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Dopamine-dependent plasticity of corticostriatal synapses

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Abstract

Knowledge of the effect of dopamine on corticostriatal synaptic plasticity has advanced rapidly over the last 5 years. We consider this new knowledge in relation to three factors proposed earlier to describe the rules for synaptic plasticity in the corticostriatal pathway. These factors are a phasic increase in dopamine release, presynaptic activity and postsynaptic depolarisation. A function is proposed which relates the amount of dopamine release in the striatum to the modulation of corticostriatal synaptic efficacy. It is argued that this function, and the experimental data from which it arises, are compatible with existing models which associate the reward-related firing of dopamine neurons with changes in corticostriatal synaptic efficacy. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Dopamine; Striatum; Corticostriatal; Reward; Learning; Plasticity

1. Introduction

Recent electrophysiological studies of the basal ganglia have provided the framework for a number of computational models of reward-related learning (Doya, 2000; Montague, Dayan, & Sejnowski, 1996; Suri & Schultz, 1999). This evidence largely originates from the work of Schultz and colleagues who have identified a reward signal encoded in the activity of midbrain dopamine neurons (Schultz, 2000). In brief, neurons in the substantia nigra pars compacta (SNc) and the adjoining midbrain areas fire short bursts of activity after the presentation of food or liquid rewards and stimuli that predict reward (Mirenowicz & Schultz, 1994, 1996). These dopamine neurons project predominantly to the striatum (Bjorklund & Lindvall, 1986). The effects of such short, phasic activation of the dopamine neurons on neural information processing in the striatum are a crucial component of computational models of the basal ganglia. The experimental evidence concerning these effects has advanced rapidly in recent years, and may challenge the assumptions of some existing computational models. This review focuses on experimental evidence that investigates the role of dopamine in modulating the function of striatal synapses. A set of rules for synaptic plasticity in the corticostriatal pathway is proposed, based on this evidence.

Such rules may need to be incorporated into future models of reward-related learning in the basal ganglia.

2. Afferent connections of the striatum

The striatum is a major site of convergence of afferents from the cerebral cortex and the SNc. These pathways converge within the striatum and terminate close to one another on individual spiny projection neurons, the principal output neurons of the striatum (Fig. 1). The spiny projection neurons effectively form a single layer between the cortical inputs and the striatal outputs, and they are also the sites at which dopaminergic inputs are integrated with cortical inputs. This implies that the functional properties of the corticostriatal synapses, the response properties of spiny projection neurons and the effects of dopamine on these properties are key determinants of the signal processing operations in the striatum.

The corticostriatal projection originates from all areas of the cerebral cortex (McGeorge & Faull, 1989) and releases glutamate into the striatum (Divac, Fonnum, & Storm-Mathisen, 1977; Perschak & Cuenod, 1990). The axon terminals form asymmetric specialisations with the heads of dendritic spines of spiny projection neurons (Somogyi, Bolam, & Smith, 1981). Dopaminergic axons of the nigrostriatal pathway synapse with the dendrites and somata of spiny projection neurons, and also with dendritic

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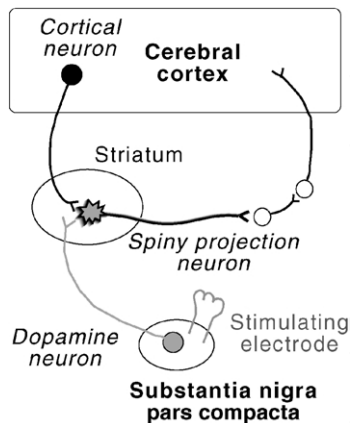


Fig. 1. Afferent connections of the striatal spiny projection neuron. (Adapted from *Nature* 413, 67–70, Reynolds, J. N. J., Hyland, B. I., and Wickens, J. R., A cellular mechanism of reward-related learning.)

spines as they pass by their necks (Bouyer, Park, Joh, & Pickel, 1984; Freund, Powell, & Smith, 1984; Smith & Bolam, 1990). In a proportion of cases, the same spines have been observed to receive both a corticostriatal input and a nigrostriatal input (Freund et al., 1984). This anatomical evidence is consistent with a functional interaction between dopamine and glutamate at the level of individual spiny projection neurons, and, occasionally, at the level of individual dendritic spines.

3. Functional interactions between dopamine and glutamate

3.1. Acute effects of dopamine

Interactions between glutamate and dopamine occur both presynaptically and postsynaptically within the striatum. These neurotransmitters act at particular receptors on the pre and postsynaptic membranes. Striatal neurons, and nerve terminals immediately afferent to them, contain both ionotropic (AMPA/kainate and *N*-methyl-D-aspartate, NMDA, type) and metabotropic (mGluR family) glutamate receptors, and D1-like (D1, D5 subtype) and D2-like (D2, D3 and D4 subtype) dopamine receptors. The precise anatomical location and the degree of receptor subtype localisation on pre and postsynaptic membranes are issues that remain particularly controversial (Gerfen et al., 1990; Gracy & Pickel, 1996; Joyce & Marshall, 1987; Le Moine & Bloch, 1995; Tarazi & Baldessarini, 1999). However, functional studies present a largely consistent picture of physiological interactions between glutamate and dopamine in the striatum.

Presynaptically, a complex arrangement of autoreceptors and heteroreceptors seem to control the release of both neurotransmitters. Functional evidence supports the existence of dopamine D2-like receptors that limit both

dopamine (Cragg & Greenfield, 1997; Tepper, Sun, Martin, & Creese, 1997) and glutamate (Cepeda et al., 2001; Hsu, Huang, Yang, & Gean, 1995; Kerkerian, Dusticier, & Nieoullon, 1987; Schwarcz, Creese, Coyle, & Snyder, 1978) release into the striatum. Similarly, there is evidence of multiple glutamate receptor subtypes on nigrostriatal dopamine nerve terminals (Tarazi & Baldessarini, 1999). Receptors for NMDA, particularly, seem to mediate glutamate-evoked dopamine release from nigrostriatal nerve terminals (Jin & Fredholm, 1997; Krebs et al., 1991; Kulagina, Zigmond, & Michael, 2001). NMDA receptors are also present on corticostriatal nerve terminals, where they colocalise with D2-like dopamine receptors (Tarazi, Campbell, Yeghiayan, & Baldessarini, 1998) and increase the excitability of cortical afferent fibres (Garcia-Munoz, Patino, Masliah, Young, & Groves, 1996). The above evidence largely supports a reciprocal regulation of dopamine and glutamate release in the striatum, through NMDA receptor-mediated augmentation and D2-like receptor-mediated reduction of neurotransmitter release.

A major form of interaction between glutamate and dopamine that occurs postsynaptically at the level of individual spiny projection neurons is the modulation of membrane excitability. This affects the probability that a spiny projection neuron will fire action potentials in response to an excitatory event. Since these particular effects of dopamine and glutamate have been reviewed recently (Cepeda & Levine, 1998; Nicola, Surmeier, & Malenka, 2000), only a brief mention will be made here.

The effect of dopamine on spiny projection neuron membrane excitability is greatly influenced by the membrane potential of the postsynaptic neuron. In vivo, the membrane potential of a spiny projection neuron shifts between a hyperpolarised DOWN state, close to the resting potential in vitro (Jiang & North, 1991), and a depolarised UP state, close to action potential threshold (Reynolds & Wickens, 2000; Wilson & Kawaguchi, 1996). At resting potential, which is largely determined by the effect of inwardly rectifying potassium currents (Kita, Kita, & Kitai, 1984; Nisenbaum & Wilson, 1995), D1-like receptor activation increases the activity of these rectifying conductances, thereby resisting the effect of excitatory input (Pacheco-Cano,argas, Hernandez-Lopez, Tapia, & Galarraga, 1996). Excitability is also reduced by D1-like receptors at potentials near the UP state, through a decrease in Na^+ and N- and P-type Ca^{2+} currents (Calabresi, Mercuri, Stanzione, Stefani, & Bernardi, 1987; Surmeier,argas, Hemmings, Nairn, & Greengard, 1995; Surmeier & Kitai, 1993). However, in response to sustained depolarising events, excitability is enhanced by a D1-dependent enhancement of an L-type Ca^{2+} current (Hernandez-Lopez,argas, Surmeier, Reyes, & Galarraga, 1997). Hence, dopamine, at least through D1 receptor activation, can show either inhibitory or excitatory actions depending on recent fluctuations in membrane potential.

Glutamate receptor activation interacts with dopamine-dependent changes in neuronal excitability in two ways. Firstly, the driving force behind the shifts in membrane potential observed in spiny projection neurons in vivo is wholly attributable to excitatory synaptic input from the cortex and thalamus (Wilson, 1993). At resting potentials, cortically induced depolarisation depends on the activation of AMPA and kainate glutamate receptors (Herrling, 1985; Kita, 1996). Thus, sufficient glutamate receptor activation is necessary to overcome the inhibitory effect of dopamine at rest and depolarise the spiny projection neuron membrane towards the UP state. Secondly, a more direct interaction between dopamine and glutamate is that dopamine D1-receptor activation increases NMDA-evoked excitation in the striatum (Cepeda, Buchwald, & Levine, 1993; Cepeda, Colwell, Itri, Chandler, & Levine, 1998; Levine, Li, Cepeda, Cromwell, & Altemus, 1996). This would presumably be a significant effect in vivo only at membrane potentials approaching the UP state, since, at resting potentials, the NMDA receptor is under significant block by magnesium ions (Kita, 1996; Nowak, Bregestovski, Ascher, Herbet, & Prochiantz, 1984). Taken together, the above findings are consistent with an antagonistic effect of glutamate and dopamine on neuronal excitability at DOWN state membrane potentials but a synergistic effect at UP state potentials. These effects stabilise the spiny projection neuron in the DOWN state but increase the probability of firing in the UP state.

Up to this point, we have limited this discussion to the effects of dopamine on neuronal excitability that are present during the period of exposure to dopamine. It is now clear that dopamine cannot be thought of as simply excitatory or inhibitory in the striatum, but rather as a neuromodulator of excitatory corticostriatal responses, at both presynaptic and postsynaptic levels. We will now consider the role of dopamine as a modulator of corticostriatal synaptic transmission over time periods that long outlast the period of dopamine exposure. Such lasting effects of dopamine on synaptic plasticity may represent the cellular substrate for learning in the striatum (Calabresi, Pisani, Mercuri, & Bernardi, 1996; Wickens & Kotter, 1995).

3.2. Lasting effects of dopamine

The anatomical arrangement of the corticostriatal and nigrostriatal pathways converging on individual spiny projection neurons brings the processes of three different neuronal populations into close proximity. This provides a favourable substrate for a three-factor interaction, which might govern synaptic plasticity (Wickens & Kotter, 1995). The three factors are: presynaptic corticostriatal activity, postsynaptic spiny projection neuron activity and dopamine.

Miller (1981) originally proposed a rule that might operate within the striatum to strengthen synaptic connections during reward-related learning. In its simplest form, this rule predicts that a conjunction of pre and postsynaptic

activity, plus a reward signal, would induce potentiation at active corticostriatal synapses. In a modification to this rule, Wickens (1993) added that if repeated conjunctions of pre and postsynaptic activity were to occur in the absence of an appropriate reward signal, then depression would result. Dopamine is proposed here as the reward signal, since rewards and reward-predicting stimuli are known to induce phasic activation of midbrain dopamine neurons (Schultz, 2000). Within the anatomical framework of the striatum, the three-factor rule predicts that phasically released dopamine will act in a punctate manner to strengthen only those corticostriatal synapses that are selected as ‘ready’, on the basis of recent activity in presynaptic corticostriatal inputs. In this manner, the phasic release of dopamine is proposed to act heterosynaptically to strengthen glutamatergic corticostriatal synapses.

4. Dopamine and the three-factor rule: experimental evidence

In the last 5 years, a great deal of experimental data has amassed regarding the role of various combinations of presynaptic activity, postsynaptic activity and dopamine in synaptic modification of the corticostriatal pathway. Some of this work intentionally or unintentionally addresses the earlier hypotheses. The experiments in question have mostly been performed using the corticostriatal brain slice preparation (Arbuthnott, MacLeod, & Rutherford, 1985). Using this in vitro preparation, individual test stimuli can be applied to the cortex overlying the striatum and the postsynaptic response recorded from a spiny projection neuron. The amplitude of the postsynaptic response can be used as a measure of corticostriatal synaptic efficacy. Presynaptic activity can be evoked by such single pulse stimuli or by stimulating the corticostriatal afferent fibres with high frequency stimulation (HFS), usually with trains of pulses at 100 Hz. Postsynaptic activity can be reliably induced when intracellular recording procedures are used, by injecting current through the electrode from which the recording is being made. Dopamine agonists and antagonists can be washed-in and out via the solution bathing the slice (Calabresi, Maj, Mercuri, & Bernardi, 1992a) or applied by pressure ejection directly onto the recorded neuron (Wickens, Begg, & Arbuthnott, 1996).

In addition to the in vitro preparation, the in vivo anaesthetised rat preparation has recently made a forceful comeback as a means for studying the rules of corticostriatal synaptic plasticity (Charpier & Deniau, 1997; Charpier, Mahon, & Deniau, 1999; Reynolds & Wickens, 2000; Reynolds, Hyland, & Wickens, 2001). In this preparation, the whole animal is left intact, and studied under general anaesthesia. This preparation carries with it a number of distinct advantages for the study of the three-factor rule. In the in vivo preparation, all afferent pathways to the striatum are intact. By placing cortical and nigral stimulating

Table 1
Lasting effects of one, two or three factors on corticostriatal responses

	Condition							
	One factor				Two factors			Three factors
	A	B	C	D	E	F	G	H
Activity								
Presynaptic activity	0	1	0	0	1	1	0	1
Postsynaptic activity	0	0	1	0	1	0	1	1
Dopamine	0	0	0	1	0	1	1	1
<i>Study</i>								
Kerr & Wickens, 2001								↑↑ ^a
Reynolds et al., 2001					↓			↑↑
Smith et al., 2001								↓↑
Tang et al., 2001								↓
Akopian et al., 2000					↓↑			
Calabresi et al., 2000								↓↑ ^a
Partridge et al., 2000					↓↑			
Reynolds & Wickens, 2000					↓			↔
Spencer & Murphy, 2000					↓↑			↓↑
Calabresi et al., 1999a,b,c		↔	↔				↔	↓
Centonze et al., 1999								↑↑ ^a
Dos Santos Villar & Walsh, 1999								↓
Nishioku et al., 1999					↓			
Wickens et al., 1998					↓			
Charpier & Deniau, 1997					↑			
Choi & Lovinger, 1997		↔	↔		↓			
Wickens et al., 1996					↓			↑
Lovinger et al., 1993					↓			
Walsh, 1993	↔				↓			
Calabresi et al., 1992a,b,c		↔	↔	↓				↓
Average effect:	↔	↔	↔	↓	↓	↔	↔	↔

The average effect of each condition has been systematically calculated across studies, by affording a resulting effect of depression – 1, potentiation + 1, no change (↔) or both effects (↓↑) noted as 0, and then adding the column totals.

^a Effect reported in slices bathed in a solution devoid of magnesium ions.

electrodes in opposite hemispheres, the effect of phasic activation of the nigrostriatal pathway can be studied independent of direct stimulation of the corticostriatal pathway. In addition, under urethane anaesthesia the corticostriatal pathway is spontaneously active, and induces membrane potential fluctuations resembling those seen in an awake animal (Stern, Kincaid, & Wickens, 1997; Wilson & Groves, 1981). The effect on corticostriatal synaptic efficacy of a natural pairing of presynaptic and postsynaptic activity, coupled with burst-like activation of dopaminergic afferents, can therefore be directly investigated.

Table 1 summarises data from experimental studies that have used either in vitro or in vivo preparations to investigate corticostriatal synaptic plasticity in the dorsal striatum. All possible combinations of presynaptic activity, postsynaptic activity and dopamine are represented, and each study is reported in terms of these combinations. Studies that replicate findings by the same research group are not included. The data in the table is organised into conditions (A to H) according to the combination of factors used in the experiment. In all conditions in which dopamine is involved, there was either application of exogenous

dopamine or dopamine agonists or evidence that endogenous dopamine was involved, such as blockade of the effect by dopamine antagonists or by dopamine depletion. The arrows indicate the direction of synaptic change. Arrows in both directions indicate that both effects were reported. This table updates the experimental data reviewed by Wickens and Kotter (1995; see their table 10.1).

Condition A. Responses evoked by corticostriatal test stimulation are stable over time, in the absence of any evoked activity (Walsh, 1993).

Condition B. Presynaptic activity alone does not change corticostriatal synaptic efficacy. This was tested by repeatedly activating the corticostriatal pathway whilst keeping the postsynaptic neuron at hyperpolarised potentials (Calabresi et al., 1992a; Choi & Lovinger, 1997). Corticostriatal synaptic responses are also unchanged when glutamate is puffed onto the slice with the neuron held at hyperpolarised potentials (Calabresi, Centonze, Gubellini, Marfia, & Bernardi, 1999b).

Condition C. Corticostriatal synaptic responses are unchanged when spiny projection neurons are depolarised by intracellular current injection, without associated

activation of the corticostriatal pathway (Calabresi et al., 1999b; Calabresi, Maj, Pisani, Mercuri, & Bernardi, 1992b; Choi & Lovinger, 1997).

Condition D. Dopamine applied in vitro via the bathing solution depresses synaptic responses, however, this depression has been shown not to last beyond the period of exposure to dopamine (Calabresi, et al., 1992b, 1987; Umemiya & Raymond, 1997).

Condition E. The effect of a combination of presynaptic and postsynaptic activity has been studied by a number of groups using a variety of experimental approaches. Classically, HFS of the corticostriatal pathway in conjunction with firing activity of the postsynaptic spiny projection neuron has been reported to induce long-term depression (LTD) of corticostriatal responses (Calabresi, et al., 1992b; Lovinger, Tyler, & Merritt, 1993; Walsh, 1993; Wickens et al., 1996). So robust was the expression of LTD in the hands of some groups, that the suggestion was made that LTD may be the normal form of plasticity expressed at healthy corticostriatal synapses (Calabresi et al., 1996). This conclusion was challenged by the first in vivo intracellular study, that showed that corticostriatal HFS applied to the cortex ipsilateral to the recorded spiny projection neuron exclusively induces long-term potentiation (LTP) (Charpier & Deniau, 1997). However, we have recently demonstrated that robust LTD is also expressed by corticostriatal synapses in vivo, when HFS is applied to the cortex contralateral to the recording site (Reynolds & Wickens, 2000). Thus, the general consensus from the foregoing is that a conjunction of presynaptic and postsynaptic activity induces LTD in the corticostriatal pathway.

More recently, however, the predominant effect of presynaptic and postsynaptic activity has been questioned by a number of groups, some of whom originally contributed work that supported the robustness of this protocol at inducing LTD. These groups now report mixed effects of corticostriatal HFS in vitro, including LTP, LTD and no change (Akopian, Musleh, Smith, & Walsh, 2000; Partridge, Tang, & Lovinger, 2000; Spencer & Murphy, 2000). Systematic analysis suggests that at least some of this variability seems to be explained by methodological factors:

The anatomical location of the recorded neurons within the striatum seems to influence the effect of corticostriatal HFS. Neurons recorded in the dorsolateral striatum, which receive input primarily from sensorimotor cortex (McGeorge & Faull, 1989), seem to show predominantly depression of corticostriatal synapses (Akopian et al., 2000; Partridge et al., 2000). In contrast, neurons located dorsomedially, in areas receiving visual and auditory inputs from cortex (McGeorge & Faull, 1989), favour potentiation following corticostriatal HFS. It is not clear if previous studies have preferentially obtained in vitro recordings from slices of lateral striatum and therefore have reported a bias towards LTD, although this seems unlikely in our experience. One possible explanation for the regional variation in plasticity is suggested by the existence of an

increasing gradient of dopamine D2-like receptors from medial to lateral (Joyce & Marshall, 1987; Russell, Allin, Lamm, & Taljaard, 1992). The relative deficiency of D2-like receptors medially could favour the induction of potentiation following corticostriatal HFS, as has been shown following D2-like receptor blockade or D2-receptor knockout (Calabresi et al., 1992b, 1997). It is also possible that the tendency towards potentiation medially reflects regional differences in glutamate and dopamine release as a result of variation in presynaptic regulation. In support of this possibility, corticostriatal synapses show a mediolateral gradient of paired-pulse neurotransmitter release (Akopian et al., 2000) and dopamine depletion eliminates differences between corticostriatal synaptic plasticity medially and laterally (Smith, Musleh, Akopian, Buckwalter, & Walsh, 2001).

Developmental changes play an important role in determining the dominant form of plasticity expressed by corticostriatal synapses. In rats, the second to third postnatal week seems to be a critical period when the induction of potentiation seems to become less prominent, and corticostriatal HFS begins to favour depression in lateral striatal regions (Partridge et al., 2000). During the same period, corticostriatal synapses are beginning to express a mechanism for limiting glutamate release, which requires the activation of dopamine D2-like receptors (Tang, Low, Grandy, & Lovinger, 2001). Taken together, this suggests that the developmental mechanisms required for the induction of LTD are related to dopaminergic mechanisms regulating glutamate release.

The location of the stimulating electrode used to activate the corticostriatal afferents also influences the change in synaptic efficacy induced by HFS (Spencer & Murphy, 2000). The electrode location and the stimulus parameters applied during HFS together determine the degree of current spread and whether the stimulation activates afferents other than corticostriatal fibres (Millar, Stamford, Kruk, & Wightman, 1985; Ranck, 1975; Yeomans, 1989). For instance, current spread beyond the corpus callosum in a corticostriatal slice preparation could directly depolarise nerve terminals and neuronal cell bodies within the striatum. The direct release of neurotransmitters such as acetylcholine, GABA and dopamine that would result could induce patterns of synaptic plasticity that differ from those seen when neurotransmitter release is driven by local glutamate release. When the distance of the cortical stimulating electrode from the striatum is made large in vitro (Wickens et al., 1996; Wickens, McKenzie, Costanzo, & Arbuthnott, 1998) or when the contralateral cortex is activated in vivo (Reynolds & Wickens, 2000), the direct activation of intrastriatal elements is minimised. Under these conditions, corticostriatal HFS coupled with postsynaptic firing of spiny neurons induces robust LTD.

From the earlier analysis, it would appear that experimental factors may alter the effect of presynaptic and postsynaptic activity by influencing dopamine release (see

Condition H). Although the studies included under condition E presume no dopamine involvement, corticostriatal HFS causes dopamine release large enough to be detected by HPLC (Calabresi et al., 1995) if vigorous stimulation is applied to the slice (Harnett, Reynolds, Russell and Wickens; unpublished observations). Therefore, there is a strong possibility that dopamine release played a part in some of effects attributed to presynaptic and postsynaptic activity alone.

In summary, the effect of a combination of presynaptic and postsynaptic activity cannot be predicted without specifying the location of the neuron and stimulating electrode, the age of the animal and the stimulus parameters used to activate the corticostriatal afferents. This variability is reflected in the range of effects reported in the studies in Table 1, although, on average, the conjunction leads to the induction of LTD. We will now consider studies that have formally investigated the effect of dopamine, when combined with presynaptic or postsynaptic activity or both.

Condition F. In the nucleus accumbens, bath-applied dopamine does not modulate synaptic plasticity when high-frequency afferent stimulation is applied without the induction of postsynaptic activity (Pennartz, Ameerun, Groenewegen, & Lopes da Silva, 1993). This suggests that the combination of presynaptic activity and dopamine is insufficient to induce changes in synaptic efficacy in spiny projection neurons. Caution must be exercised, however, before generalising this result to the dorsal striatum, because of known differences in the effect of dopamine on corticostriatal synaptic transmission in the two brain areas (Nicola & Malenka, 1998; Thomas, Malenka, & Bonci, 2000). The only investigation of this condition in the dorsal striatum used pressure ejection of glutamate onto spiny neurons to simulate corticostriatal HFS (Calabresi et al., 1999b), in a similar manner as used previously to simulate phasic dopamine release (Wickens et al., 1996). Phasic glutamate application induced membrane depolarisation and LTD, which required activation of dopamine receptors. However, when the membrane potential was clamped at resting levels during glutamate release, corticostriatal responses did not change. This indirect evidence also suggests that the two factors, presynaptic activation and dopamine, do not change corticostriatal synaptic efficacy.

Condition G. Depolarisation of spiny projection neurons by intracellular current injection, in the presence (or absence) of bath-applied dopamine, does not alter corticostriatal responses (Calabresi et al., 1999b). Therefore, the combination of postsynaptic activity and dopamine is insufficient to modulate corticostriatal synaptic efficacy.

Condition H. A number of studies have reported effects on corticostriatal synaptic efficacy of a combination of presynaptic activity and postsynaptic activity, and have demonstrated the role of dopamine in these effects. A perplexing conclusion from Table 1 is that both LTD and LTP have been reported in condition H. This apparent

contradiction may be explained by details of the experimental procedures.

A degree of consistency emerges when the studies described under condition H are regrouped by experimental preparation (Table 2). Under normal in vitro conditions (Table 2; column 2), the conjunction of presynaptic and postsynaptic activity favours the induction of LTD. This LTD is dependent on the activation of both dopamine D1 and D2-like receptors (Calabresi et al., 1992a,b; Tang et al., 2001).

The induction of LTP in vitro usually requires specific experimental manipulations. Most commonly, LTP is induced by applying corticostriatal HFS while the slice is bathed in a solution with magnesium ions removed (Table 2; column 3) (Calabresi, Pisani, Mercuri, & Bernardi, 1992c; Walsh & Dunia, 1993). This manipulation relieves striatal NMDA receptors from physiological blockade at resting potentials (Kita, 1996; Nowak et al., 1984). Although other work has shown that the induction of corticostriatal LTP in Mg^{2+} -free solution requires NMDA-receptor activation (Calabresi et al., 1992c; Walsh & Dunia, 1993), blockade of dopamine D1-like receptors completely blocks the induction of this form of LTP (Calabresi et al., 2000; Kerr & Wickens, 2001). Thus, NMDA receptor activation is not sufficient for LTP induction in Mg^{2+} -free solution, and dopamine acting at D1-like receptors is a mandatory requirement.

LTP can also be induced in solutions containing a normal concentration of magnesium ions, by the application of brief pulses of dopamine coinciding with the conjunction of presynaptic and postsynaptic activity (Table 2; column 4) (Wickens et al., 1996). In contrast, application of dopamine via the bathing solution enables LTD induction but does not itself favour LTP induction (not shown) (Calabresi et al., 1992a,b), suggesting that continuous dopamine receptor activation does not induce the same effect as phasic activation.

Pulsatile dopamine application probably leads to LTP induction by phasically increasing the concentration of dopamine around the recorded neuron during corticostriatal HFS. Such temporally restricted dopamine application probably avoids the effect of D1-receptor desensitisation that follows prolonged bath application of dopamine (Memo, Lovenberg, & Hanbauer, 1982). The application of HFS in Mg^{2+} -free conditions may produce a similar phasic effect by activating NMDA receptors on dopamine terminals (Krebs et al., 1991), thereby augmenting local dopamine release during HFS (Jin & Fredholm, 1997; Ochi, Inoue, Koizumi, Shibata, & Watanabe, 1995). Taken together, the above data lead to the suggestion that the normal release of dopamine during corticostriatal HFS (Calabresi et al., 1995) provides an appropriate dopamine level for the induction of LTD, whereas a phasic augmentation of dopamine release around the time of HFS provides a switch from LTD to LTP.

The requirement for dopamine in both LTD and LTP

Table 2
 Lasting effects of pre and postsynaptic activity and dopamine receptor activation on corticostriatal responses in various experimental preparation

Study	Experimental preparation					
	In vitro				In vivo	
	(1) HFS with DA depleted	(2) HFS in normal conditions	(3) HFS in Mg ²⁺ -free solution	(4) HFS and exogenous DA	(5) LFS SN	(6) HFS SN
Reynolds et al., 2001						↑
Reynolds & Wickens, 2000					↔	
Wickens et al., 1996		↓		↑		
Kerr & Wickens, 2001			↑			
Calabresi et al., 2000		↓	↑			
Centonze et al., 1999	↔		↑			
Tang et al., 2001	↔	↓				
Calabresi et al., 1999a,b,c		↓				
Smith et al., 2001	↑ ^a	↓ ↑				
Spencer & Murphy, 2000		↓ ↑				
Dos Santos Villar & Walsh, 1999	↑ ^a	↓				
Calabresi et al., 1992a,b,c	↔	↓				
	↑	↓	↑	↑	↔	↑

HFS is high-frequency stimulation; LFS is low-frequency stimulation; DA is dopamine. The average effect using each experimental preparation was calculated by affording a resulting effect of depression -1, potentiation +1, no change (↔) or both effects (↓ ↑) noted as 0, and then adding the column totals.

^a Effect reported in the presence of a GABA_A receptor antagonist.

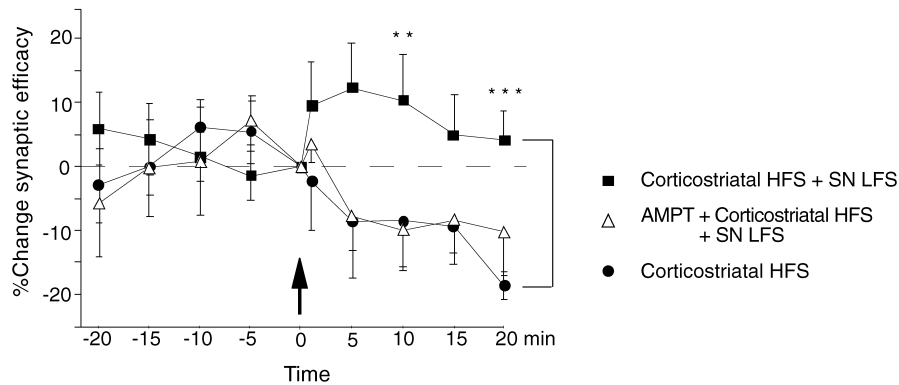


Fig. 2. Modification of the effect of corticoatrial high-frequency stimulation by dopamine release *in vivo*. Changes in synaptic responses (as a percentage of baseline) are shown in relation to the application of three different stimulation protocols (arrow). Asterisk, changes significantly different at 10 min and 20 min. SN LFS is low-frequency stimulation of the substantia nigra; HFS is high-frequency stimulation; AMPT is α -methyl paratyrosine. (Reprinted from Reynolds and Wickens (2000), with permission from Elsevier Science.).

induction processes is confirmed following dopamine depletion. Neither LTD nor LTP can be induced in slices prepared from animals chronically depleted of dopamine (Table 2; column 1) (Calabresi et al., 1992b; Centonze et al., 1999; Tang et al., 2001). However, slices with lesser degrees of dopamine depletion seem to somehow retain the capacity for LTP induction if intrinsic striatal inhibitory circuits are blocked with a GABA_A antagonist (Dos Santos Villar & Walsh, 1999; Smith et al., 2001). It is possible that dopamine levels remaining after chronic dopamine depletion are sufficient for LTP induction when coupled with (i) mechanisms that enhance postsynaptic activation by corticoatrial inputs (Kita, 1996) and (ii) compensatory changes that enhance residual dopamine activity (Zigmond, Abercrombie, Berger, Grace, & Stricker, 1990).

Collectively, the results presented in Tables 1 and 2 are for the most part compatible with the following three-factor rule for synaptic modification:

A conjunction of presynaptic activity and postsynaptic depolarisation, under normal dopamine conditions, will result in depression of corticoatrial synapses; the same conjunction in association with a large phasic increase in dopamine concentration will result in potentiation of corticoatrial synapses; all other conditions that do not include a conjunction of presynaptic activity and postsynaptic depolarisation do not effect a lasting change in synaptic transmission.

In those cases where dopamine receptor stimulation was not determined, a number of experimental variables influenced the type of plasticity expressed. These variables may, in fact, have provided a mixed picture by varying the degree of endogenous dopamine release.

5. Phasic activation of dopamine cells induces potentiation

In order to investigate specifically the effect of phasic release of endogenous dopamine, we have recently studied

the effect of stimulating the substantia nigra dopamine neurons in an intact, anaesthetised animal. Corticoatrial synaptic efficacy was measured before and after electrically activating the dopamine cells of the substantia nigra with brief trains of pulses (Reynolds & Wickens, 2000). In agreement with most *in vitro* studies, we found that HFS of the contralateral cortex induced robust LTD (Fig. 2). Stimulation of the substantia nigra with low-frequency trains (20 Hz) concurrently with corticoatrial HFS blocked LTD and instead induced short-lasting potentiation. Inhibition of dopamine synthesis by pretreatment with α -methyl paratyrosine (AMPT) rendered concurrent stimulation of the substantia nigra ineffective at blocking the depression induced by corticoatrial HFS. Thus, by investigating the effect of corticoatrial HFS in physiological conditions, we were able to confidently conclude that dopamine released by phasic activation of the substantia nigra switches the effect of corticoatrial HFS from depression to potentiation.

Some of the findings from our *in vivo* model seem to differ from reports *in vitro* regarding the role of dopamine in synaptic modification (Centonze, Picconi, Gubellini, Bernardi, and Calabresi, 2001). First, the persistence of LTD following depletion of striatal dopamine with AMPT seems to speak against the known requirement for dopamine receptor activation in corticoatrial LTD (Calabresi et al., 1992a; Tang et al., 2001). However, the AMPT dose regimen that we used reduces striatal dopamine levels by just under 80% (Carlson, Bergstrom, Demo, & Walters, 1988; White, Bednarz, Wachtel, Hjorth, & Brooderson, 1988). The release of dopamine under these conditions may still be sufficient for LTD induction. Second, unlike the effect of pulsatile application of dopamine *in vitro* (Wickens et al., 1996), in the majority of neurons the potentiation induced by substantia nigra stimulation did not persist for longer than 10–15 min (Reynolds & Wickens, 2000). This raises the possibility that the substantia nigra stimulation we used did not evoke similar levels of striatal dopamine to those obtained with exogenous application. To engage the

mechanisms necessary for lasting potentiation. In vivo, a greater degree of dopamine release might be necessary than that required to block the induction of LTD. Since the release of striatal dopamine by electrical stimulation is frequency and current dependent (Garris, Christensen, Rebec, & Wightman, 1997), it is possible that longer-lasting potentiation could be induced with stronger substantia nigra stimulation.

The frequency we (and others) used to stimulate the nigrostriatal pathway to evoke phasic dopamine release is within the range 10–20 Hz (Gonon, 1997; Hirata, Yim, & Mogenson, 1984; Reynolds & Wickens, 2000). This range represents the average firing frequency within bursts, recorded from dopamine neurons in anaesthetised animals (Grace & Bunney, 1984). However, we have recently found the range of intraburst frequencies in an animal engaged in reward-related tasks to be greater than this (Reynolds, Hyland, Perk, & Miller, 1999), averaging over 30 Hz but frequently reaching as high as 100 Hz (Hyland, Reynolds, Hay, Perk, & Miller, 2002). This was significantly higher than that seen when the animals were not engaged in any particular activity, where average frequencies were more similar to the above range reported in anaesthetised animals. Since brief bursts at higher frequencies release more dopamine into the striatum (Stamford, Kruk, & Millar, 1987), it appears that reward-relevant information may be carried by high intraburst frequencies of dopamine cells, and that these induce relatively greater striatal dopamine release. We have, therefore, undertaken further studies in which we attempted to address the effects of reward-related activity of dopamine cells.

6. The effect of rewarding stimulation on corticostriatal synaptic efficacy

We tested the effect of reward-related stimulation on corticostriatal synaptic efficacy using intracranial self-stimulation (ICSS) as a behavioural model of reward-related learning (Olds & Milner, 1954). In this protocol, animals learnt to press a lever repeatedly for the rewarding effect of electrical stimulation of their own substantia nigra (Beninger, Bellisle, & Milner, 1977). This provided direct experimenter control over the reward signal, enabling the same reward signal to be activated during intracellular recording. In our behavioural experiments, we measured the optimal current required to maximise the lever-pressing rate (Hodos & Valenstein, 1962; Reynolds, 1958) and the time taken for each animal to acquire ICSS (Reynolds et al., 2001).

After behavioural testing, in vivo intracellular recording was used to measure the effect of ICSS-like stimulation on corticostriatal synaptic responses. Spiny projection neurons were depolarised during ICSS-like stimulation by the spontaneous corticostriatal input present under urethane anaesthesia (Stern et al., 1997). We found that concurrent

stimulation of the substantia nigra with optimal parameters for lever-pressing behaviour induced lasting potentiation (Fig. 3(a)). This potentiation was dependent on the activation of dopamine D1-like receptors, consistent with previous findings in vitro (Calabresi et al., 2000; Kerr & Wickens, 2001). These data support the hypothesis that activation of the substantia nigra with behaviourally relevant stimuli induces LTP in the corticostriatal pathway.

In addition to showing that synaptic modification was facilitated by reward-related stimulation, we also found that the degree of synaptic modification induced by ICSS-like stimulation was correlated with the time taken to acquire the lever-pressing task. This is strong evidence that changes in corticostriatal efficacy were involved in the learning of ICSS behaviour (Fig. 3(b)). To our knowledge, this is the first evidence directly linking ICSS, corticostriatal potentiation, dopamine and learning (Reynolds et al., 2001). It is possible that the induction of LTP by dopamine release following ICSS-like stimulation represents the physiological changes underlying the learning of ICSS. These mechanisms may generalise to other forms of learning facilitated by positive reinforcement.

7. Dopamine-plasticity function

The findings from our in vivo model and established in vitro data suggest that the level of evoked dopamine release around the time of corticostriatal activation is a critical determinant of the direction of synaptic modification in the striatum. At one extreme, near total depletion of dopamine renders corticostriatal stimulation ineffective at inducing LTD (Calabresi et al., 1992a) or LTP (Centonze et al., 1999). In vitro, the drug AMPT, which depletes striatal dopamine by a lesser degree, also abolishes the induction of LTD or LTP by corticostriatal HFS (Kerr & Wickens, 2001). However, a similar AMPT dose regimen fails to block LTD induction in vivo when the residual dopamine released by corticostriatal HFS is augmented by nigrostriatal activation. Modest increase of dopamine levels induced by activating the substantia nigra using low frequencies (which are not reward-related), blocks the induction of LTD and sets the stage for the induction of potentiation. Finally, large increases of dopamine concentration induced by pulsatile application of exogenous dopamine (Wickens et al., 1996) or by activation of the substantia nigra with high frequencies (which are reward-relevant; Reynolds et al., 2001) induce lasting potentiation.

These results are suggestive of a biphasic relationship between dopamine levels in the microenvironment surrounding corticostriatal synapses and changes in synaptic efficacy (Fig. 4). Low levels of dopamine during corticostriatal activation induce depression. High levels induce potentiation. Ongoing activity in the corticostriatal and nigrostriatal pathways maintains an equilibrium level of synaptic efficacy at the zero-crossing point on the figure.

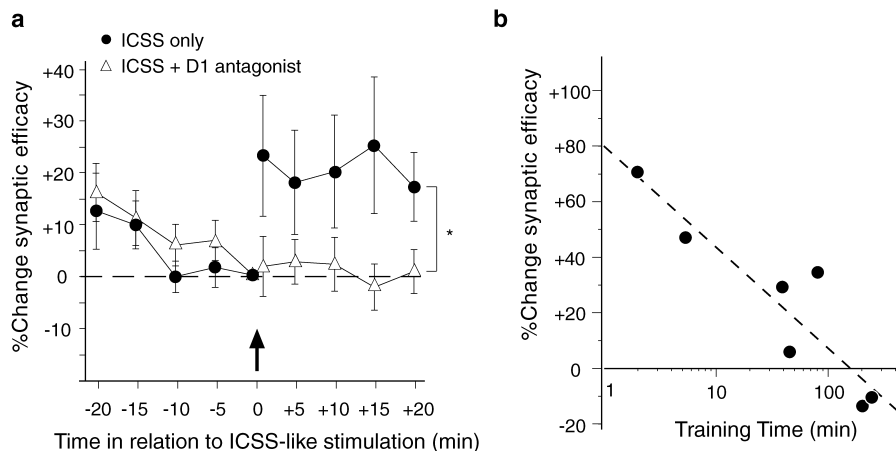


Fig. 3. Changes in corticostriatal synaptic responses by ICSS-like stimulation and their relationship to ICSS learning. (a). Changes in synaptic responses (as a percentage of baseline) in two groups that received ICSS-like stimulation. Asterisk, significantly different between no-drug and D1-receptor antagonist group at +20 min. (b). Correlation between degree of potentiation induced at +1 min following ICSS-like stimulation and ICSS training time ($r = -0.91$, $P < 0.01$). Each point is from a single animal in the no-drug ICSS group. (Adapted from Nature 413, 67–70, Reynolds, J. N. J., Hyland, B. I., and Wickens, J. R., A cellular mechanism of reward-related learning.).

Future studies are necessary to accurately map this proposed dopamine-plasticity function, by measuring striatal dopamine release at various levels of stimulation and determining if this correlates with changes in corticostriatal synaptic efficacy.

8. Other requirements for corticostriatal LTD and LTP

Our proposal of a relationship between dopamine release and the modulation of corticostriatal synaptic efficacy is not intended to disregard the contribution of other biophysical factors that have been implicated as necessary for the induction of LTD and LTP. For LTD these include the activation of group I metabotropic glutamate receptors (mGluR1s) (Calabresi et al., 1999b; Dos Santos Villar & Walsh, 1999; Gubellini et al., 2001) and activation of the enzyme nitric oxide synthase (Calabresi, Centonze, Gubellini, & Bernardi, 1999a; Calabresi et al., 1999c), which is only present in a small population of striatal interneurons

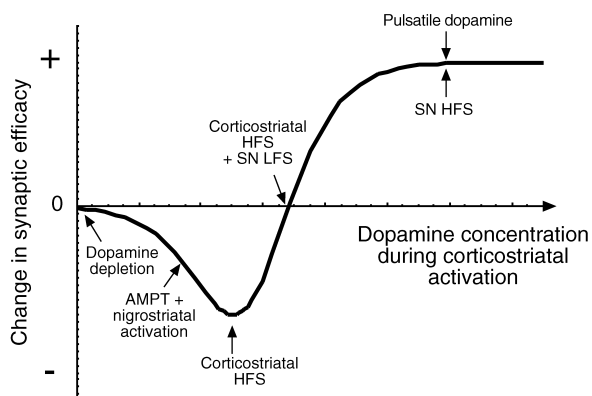


Fig. 4. Function that relates dopamine release to changes in corticostriatal synaptic efficacy.

(Kawaguchi, 1993). Another population of striatal interneurons that synthesis acetylcholine seem to play a role in the induction of LTP (Calabresi et al., 1999a). It remains, however, unclear whether these factors affect synaptic plasticity induction directly or by modulating presynaptically the release of other neurotransmitters during corticostriatal HFS (Calabresi, Centonze, Gubellini, Pisani, & Bernardi, 1998).

Both LTD and LTP involve postsynaptic mechanisms in their induction. Both processes are depolarisation-dependent and require the entry of calcium into the postsynaptic spiny projection neuron (Calabresi et al., 1992a; Calabresi, Pisani, Mercuri, & Bernardi, 1994; Charpier & Deniau, 1997; Choi & Lovinger, 1997). The portal of calcium entry appears to be specific to the type of plasticity induced. LTD requires the activation of L-type calcium channels (Calabresi et al., 1994; Choi & Lovinger, 1997) and is independent of NMDA receptor activation (Calabresi et al., 1992b, 1997; Lovinger et al., 1993; Partridge et al., 2000; but see Spencer & Murphy, 2000). LTP appears to require the reverse conditions, since its induction is blocked by NMDA channel antagonists (Calabresi et al., 1997; Partridge et al., 2000) but not by blockade of L-type calcium channels (Akopian et al., 2000; Calabresi et al., 2000). Although this is consistent with corticostriatal LTP being an NMDA-dependent process, further experiments are needed to determine the relative contribution of presynaptic and postsynaptic NMDA receptors.

The level of postsynaptic activity during synaptic plasticity induction might serve as a clue to the pre or postsynaptic locus of NMDA activation. Both in vivo and in vitro, a similar level of depolarisation and firing activity is induced during protocols that induce corticostriatal LTD and LTP (Calabresi et al., 1997; Reynolds and Wickens, unpublished observations). Hence, unlike other brain areas

(Artola, Brocher, & Singer, 1990), the expression of LTP is not directly determined by the level of postsynaptic activity and, by implication, the degree of activation of NMDA receptors. Clearly, calcium entry through specific receptors represents a necessary but not sufficient condition for the induction of corticostriatal synaptic plasticity. This process presumably determines the eligibility of a particular synapse for modification, whereas the direction of change in synaptic efficacy is determined by the proposed dopamine-plasticity function.

9. Induction of synaptic plasticity by behavioural events—a hypothesis

How might this model of corticostriatal synaptic plasticity be reconciled with the known firing patterns of dopamine neurons? In the behaving monkey, a number of observations have been made that suggest that the firing of dopamine neurons reports an error between the occurrence and the prediction of reward (Schultz, 1998). Dopamine neurons are activated phasically to fire bursts in response to unpredicted rewards during learning. Their tonic activity is uninfluenced by totally predicted rewards and is phasically suppressed when a predicted reward is surprisingly omitted. Therefore, it is reasonable to suggest that the presence of reward in a novel situation, and the omission of reward when fully predicted, is conveyed to the striatum by phasic changes in striatal dopamine release. These observations of Schultz and colleagues, taken together with our models of synaptic plasticity, suggest three hypotheses regarding the downstream effect on corticostriatal plasticity of dopamine cell firing patterns.

(i) *The arrival of an unexpected reward corresponds to a period of high frequency burst firing of dopamine neurons.* This situation was modelled in our *In vivo* experiments by the application of high-frequency ICSS-like stimulus trains to the substantia nigra (Figs. 2 and 4). In the behaving animal, such a situation would be expected to lead to the induction of corticostriatal LTP at active corticostriatal synapses involved in bringing about the delivery of reward. In this manner, the behaviour is reinforced.

(ii) *The omission of a fully predicted reward when a task is well practiced results in a transient depression in dopamine cell firing at the time the reward was expected. This situation favours LTD induction.* The effect of a transient reduction in dopamine levels on corticostriatal synaptic efficacy has not been reported as yet. However, since dopamine cells fire tonically *In vivo*, the absence of dopamine cell activity in a deafferented corticostriatal slice preparation might approximate the depressed levels of striatal dopamine expected in this behavioural situation. In normal solution bathing a slice, HFS of the corticostriatal pathway induces LTD (Fig. 4), which is dependent on basal dopamine levels in a slice. Therefore, the transient reduction in dopamine cell firing at the time of activation of

corticostriatal synapses involved in generating a behavioural response would be expected to also lead to LTD. Consequently, synaptic connections that were strengthened by a behavioural response that previously led to reward would be depressed.

(iii) *A fully predicted reward does not change dopamine cell firing patterns and corticostriatal synaptic efficacy is maintained.* The activation of substantia nigra dopamine cells with 20 Hz stimulus trains in conjunction with corticostriatal HFS (Fig. 2) or in isolation (Reynolds and Wickens, unpublished observations) maintained long-term synaptic efficacy at prestimulus levels. Possibly, the moderate dopamine release evoked by such low-frequency bursts (Fig. 4) is insufficient to diffuse outside synaptic clefts and activate extrasynaptic D1-like receptors (Gonon, 1997). As discussed earlier, this frequency of dopamine cell activation represents a naturally occurring intraburst frequency that is observed in animals that are not engaged in any particular activity. It is also typically reported in animals anaesthetised with certain anaesthetic agents (Grace & Bunney, 1984), although urethane, as used in our study, reduces dopamine cell burst firing (Kelland, Chiodo, & Freeman, 1990). This raises the possibility that low-frequency bursts occurring naturally during non-reward related activity, and evoked by electrical stimulation in urethane-anaesthetised animals, may be involved in maintaining corticostriatal synaptic efficacy at preexisting levels. Thus, the firing of spiny projection neurons by corticostriatal activity that accompanies non-task-related movement would induce no net change in synaptic efficacy. Similarly, the continuation of normal dopamine cell firing patterns at the time of a fully predicted reward will maintain synaptic efficacy. In this manner, predicted rewards will maintain ‘business as usual’.

These hypotheses, in the behavioural context given here, are largely consistent with various theoretical and computational reward models (Miller, 1981; Montague et al., 1996; Schultz, Tremblay, & Hollerman, 1998; Suri & Schultz, 1999; Wickens & Kotter, 1995).

10. Conclusions

Dopamine is now known to play a role in processes leading to corticostriatal synaptic plasticity. However, experiments over recent years have only begun to elucidate its mechanism of action in these processes. Dopamine is involved in the induction of both LTD and LTP. The mandatory requirement for associated presynaptic and postsynaptic activity is consistent with a three-factor rule of heterosynaptic plasticity. The induction of LTD requires a conjunction of presynaptic activity, postsynaptic depolarisation and low levels of dopamine. Reward-related burst firing of dopamine neurons induces sufficient dopamine release to activate intracellular cascades that lead to LTP induction and reinforcement learning. However, bursts

induced by other types of stimuli are of a lower intraburst frequency, release less striatal dopamine and do not induce a net change in synaptic efficacy. In contrast, omission of reward at an expected time leads to a relative depression of dopamine release, to a level that is compatible with the induction of LTD following a conjunction of presynaptic and postsynaptic activity. Further studies are required to elucidate the additional effects of the timing of the dopamine signal and its interaction with neuromodulators such as acetylcholine, factors that have been shown earlier to independently modulate the induction of corticostriatal synaptic plasticity (Calabresi et al., 1998, 1999a; Wickens, 2000).

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