

# REVIEW ARTICLE

## Dopamine gating of forebrain neural ensembles

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### Abstract

Dopamine may exert different actions depending on a number of factors. A common view is that D<sub>1</sub> receptors may be responsible for excitatory actions whereas D<sub>2</sub> receptors are involved in inhibitory actions. However, this position cannot be reconciled with several findings indicating otherwise. The role of dopamine on forebrain neural ensembles may be better understood in the light of functional states of the system. Pyramidal cortical neurons and striatal medium spiny neurons alternate between two membrane potential states ('up' and 'down') that could shape dopamine actions. It is proposed that D<sub>1</sub> receptors can act as state-stabilizers by sustaining up states and thereby facilitating plasticity mechanisms by providing postsynaptic depolarization and increasing NMDA function. In this way, dopamine can sustain activity in depolarized units. This action is accompanied by a decrease in cell firing (perhaps mediated by D<sub>2</sub> receptors), which renders the cells responsive only to strong stimuli. The result would be a net increase in signal-to-noise ratio in a selected assembly of neurons.

### Introduction

Dopamine (DA) has been known as a neurotransmitter for several decades, since its discovery by Arvid Carlsson (Carlsson *et al.*, 1958). The involvement of DA in Parkinson's disease pathophysiology (Hornykiewicz, 1993; Carlsson, 2001), as well as in schizophrenia, Tourette's syndrome and other neuropsychiatric disorders (Grace, 1991; O'Donnell & Grace, 1998a; Grace, 2000; Carlsson, 2001) prompted a long list of studies on this transmitter's actions. Despite this vast effort, a clear picture of its physiological effects has remained elusive. An excellent recent review summarized how misguided has been the prevailing discussion of whether DA is excitatory or inhibitory (Nicola *et al.*, 2000). The authors reviewed abundant evidence that may suggest a somewhat clear role for DA D<sub>1</sub> receptors; i.e. they increase activity of strongly activated neurons while decreasing weakly driven units, in a reformulation of the 'increase signal-to-noise' theory (DeFrance *et al.*, 1985). Thus, DA actions on individual neurons may have to be considered in the light of whether they are part of an active neural ensemble. DA actions may change with physiological states of target neurons or even the network they are connected to. Here I present an overview of the mechanisms that may be involved in establishing behaviourally relevant neural ensembles in target areas during discrete temporal windows.

### Membrane potential states in striatal and cortical neurons

An important element to consider is the alternation between different membrane potential states that striatal medium spiny neurons and pyramidal cortical cells exhibit. These cells have a very negative resting membrane potential (down state) periodically interrupted by

plateau depolarizations (up state), and it is only during up states that they exhibit action potential firing (Fig. 1). Up and down states have been observed with *in vivo* intracellular recordings from anaesthetized animals in the caudate–putamen (Wilson & Kawaguchi, 1996; Wickens & Wilson, 1998; Mahon *et al.*, 2001; Tseng *et al.*, 2001), nucleus accumbens (Leung & Yim, 1993; O'Donnell & Grace, 1995; Goto & O'Donnell, 2001a,b) and in cortical neurons (Steriade *et al.*, 1993b; Cowan & Wilson, 1994; Cowan *et al.*, 1994; Amzica & Steriade, 1995; Contreras & Steriade, 1995; Branchereau *et al.*, 1996; Lampl *et al.*, 1999; Lewis & O'Donnell, 2000). Up states cannot normally be detected in the slice preparation, indicating that they require the integrity of excitatory inputs. Indeed, the dependence of up states on excitatory afferents has been ascertained by the elimination of striatal up states in decorticated animals (Wilson, 1993), the elimination of nucleus accumbens (NAcc) up states by a fimbria–fornix transection (O'Donnell & Grace, 1995) and by recent studies showing synchronization of caudate–putamen or NAcc neuron up states with cortical or hippocampal electrical activity (Goto & O'Donnell, 2001a; Mahon *et al.*, 2001; Tseng *et al.*, 2001). Up states are therefore active periods driven by excitatory afferents, and information processing in neurons exhibiting them will depend on their modulation.

It has been suggested that task-related neural ensembles in cortical and striatal networks are defined by the spatial distribution of neurons in the up state (O'Donnell, 1999). There is indeed evidence indicating that medium spiny neurons in the dorsal striatum and NAcc show up states in synchrony (Stern *et al.*, 1998; Goto & O'Donnell, 2001b). The slow oscillatory (< 1 Hz) nature of up–down transitions resembles cortical electrical activity during slow wave sleep (Steriade *et al.*, 1993a), suggesting that up state synchronization may be a consequence of anaesthesia. In fact, anaesthetics impact differently on up–down oscillations, with urethane and chloral hydrate allowing their appearance and barbiturates blocking them (Mahon *et al.*, 2001). Early studies using paralysed, unanaesthetized animals also revealed plateau depolarizations (Wilson & Groves, 1981), indicating that cortical and

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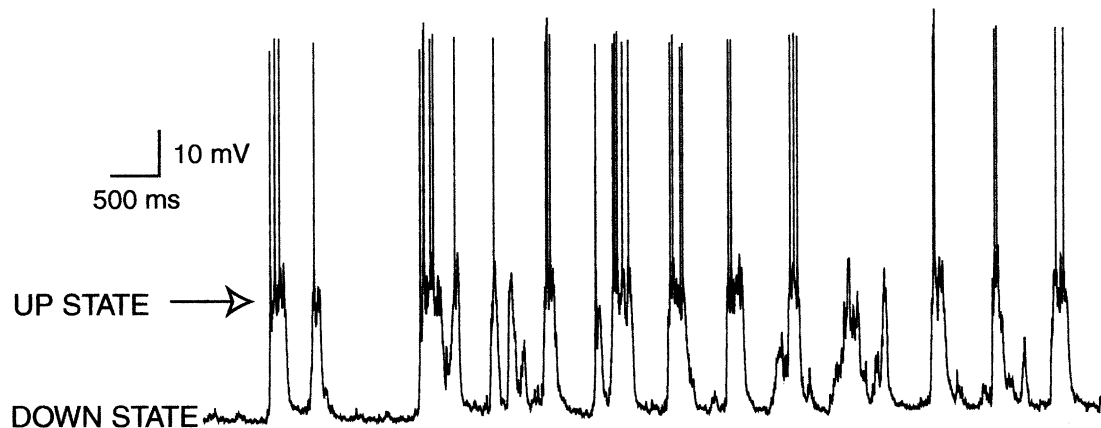


FIG. 1. Representative tracing from a pyramidal neuron in the prefrontal cortex recorded *in vivo* and exhibiting up and down membrane potential states. The down state is found at  $\approx -77$  mV and the up state is  $\approx -55$  mV. The latter is close to firing threshold, so it is possible to observe action potential firing during the up state. Silent neurons can also exhibit up and down states. The alternation between states occurs at slightly less than 1 Hz. This recording was obtained from a cat anaesthetized with chloral hydrate (400 mg/kg *i.p.*).

striatal neurons can exhibit up–down alternation even in the absence of anaesthesia. With chloral hydrate or urethane, it is likely that the up depolarizations become synchronized at a low frequency, while barbiturates shut them down completely by their stronger overall cortical depression. A recent study in cats trained to become accustomed to being held in a stereotaxic apparatus has shown up–down transitions oscillating at near 1 Hz while the animals are asleep and a sustained depolarization to the up state upon awakening (Steriade *et al.*, 2001). It is possible that the awake ‘desynchronized’ electroencephalogram (EEG) is expression of a large number of neurons in a prolonged up state, allowing higher frequency components (30 Hz or higher), typically embedded within up states (Stern *et al.*, 1997), to become apparent in the EEG. Up states during sleep may also be important for information processing. Given that firing during up states observed in slow-wave sleep is not different from what is observed in the awake condition, cortical neurons in the sleeping brain may be processing internally generated information during up states (Steriade *et al.*, 2001). Synaptic responses to thalamocortical or corticostriatal activation would be facilitated in neurons in the up state and rendered more difficult in neurons in the down state. In this way, arousing stimuli may enhance cortical and striatal activity by setting a population of neurons in the up state. Likewise, attention towards salient stimuli may be obtained by setting the relevant population of neurons in the up state. Thus, membrane potential oscillations are important elements modulating information processing in both cortical and striatal neurons.

### Dopamine and up states in neural ensembles

The presence of neural ensembles defined by membrane potential up and down states may be critical for DA actions in two ways: first, DA may have different effects when acting upon cells in the up or down state; second, an important action of DA may be to facilitate transitions or to sustain such states in target neurons. Recent findings support both possibilities. Electrical stimulation of the ventral tegmental area (VTA) evokes different responses in prefrontal cortical pyramidal neurons recorded *in vivo*, depending on whether the stimulation occurred during an up or down state (Lewis & O'Donnell, 2000). Nicola *et al.* (2000) have also reviewed evidence indicating that  $D_1$  receptors may sustain up states by virtue of their effects on slow intrinsic ionic conductances. Furthermore, the facilitation of NMDA responses by  $D_1$  receptors observed in medium spiny neurons (Cepeda *et al.*, 1998) and prefrontal cortex (PFC) pyramidal neurons (Wang & O'Donnell, 2001)

could enhance up states. Also,  $D_1$  receptors facilitate striatal NMDA receptor trafficking to the postsynaptic membrane (Dunah & Standaert, 2001). Although there is no direct evidence linking NMDA receptors to up states, the noncompetitive antagonist phencyclidine has been observed to block NAcc up states (O'Donnell & Grace, 1998b). Thus, a support of striatal and cortical up states may be a major effect of DA, mediated by  $D_1$  interactions with NMDA receptors and intrinsic slow conductances.

A  $D_1$ -sustained up state has indeed been observed *in vivo*. An elegant study by West & Grace (2002) with local application of DA drugs through a microdialysis cannula during intracellular recordings revealed that up states are under dopaminergic control: blockade of  $D_1$  receptors reduced up state amplitude in caudate–putamen neurons. Furthermore, stimulation of the VTA with trains of pulses mimicking DA cell burst firing evoked a prolonged depolarization resembling the up state in the medial PFC (Lewis & O'Donnell, 2000) and in the NAcc (Goto & O'Donnell, 2001b). In the PFC, this effect was also observed with chemical VTA activation, and its duration was shortened by administration of DA antagonists in both areas. A  $D_1$  antagonist was sufficient to reduce the evoked depolarization in the PFC (Lewis & O'Donnell, 2000) whereas in the NAcc both  $D_1$  and  $D_2$  receptors had to be blocked to reduce this response (Goto & O'Donnell, 2001b). In both regions, DA antagonists decreased the duration of evoked up states but failed to eliminate their onset. This finding indicates that the actual transition up is mediated by a non-DA mechanism, with DA acting to sustain the depolarization. The exact nature of the non-DA depolarizing mechanism is unclear, but it is likely to be glutamatergic. There is some evidence suggesting that DA cells can also release glutamate (Sulzer *et al.*, 1998), but this phenomenon has been observed primarily in cultured cells; it remains to be established in the intact brain. The VTA-dependent depolarization may involve activation of limbic inputs, because it could not be evoked in animals with a ventral hippocampal lesion (Goto & O'Donnell, 2002; O'Donnell *et al.*, 2002). On the other hand, a role of DA in the depolarization cannot be completely ruled out because locally applied DA can depolarize cortical cells (Bernardi *et al.*, 1982). The complexity of DA actions is demonstrated by the decrease in prefrontal and NAcc cell firing during the VTA-evoked depolarization (Lewis & O'Donnell, 2000; Goto & O'Donnell, 2001b) and during the iontophoretic DA-evoked depolarization (Bernardi *et al.*, 1982). This is in line with the finding that DA causes both depolarization and reduced cell excitability in NAcc neurons (O'Donnell & Grace, 1996). Earlier work by the late Gordon Mogenson's lab revealed that DA administration or VTA stimulation reduced synaptic

responses to amygdala (Yim & Mogenson, 1982, 1986) and hippocampal stimulation (Yang & Mogenson, 1984). We also have data indicating that a similar DA-mediated reduction in excitatory synaptic responses occurs for PFC-evoked EPSPs. Such reduction in PFC responses occurs in NAcc neurons during VTA-evoked up states (Himmelheber & O'Donnell, 2001). Thus, activation of the mesolimbic system has the dual effect of depolarizing the cells (thereby bringing them closer to firing threshold) and reducing the efficacy of weak synaptic inputs (Fig. 2). This action would work as a filtering mechanism by which neural ensembles are gated (driven to the up state) but only strong inputs allowed to elicit cell firing.

DA cells fire in a tonic manner between bursts. Tonic firing yields basal DA levels in target areas; it has been proposed that these levels set the gain for subsequent burst-evoked DA release (Grace, 1991). It is

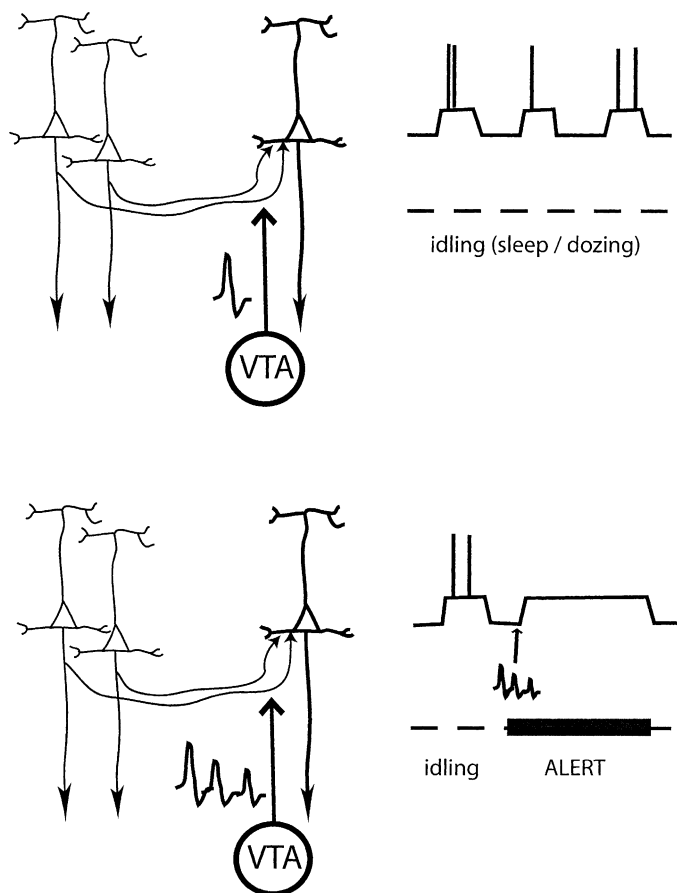


Fig. 2. Schematic representation of mesolimbic control of up-down states and filtering of weak inputs. (Top) During tonic VTA cell firing, DA levels in the prefrontal cortex are steady, contributing to the oscillatory and synchronized nature of up-down transitions in pyramidal neurons (thick cell in the middle). Cortico-cortical projections (thin cells to the left) were included to illustrate the cortical origin of excitatory inputs driving cells into the up state. Action potentials from the recorded pyramidal neuron are illustrated with vertical lines, and occur only during up states. (Bottom) In the presence of salient stimuli, DA cells fire in bursts. This results in a large increase in DA levels which, upon activation of  $D_1$  receptors, can sustain pyramidal neurons in a prolonged up state (trace at right). The depolarization is accompanied by a decrease in action potential firing, so only strong stimuli will be allowed to activate cortical cells, eliminating irrelevant information. It is proposed that a similar mechanism exists in NAcc and striatal medium spiny neurons, with their spontaneous up states driven by their cortical afferents. The synchronous oscillation may occur during sleep or quiet rest conditions (top), whereas the persistent depolarization in selected units may occur during attention-demanding conditions (bottom).

possible that, while phasic DA release results in prolonged up events in forebrain neural ensembles, tonic DA release contributes to the oscillatory nature of up-down alternation, resulting in an idling state in the system. We have preliminary data indicating that lidocaine injection in the VTA suppresses PFC field potential oscillations (Peters & O'Donnell, 2002), which are reflective of synchronous up-down alternation in pyramidal neurons (Steriade, 1999), without eliminating individual neuron up-down oscillations (Y.M. Peters & P. O'Donnell, unpublished observations). Thus, tonic DA levels may contribute to synchronization of up-down transitions in the anaesthetized preparation and in slow wave sleep.

A gating of forebrain neural ensembles could be an important mechanism in behavioural effects of DA. DA cells in the VTA fire in bursts when salient or unexpected stimuli are present (Ljungberg *et al.*, 1992; Overton & Clark, 1997; Hyland *et al.*, 2002), especially if detection of those stimuli is important for response selection (Schultz *et al.*, 1993). DA cell burst firing results in higher DA release, given the nonlinear relationship between impulse flow and release measured by voltammetry (Chergui *et al.*, 1994). In our experiments, VTA stimulation with a train of pulses mimicking burst firing yielded consistent and sustained transitions to the up state, whereas single pulse stimulation produced variable responses (Lewis & O'Donnell, 2000). It is conceivable that DA-sustained up states are temporal windows driven by stimuli related to arousal and attention mechanisms during which information throughput is enabled, although only for strong inputs. It is worth noting that DA cells also signal absence of expected reward by decreasing their firing (Hollerman & Schultz, 1998). The consequence would probably be that a failed reward would lead to the destabilization of the neural ensemble. Thus, in the presence of salient stimuli, neurons already in the up state may be sustained there, tagging the active ensembles associated with those stimuli (Fig. 3). An enhancement of activation by DA of strongly excited target cells has been also proposed based on modelling studies in which  $D_1$  receptors enhanced NMDA responses and an activation of GABA responses was added to provide a break for uncontrolled activation (Durstewitz *et al.*, 2000). DA-sustained up states should define an active ensemble that is appropriate for the context. Cell firing in such ensembles would be filtered so only relevant activity drives the system and the animal's attention can thereby be focused. It can be assumed that action potential firing recorded from behaving animals occurs only during up states. In striatal neurons, some cells fire when preferred reward is expected compared with nonpreferred reward (Hassani *et al.*, 2001), indicating that a different set of medium spiny neurons is gated in different contexts (preferred vs. nonpreferred rewards). Also, different NAcc cell populations become active in the presence of natural rewards compared to cocaine reward (Carelli *et al.*, 2000), further suggesting that different conditions activate different ensembles. Because a prolonged depolarization can enable synaptic plasticity in the form of long-term potentiation (LTP), DA (or better, the mesolimbic/mesocortical system) could be described as facilitating Hebbian mechanisms via  $D_1$  receptors. In the PFC, LTP requires the integrity of the mesocortical projection (Gurden *et al.*, 1999) and activation of  $D_1$  receptors (Gurden *et al.*, 2000). Similarly, corticostriatal LTP requires activation of  $D_1$  receptors (Kerr & Wickens, 2001) and can be potentiated by substantia nigra stimulation (Reynolds *et al.*, 2001). This could be explained by a  $D_1$  support of up states in pyramidal neurons and medium spiny neurons. It has been shown that correlated  $D_1$ -NMDA activation in the NAcc and PFC is necessary for appetitive learning (Smith-Roe & Kelley, 2000; Baldwin *et al.*, 2002). Furthermore, administration of DA antagonists in the NAcc disrupts pavlovian learning (Di Ciano *et al.*, 2001; Fenu *et al.*, 2001), and  $D_1$  agonists improve performance in delayed radial arm maze tasks

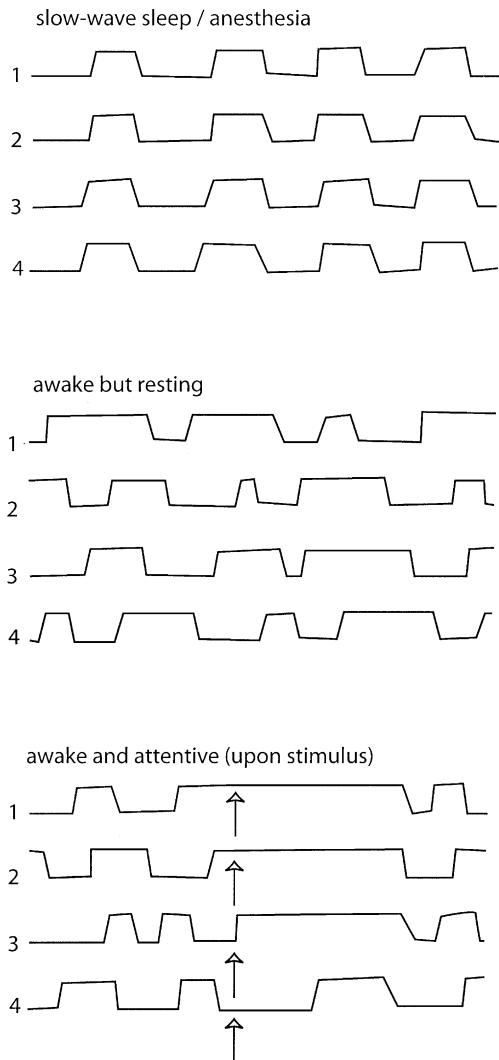


FIG. 3. Schematic illustration of up-down activity in a hypothetical set of four cortical neurons. During slow-wave sleep or in anaesthetized animals (top), neurons alternate between up and down states in synchrony. The resulting EEG would display a strong low-frequency component. In wake and resting conditions, it is possible that neurons still alternate between up and down states. The higher frequency typically observed in EEG signals may reflect either synchronous alternation at higher frequencies or cells exhibiting asynchronous up-down oscillations (middle). Given the strong excitatory input required to drive cells into the up state, it is likely that small clusters of cells rather than individual neurons alternate between up and down states. Thus, each trace in the panel represents a distributed population of neurons alternating between up and down states at a different pace from others with which they may on occasion become synchronized. When salient stimuli demand the animal's attention (bottom), the relevant population of neurons is sustained in the up state for periods ranging from a few hundred milliseconds to seconds and even minutes.

when an extended delay renders the task challenging (Floresco & Phillips, 2001).  $D_1$  receptors are also necessary for working memory functions (Aultman & Moghaddam, 2001). Indeed, a subset of monkey PFC neurons exhibit persistent firing during delays in which they have to hold on to clues in an oculomotor delayed response task. This activity requires mesocortical DA and adequate activation of  $D_1$  receptors (Sawaguchi & Goldman-Rakic, 1994). By gating forebrain neural ensembles,  $D_1$  receptors may contribute to establishing a sequence of activation patterns in striatal medium spiny neurons. It has been shown that  $D_1$  receptors enhance, for example, complex motor sequences (Berridge & Aldridge, 2000). Once learning is

complete, DA cell bursts no longer occur in response to reward, but to stimuli predicting reward (Schultz *et al.*, 2000). It is possible that neural ensembles are activated without the need of a DA burst once the association has been learned; ensembles would have been established during the learning phase. DA is certainly involved in reward, but is also activated in response to aversive stimuli (Horvitz, 2000). It would perhaps be more appropriate to say that DA cell bursts signal saliency or novelty. The plasticity mechanisms that such activation may enable would strengthen the spatial distribution of active neurons associated with the reward-related or salient condition (O'Donnell, 1999), an action that may contribute to defining context. The filtering of irrelevant information that may occur in the gated ensembles by the mesolimbic-induced decrease in firing may be demonstrated in the phenomenon of latent inhibition, a behaviour in which the animals learn to ignore irrelevant stimuli (i.e. neutral, nonrewarded stimuli that the animal had been previously exposed to).  $D_2$ , but not  $D_1$ , antagonists disrupt this phenomenon (Trimble *et al.*, 2002) indicating that a previously neutral stimulus cannot be ignored unless there is  $D_2$  receptor activation. Thus, a DA-sustained depolarization with reduced firing may both reinforce learning and contribute to selecting appropriate strategies.

A DA-sustained depolarization may be important for learning and cognitive functions that are the realm of global cortical function. How can a DA modulation of corticostriatal function affect overall cortical activity? Basal ganglia circuits eventually feed information back to the cortex by a variety of pathways. Striato-pallidal projections control thalamocortical function (Alexander & Crutcher, 1990). Also, NAcc output can target the reticular thalamic nucleus (O'Donnell *et al.*, 1997), which has a widespread control of thalamocortical activity that may allow for arousal and enhanced attention. In addition, the ventral pallidal neurons receiving inputs from the NAcc include some cortical-projecting cholinergic neurons (Záborszky & Cullinan, 1992). A recent study indicated that glutamatergic transmission in the NAcc is important for basal forebrain-cortical cholinergic system activity (Neigh-McCandless *et al.*, 2002). Thus, basal forebrain cholinergic projections may also be a gateway for ventral striatal DA actions (Sarter *et al.*, 1999) on cortical attention mechanisms.

## Role of $D_2$ receptors

The role of  $D_2$  DA receptors on ensemble coding is less clear. Some evidence indicates that  $D_2$  receptors may reduce cell excitability acting postsynaptically in striatal (Levine *et al.*, 1996) and cortical (Cepeda *et al.*, 1999) neurons. There are also presynaptic  $D_2$  heteroreceptors on glutamatergic terminals (Schwarcz *et al.*, 1978; Maura *et al.*, 1988) that may modulate glutamate release, controlling excitatory synaptic efficacy. It is not yet clear whether  $D_2$  receptors contribute to the reduced firing during VTA-evoked up states (other possibilities are activation of GABA projection neurons in the VTA or GABA interneurons). Several aspects of  $D_2$  anatomy and function contribute to the current uncertainty regarding their effects. For example, it has not yet been determined without controversy the extent of overlap of  $D_1$  and  $D_2$  receptors in striatal medium spiny neurons. Also, some effects of DA may require coactivation of both receptor subtypes. Thus, a complete picture of DA action on ensemble coding cannot be achieved until  $D_2$  receptor function and their interaction with  $D_1$  are better understood.

## Implications for pathophysiology of dopamine systems

Altered DA systems may result in behavioural deficits by impairing Hebbian processes. With reduced DA levels in the nigrostriatal

projection, gating may not be sufficient and a reduced number and breadth of activated neural ensembles in motor regions may give rise to Parkinson's disease akinesia. Conversely, it could be speculated that high phasic DA levels may blur neural ensembles (i.e. most cells in the up state), impairing functionality of the network. This is likely to result in stereotyped responses and poor selection from behavioural repertoires. In schizophrenia, for example, patients exhibit a clear inability to switch strategies, revealed as perseveration in the Wisconsin Card Sorting Test (Fey, 1951). Abnormal DA levels may also affect the filtering of irrelevant information. It is conceivable that hallucinations and other positive symptoms in schizophrenia arise from a loss of such filtering. Furthermore, schizophrenia patients exhibit altered PFC function (Berman *et al.*, 1986; Buchsbaum *et al.*, 1992) and deficits in working memory tasks (Javitt *et al.*, 2000), which correlate with increased D<sub>1</sub> receptor availability (Abi-Dargham *et al.*, 2002). This finding is probably due to inefficient compensations for sustained DA deficits (Abi-Dargham *et al.*, 2002). Although drugs that block D<sub>2</sub>, not D<sub>1</sub>, receptors are effective antipsychotics, it is likely that their action (which is different from placebo only after a couple of weeks of treatment) is not mediated by direct D<sub>2</sub> blockade but by DA cell depolarization block (Grace *et al.*, 1997). This phenomenon would bring an abnormal DA system to a new balance in which its activation does not cause abnormal behaviours. Indeed, we have some recent data indicating that, in animals with a neonatal ventral hippocampal lesion (a developmental animal model of schizophrenia), responses of NAcc and PFC neurons to VTA stimulation become abnormal (Goto & O'Donnell, 2002; O'Donnell *et al.*, 2002). This deficit is characterized by an enhanced firing, as opposed to the reduced firing observed in naïve and control animals, and has been interpreted as responsible for a loss of DA filtering on ensemble activity. Thus, altered DA gating of cortical and subcortical neural ensembles may be an important element in schizophrenia pathophysiology.

In drug abuse, it has been suggested that addiction is due to an 'usurpation' of DA-dependent plasticity by psychostimulants (Everitt & Wolf, 2002). Drugs may activate mesolimbic and mesocortical systems as natural rewards do, and change their gain (Kelley & Berridge, 2002). The consequence would be a strengthening of forebrain neural ensembles associated with drug intake contexts. Because exposure to cocaine-associated cues, for example, may provoke relapse (Self & Nestler, 1998), it is conceivable that exposure to such cues activates neural ensembles that had been associated with the drug, resulting in craving. Stress is also a condition in which DA systems are affected (Finlay & Zigmond, 1997; Enrico *et al.*, 1998) and, under these conditions, forebrain neural ensembles will be affected, either if they are normal (resulting in cognitive changes) or abnormal (causing stress-induced relapse in schizophrenia) (Moghaddam, 2002). It is possible that when stress-related responses become maladaptive, a number of deficits arise from overdriving the otherwise fine-tuned DA tagging of neural ensembles. Finally, it is likely that the gating and filtering of forebrain neural ensembles is not unique to DA systems. Activation of the locus coeruleus and pontine tegmental nucleus also can evoke persistent up states in cortical neurons (Steriade *et al.*, 1993c), suggesting that cholinergic and noradrenergic systems may exert their actions via a similar mechanism. It is conceivable that all diffuse forebrain monoaminergic projections contribute to sustaining neural ensembles, albeit driven by different conditions.

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## Abbreviations

EEG, electroencephalogram; LTP, long-term potentiation; NAcc, nucleus accumbens; PFC, prefrontal cortex; VTA, ventral tegmental area.

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