonists attenuate the ability of electrical stimulation to provide behavioral reinforcement when ICSS stimuli are delivered during learning, and this attenuation is not simply caused by motor side effects [10]. Although dopamine release appears to be necessary for establishing ICSS [11], the dynamics of dopamine

Figure 1



A diagram showing the connections of the striatum and basal ganglia output nuclei with the cerebral cortex and substantia nigra pars compacta. Reward-related dopamine pulses released in the striatum are proposed to facilitate the selection of particular pathways through the basal ganglia to the motor cortex, and hence of particular actions, according to past and anticipated rewards.

release during ICSS are complex. Dopamine release increases when ICSS stimuli are delivered during learning but declines after behavior is well established [12]. These ICSS data link to a considerable body of evidence from single neuron recordings in monkeys that shows that the nigrostriatal pathway signals the occurrence of unexpected primary and secondary reinforcers. In particular, the majority of nigrostriatal dopamine neurons show phasic activations after unexpected primary rewards and conditioned reward-predicting visual and auditory stimuli [13]. Dopamine cell activation in response to reward-predicting stimuli is also reflected in dopamine concentration changes [14••]. Collectively, this evidence indicates that the dopamine input to the striatum is crucial for its reward-related learning functions.

It should be noted that the majority of dopamine cells reported to have reward-related activity were cells in the substantia nigra, which project particularly to the dorsal striatum, and which degenerate in Parkinson's disease. This reward-related activity of substantia nigra cells is somewhat counter-intuitive, given the profound motor deficits that occur in Parkinson's disease. However, it is consistent with the paucity of movement-related activity in dopamine cells in monkeys [15–19], rats [20•,21,22], or cats [23], and imaging studies in humans that indicate responses to reward in the striatum [24–26]. A special relationship between the phasic processing of reward information and the striatal contribution to the generation of action is suggested by the movement deficit in Parkinson's disease. Resolving this question rests on an improved understanding of how reward signals are integrated into behavior.

Reward-related learning and changes in movement-related striatal cell firing

Neural activity in the striatum of behaving animals is associated with several aspects of learning [27,28]. Two broad groupings of neurons have been characterized. Relatively quiescent cells that fire phasically in a context-dependent association with movement are presumed to be spiny projection neurons. Tonically active neurons are cholinergic interneurons. These neurons do not show movement-related activity, but do show sensory responses that change during learning. Other groups exist, such as feed-forward interneurons. These other cells cannot yet be confidently extracted from the general population of phasic cells, but may be functionally identifiable [29].

An important feature of phasic, presumably spiny cell, movement-related activity is its context dependence. These cells appear to be involved in the learned association of sensory stimuli with movement. After learning, they respond to movement triggered by stimuli, without necessarily responding to the stimuli or movement outside of the task. Progressive changes in the responses of these cells have been described during the association of new visual stimuli with established behavioral responses and reward [30] and during learning of a simple maze [31].

An important new development concerns how the expectation of reward influences movement-related activity in spiny cells [32]. This has involved the use of tasks in which the cognitive requirements stay the same (memory guided saccade) while motivational significance is varied. Studies with such tasks have revealed responses that are modulated by expectation of reward, either as enhancement of responses in the rewarded direction (reward-facilitated responses) or as enhancement in response to non-rewarded directions (reward-suppressed responses). With each change of the preferred direction, these changes in responses occur rapidly. Such changes are also seen in cells that show a reward-oriented response bias before the presentation of the stimulus [33••,34]. The mechanism underlying these changes in cell selectivity is the focus of this review.

Striatal cholinergic neuron activity has also been implicated in the acquisition of reward-related learning. The cholinergic interneurons are a small minority of striatal cells, but contribute extensive axonal arborizations and produce high levels of acetylcholine. Similar to dopamine neurons, cholinergic interneurons do not fire in relation to movement, but they respond to sensory stimuli that have

been associated with reward during sensorimotor learning [35]. The acquired response is a transient suppression (pause response) of the tonic activity of the cholinergic interneurons, which is often preceded by an excitation [36]. The maintenance of these responses is dopamine-dependent [37], and is associated with, but not identical to, learning-related changes in dopamine cell firing that occur over a similar time period [38].

Mechanism for reward-related changes

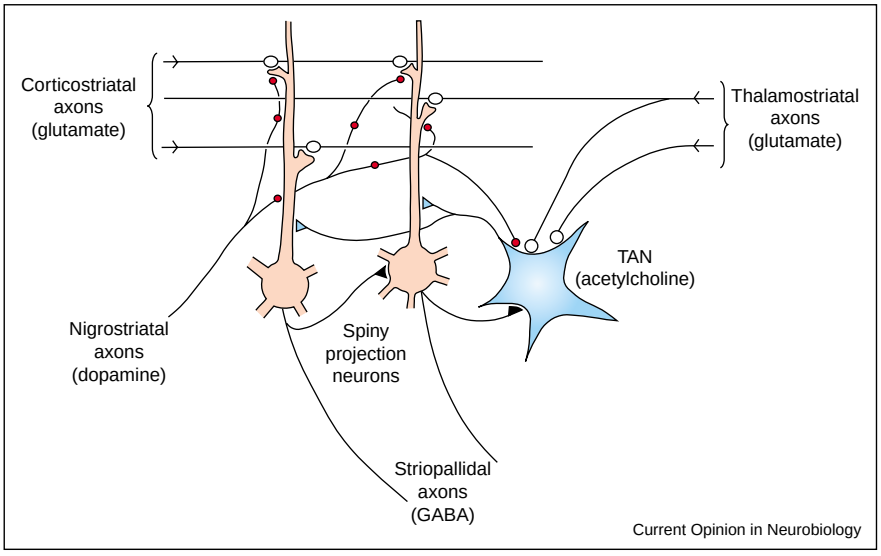
The foregoing evidence regarding reward-related activity in nigrostriatal dopamine projections, and reward-dependent modification of striatal cell responses suggests that dopamine afferents are involved in an essential way in the changes in neural responses that occur in the striatum in association with learning. These changes may take place at specific synapses or, as has been described in invertebrates, affect the whole cell [39•]. Dopamine-dependent modulation or plasticity of the corticostriatal and thalamostriatal pathways is a probable basis for these changes.

The spiny projection neurons receive excitatory synaptic inputs from the cortex and thalamus (Figure 2). Action potential firing activity in spiny projection neurons requires this excitatory drive [40]. Thus, changes in the afferent activity or efficacy of these corticostriatal and thalamostriatal inputs probably underlie the specific learning-related changes in striatal cell activity that are reviewed above. Pulsatile dopamine release evoked during reward-related learning occurs in close proximity to the excitatory corticostriatal and thalamostriatal synapses [41]. There has been growing interest in the hypothesis that reward-related release of dopamine controls synaptic plasticity in these inputs.

Activity-dependent potentiation and depression both occur in the striatum [42]. Long-term depression (LTD) can be induced in the corticostriatal synapses by high-frequency stimulation (HFS) of the cerebral cortex. LTD is a depolarization-dependent process that requires activation of voltage-sensitive calcium channels in the postsynaptic cell during the conditioning HFS, and an increase in intracellular calcium concentration [43]. These conditions are likely to be met in striatal cells, which fire action potentials in response to excitatory synaptic input [44•].

Long-term potentiation (LTP) also has been reported in the striatum. Initial reports of striatal LTP were formed on the basis of the effects of HFS in slices bathed in magnesium-free fluid [45] and regarded as a pathological phenomenon [46]. However, both dopamine depletion and dopamine D-1 receptor antagonists block LTP in magnesium-free fluid [47]. Conversely, dopamine, applied in a manner that mimics the natural release of dopamine produced by reward, is sufficient to facilitate LTP [48]. In order to mimic natural release, dopamine was applied in brief pulses coinciding with a pre- and postsynaptic conjunction of activity. The pulsatile application of dopamine reversed the long-term depression

Figure 2



Schematic diagram of striatal microcircuitry involved in reward-related motor learning. Corticostriatal and thalamostriatal axons make glutamatergic synaptic contacts (open circles) with spiny projection neurons and cholinergic interneurons (TAN). Nigrostriatal axons make dopaminergic synapses (red circles) in the vicinity of corticostriatal and thalamostriatal synapses. Spiny projection neurons make GABAergic synapses (black triangles) on other spiny projection neurons and TANs, which in turn make cholinergic synapses (blue triangles) on spiny projection neurons. Phasic activity in the dopamine neurons produces pulses of dopamine able to act on corticostriatal and thalamostriatal synapses. This leads to strengthening of some synapses and weakening of others, which in turn facilitates selection of particular pathways.

that normally follows HFS, and potentiation of responses was induced.

Several groups have reported variability in synaptic plasticity with the same HFS protocol [49,50]. Variability in effect direction and extent suggests the presence of an uncontrolled variable, and efforts have been made to identify what this may be. The location of the postsynaptic neuron is a possible factor. It is plausible that location effects are mediated by regional differences in dopamine innervation or dopamine receptor expression, and dopamine depletion eliminates mediolateral differences in striatal synaptic plasticity [51]. There are also regional differences in glutamate release that may contribute to regional differences in synaptic plasticity [49]. To determine the basis for such differences it is important to ensure that HFS stimuli are selective for the corticostriatal pathway and not directly activating intrastriatal terminals by current spread.

The use of intracellular recording in whole animal preparations has enabled greater separation of stimulating electrodes and more specific activation of afferents than is possible in brain slices. Using this method, HFS of the cerebral cortex induces LTD of the corticostriatal pathway, as occurs in slices. When low-frequency stimulation of the pars compacta of the substantia nigra is paired with cortical HFS, a short-lasting potentiation is induced [52]. This short-lasting potentiation is blocked by dopamine depletion. Thus, the phasic activation of dopamine afferents induced potentiation *in vivo*, although this was less enduring than the effect of pulsatile application of dopamine seen *in vitro* [48]. Experiments using extracellular single unit recordings of nucleus accumbens neurons in combination with rapid electrochemical measures of dopamine efflux have led to a similar conclusion [53••].

It is important to address the question of whether or not the dopamine-dependent synaptic plasticity described could, in principle, underlie learning-related changes in the brain. The role of synaptic plasticity in normal reward-related learning has been investigated using substantia nigra ICSS. Using the same animals in which ICSS responses had been measured, Reynolds *et al.* [54••] then made *in vivo* intracellular recordings from striatal neurons, and measured responses to cortical afferents before and after ICSS-like stimulation of the substantia nigra dopamine cells. Stimulation of the substantia nigra with behaviorally reinforcing parameters induced potentiation of corticostriatal synapses. In addition, the degree of potentiation up to 10 min after the stimulus trains was correlated with the rate of learning of ICSS. Animals showing a greater degree of potentiation were correspondingly faster to reach criteria for ICSS, and vice versa. Potentiation was blocked in control animals administered a dopamine D1-like receptor antagonist [54••]. These findings suggest that stimulation of the substantia nigra may positively reinforce behavior by dopamine D1 receptor-dependent potentiation of cortical inputs to the striatal spiny neurons.

Dopamine-dependent synaptic plasticity has also been described in the striatal cholinergic interneurons [55••]. Stimulation of the corticostriatal and thalamostriatal afferents with single pulses produced a depolarizing and hyperpolarizing postsynaptic potential, thought to reflect an initial excitation by the stimulated afferents followed by an inhibitory postsynaptic potential mediated by intrastriatal collaterals of the spiny projection neurons [56]. High frequency stimulation of the excitatory afferents produced dopamine-dependent LTP of the excitatory postsynaptic potential, and an increase in the probability of the disynaptically mediated inhibitory potential [55••]. These two effects may combine in the acquisition of the pause responses of the cholinergic interneurons, as described above [37].

Conclusions

In summary, dopamine-dependent synaptic plasticity is a potential cellular mechanism for reward-related learning in the striatum. Dopamine pulses produced by cortical HFS, pressure-ejection or substantia nigra stimulation may mimic the effects of natural reward. The correlation of degree of synaptic change with rate of learning is highly suggestive of a relationship between reward-related learning and dopamine-dependent synaptic plasticity in the striatum. The data reviewed above encourage the conceptualization of models of reward-mediated learning, in which dopamine pulses acting on corticostriatal synapses at appropriate times lead to strengthening of some synapses and weakening of others. This in turn facilitates selection of particular pathways through the basal ganglia to the motor cortex, and hence of particular actions, according to past and anticipated rewards.

A major challenge for the future is to extend and integrate three different areas of investigation into reward-related learning mechanisms. First, it is important to detail the requirements for induction of synaptic plasticity, in terms of the timing and magnitude of activity in cortical, striatal and nigral cells. For example, preliminary work suggests that the induction of plasticity by pulsatile application of dopamine requires advance application of dopamine, before activity in excitatory afferents [57]. This is an important constraint on models of the learning mechanism. Second, recent work has highlighted a somewhat enigmatic dissociation of dopamine release from dopamine cell firing [11]. It is therefore important to detail the actual dopamine concentration changes that occur during different stages of learning, and the precise temporal relationship of these changes to presynaptic (corticostriatal, thalamostriatal) and postsynaptic striatal activity. Third, there is a need for the changes in striatal cell firing that occur in association with learning to be compared

with the predicted effects of synaptic plasticity on striatal cell firing. For example, models are needed to account for both reward-facilitated and reward-suppressed responses [32] in spiny cell firing. The combination of these three areas should lead to models integrating the microcircuitry of the striatum with experimentally demonstrated mechanisms of synaptic plasticity. This may provide a better understanding of the mechanisms that underlie learning-related changes in neural activity of striatal cells. Such understanding will be a major step towards explaining the behavioral features of reward-related learning in terms of the underlying neural mechanisms.

Acknowledgements

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