Review TRENDS in Neurosciences Vol.30 No.5

Regulation of firing of dopaminergic neurons and control of goal-directed behaviors

Anthony A. Grace[1], Stan B. Floresco[2], Yukiori Goto[3] and Daniel J. Lodge[1]

[1] Departments of Neuroscience, Psychiatry and Psychology, University of Pittsburgh, Pittsburgh, PA 15260, USA
[2] Department of Psychology, University of British Columbia, Vancouver, British Columbia, V6T 1Z4, Canada
[3] Department of Psychiatry, McGill University, Montreal, Quebec, H3A 1A1, Canada

There are several brain regions that have been implicated in the control of motivated behavior and whose disruption leads to the pathophysiology observed in major psychiatric disorders. These systems include the ventral hippocampus, which is involved in context and focus on tasks, the amygdala, which mediates emotional behavior, and the prefrontal cortex, which modulates activity throughout the limbic system to enable behavioral flexibility. Each of these systems has overlapping projections to the nucleus accumbens, where these inputs are integrated under the modulatory influence of dopamine. Here, we provide a systems-oriented approach to interpreting the function of the dopamine system, its modulation of limbic–cortical interactions and how disruptions within this system might underlie the pathophysiology of schizophrenia and drug abuse.

Introduction

The physiology of dopamine neurons has been a subject of investigation for several years. This is as a result of the known involvement of this transmitter system in a broad array of behaviors and disorders, ranging from loss of nigrostriatal dopamine neurons in Parkinson's disease [1] to hyperactive dopamine responses in schizophrenia [2] and the common denominator of this transmitter system in the pathologic consequences of drug abuse [3]. Substantial insight into the pathophysiology of these disorders has arisen from electrophysiological investigations of dopamine neurons, the structures that they modulate and that regulate them (Figure 1). Recent studies of the regulation of the dopamine system and its effect on the integration of information flow provide an important insight into how these systems interact in a manner that can most effectively guide behavior towards the goal of obtaining a reward or reinforcement in the normal individual but exhibit disruptions in pathologic states.

Identification of dopamine neurons

The ability to accurately identify dopamine neurons *in vivo* by their unique electrophysiological signature has been a major factor in evaluating the role of this neuron class in neurologic and psychiatric disorders and their treatment. Identification based on numerous criteria, including antidromic activation from projection sites, loss of spike phenotype following dopamine-specific lesions, pharmacologic responses that parallel neurochemical measures, and direct identification by intracellular injection and dopamine-specific staining [4–7]. Using these methods, a unique electrophysiological waveform was proposed and has been consistently and reproducibly associated with the dopamine neuron phenotype *in vivo*. Moreover, this waveform precisely reflects the distinctive characteristics of the action potential recorded intracellularly. Thus, the slow depolarization that triggers spike firing at the distally located initial segment [8,9] creates variability in the threshold membrane potential, leading to a highly variable waveform. Furthermore, the significant Ca^{2+} component of the action potential [9] underlies the large negative segment of the waveform. Thus, the unique membrane properties of the neuron lead to the distinct waveform that has been linked specifically to this type of neuron. However, these criteria are totally dependent on the use of electrophysiological techniques that enable accurate recording of the unaltered waveform of the action potential. A recent study, in which dopamine neurons were indirectly identified by extracellular ejection of neurobiotin in the vicinity of a recorded neuron, questioned these well-established criteria [10]. Unfortunately, the amplifier filter settings used by these investigators distorted the electrophysiological signal to such a degree that identification using standard criteria was virtually impossible. Indeed, the exceedingly long-duration, triphasic action potential reported is consistent with gross overfiltering and is vastly different from the biphasic action potentials observed with both classical filter settings and differentiation of intracellular waveforms [8]. An additional caution relates to recordings obtained from immature rats [11], in which the activity patterns of dopamine neurons [12,13] and autoreceptors [14] are inconsistent compared with those of adult rats. Thus, care must be exercised in applying identification criteria, to appropriately use the volume of work that has accurately and reproducibly identified this neuronal class.

Regulation of the activity states of dopamine neurons

Dopamine neurons recorded *in vivo* are reported to display three main patterns of activity: an inactive, hyperpolarized

Corresponding author: Grace, A.A. (Grace@bns.pitt.edu).
Available online 2 April 2007.

 0166-2236/$ – see front matter doi:10.1016/j.tins.2007.03.003

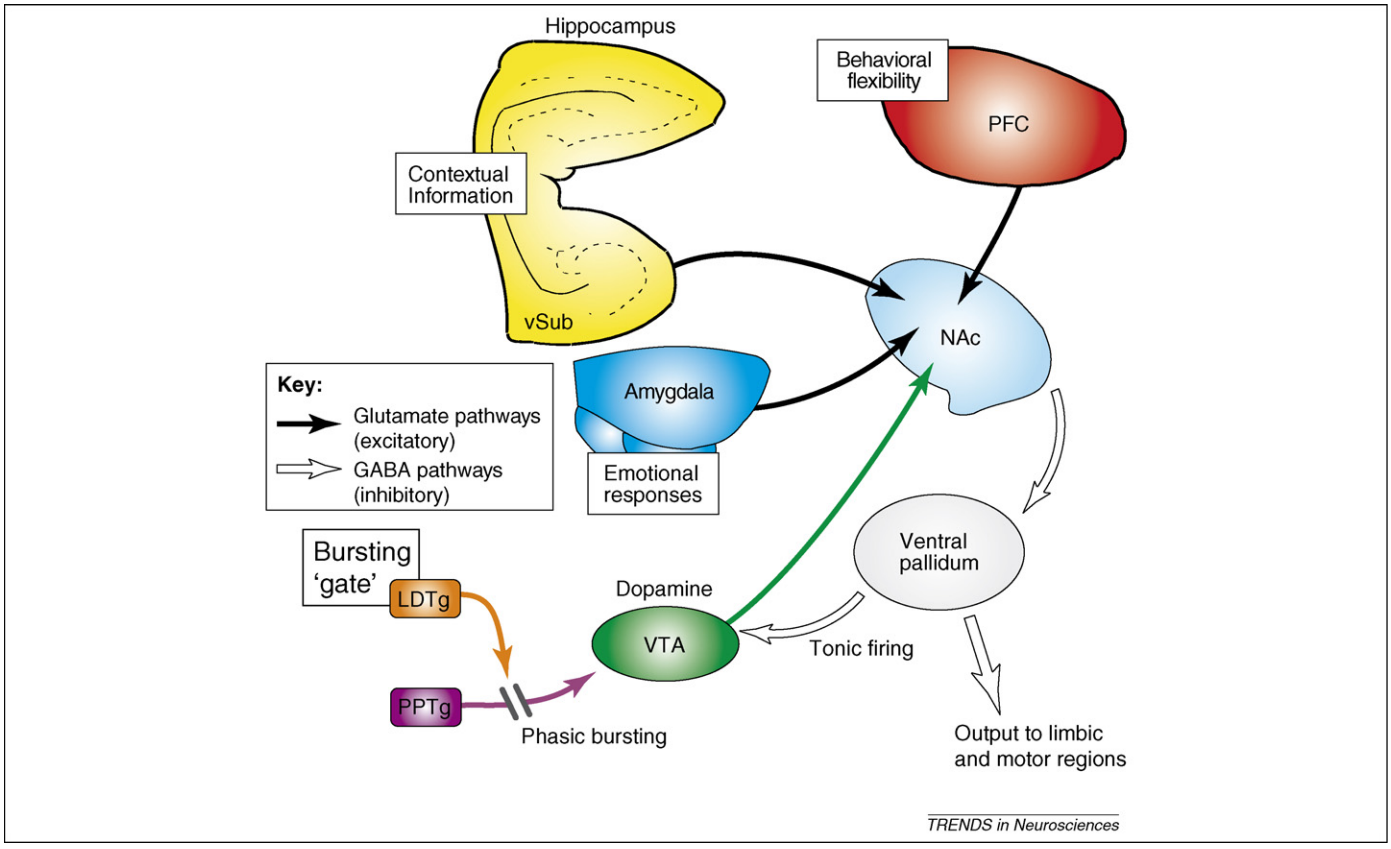

Figure 1. A summary of the primary components that control firing of dopamine neurons and the systems on which the dopaminergic system acts in the control of goal-directed behavior. Tonic and phasic activity of dopamine neurons is regulated by inputs from the ventral pallidum and tegmental nuclei (PPTg and LDTg, respectively). Dopamine, in turn, regulates the interaction of higher-level systems controlling different aspects of behavior within the NAc. The integrated output of these interactions is then funneled through the ventral pallidal system to limbic and motor control regions. These interactions are shown in detail in subsequent figures.

state; a slow (2–10 Hz), irregular, single-spike or 'tonic' firing pattern; and a burst or 'phasic' mode [7]. Single-spike or 'tonic' firing is driven by an intrinsic pacemaker potential [15], similar to how the pacemaker of the heart maintains activity in this organ. Burst firing or 'phasic' activity is crucially dependent on afferent input [16,17] and is believed to be the functionally relevant signal sent to postsynaptic sites to indicate reward and modulate goal-directed behavior [18–20]. Accordingly, much research has focused on the regulation of the firing patterns of dopamine neurons and mechanisms that lead to the transitions among these activity states.

In the normal animal, ~50% of all mesencephalic dopamine neurons are not spontaneously active [15,21], independent of the state of anesthesia [22]. Indeed, dopamine neurons recorded *in vivo* are observed to be bombarded constantly with high-amplitude GABA-mediated inhibitory postsynaptic potentials (IPSPs) [23]. Moreover, studies suggest that the source of the IPSPs is the ventral pallidum [24,25], a GABA-producing region known to exhibit high levels of spontaneous activity [26]. Therefore, a subpopulation of dopamine neurons in the ventral tegmental area (VTA) seem to be held at a constant hyperpolarized, inactive state by the ventral pallidum and inactivation of this structure releases the dopamine neurons from inhibition and enables them to fire spontaneously [25,27]. This spontaneous firing state of the population of dopamine neurons supplies the stable baseline level of extrasynaptic dopamine in postsynaptic structures and has been termed the 'tonic' dopamine state [20,25]. An important regulatory pathway arises from the ventral subiculum (vSub) of the hippocampus; thus, activation of the vSub drives neuronal firing in the nucleus accumbens (NAc), which, in turn, inhibits the ventral pallidum and releases dopamine neurons from inhibition (Figure 2). This circuit has been implicated in the ability of the hippocampus to modulate novelty-gated information storage [28].

The transition from irregular single-spike firing to a burst-firing pattern represents the high-level 'phasic' dopamine response [20,25] that has been associated with reward-related cues [19]. Phasic bursting is dependent on an excitatory amino acid, because activation of glutamatergic afferents or direct microiontophoretic application of glutamate induces burst firing in dopamine neurons *in vivo* [16,25,29]. Furthermore, direct application of competitive NMDA receptor antagonists has been shown to potently inhibit spontaneous burst firing [30,31]. By contrast, glutamate alone is insufficient to mediate burst firing. Thus, dopamine neurons from mesencephalic slices obtained from adult rats, in which the afferent input has been severed, display a regular pacemaker firing pattern and cannot be made to fire in bursts in response to the administration of a glutamate agonist or alterations in membrane potential alone [17,32–34]. These data suggest the presence of a permissive afferent 'gate' that enables dopamine neurons to respond to glutamate and initiate burst firing.

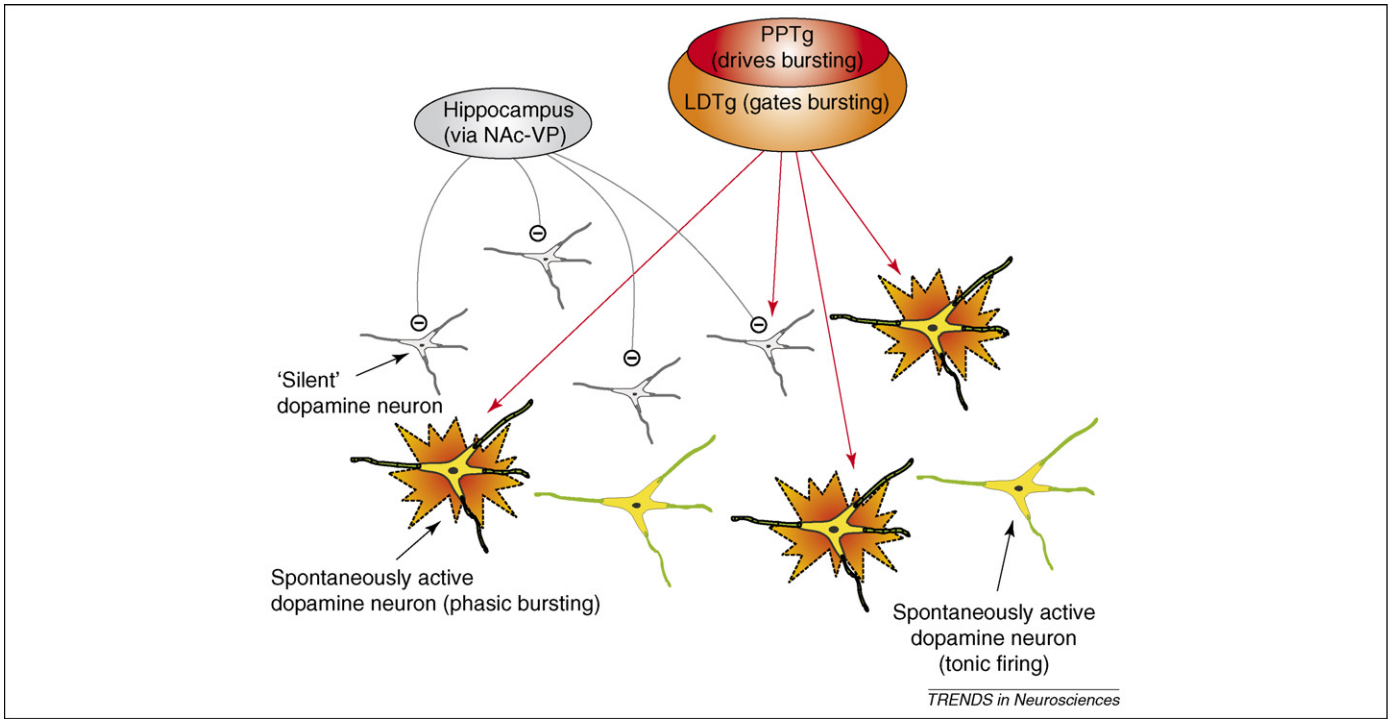

Figure 2. The activity states of dopamine neurons are regulated by intrinsic and extrinsic factors. Dopamine neurons are known to generate their own activity through a pacemaker conductance [7]. However, in the intact animal, a substantial population of dopamine neurons is not firing spontaneously, being held in a hyperpolarized state by GABA-mediated inhibitory inputs from the ventral pallidum. The spontaneous tonic firing state is regulated by the vSub of the hippocampus through excitatory projections to the NAc, which, in turn, inhibits the ventral pallidum and releases silent dopamine neurons from inhibition, resulting in spike activity. This pathway controls the tonic baseline state of the dopamine system. By contrast, phasic burst firing, which is believed to be the behaviorally relevant parameter of the activity of dopamine neurons, is dependent on glutamatergic inputs arising from several areas, primary among these being the PPTg. The ability of the PPTg to elicit bursting, however, is dependent on a permissive 'gate' from the LDTg; only if this 'gate' is engaged can the PPTg enable burst firing. These two afferent systems work in concert to regulate activity states within the population of dopamine neurons, because only neurons that are in a tonic spontaneously firing state can be phasically activated by the PPTg–LDTg system [25,35].

It was recently demonstrated that a crucial factor required to enable spontaneous and glutamate-driven burst firing *in vivo* was an active input from the laterodorsal tegmentum (LDTg; Figure 2) [35]. Thus, inactivation of the LDTg causes the discharge patterns of dopamine neurons to more closely resemble those observed *in vitro*, that is pacemaker firing lacking spontaneous bursting [35]. Interestingly, neither activation of glutamatergic afferents nor direct glutamate iontophoresis can induce burst firing, either *in vitro* [17,32–34] or following LDTg inactivation [35]. Therefore, these data demonstrate that a functional input from the LDTg is essential for burst firing of dopamine neurons *in vivo*. The neurotransmitter provided by the LDTg that permits burst firing of dopamine neurons is currently unknown; however, recent data examining the spontaneous activity of dopamine neurons in nicotinic acetylcholine receptor subunit knockout mice have suggested a role for cholinergic transmission. More specifically, nicotinic acetylcholine receptor β2 subunit knockout mice exhibit a global decrease in the excitability of midbrain dopamine neurons [36]. Therefore, the results of this study parallel those following LDTg inactivation, that is a global decrease in burst firing of dopamine neurons.

The LDTg input provides the permissive 'gate' that enables dopamine neurons to respond to a glutamatergic input with a transition to this behaviorally relevant phasic burst-firing mode. There are several potential sources for this glutamatergic input, including the prefrontal cortex (PFC), pedunculopontine tegmentum (PPTg) and lateral preoptic–rostral hypothalamic area [37]. The PPTg is a glutamatergic–cholinergic region driven by limbic afferents, including the PFC and extended amygdala, and activated by auditory, visual and somatosensory stimuli [38]. Moreover, the PPTg has been demonstrated to directly regulate burst firing of dopaminergic neurons in the VTA [25,27,39]. Thus, activation of the PPTg triggers a transition to burst firing in dopamine neurons of the VTA [25,27]. The PPTg is, therefore, positioned to serve as a site of convergence, whereby a variety of sensory inputs can modulate burst firing of dopamine neurons. Indeed, such a role might be related to the propensity of this region to control conditioned responses in dopamine neurons in the VTA [40]. By contrast, in the substantia nigra the glutamatergic input from the subthalamic nucleus seems to be more relevant to engaging burst firing [41].

Because individual afferent inputs to the VTA can selectively alter the activity states of dopamine neurons, these pathways are positioned to function in concert to regulate the output of the dopamine system [27]. Thus, glutamate-driven burst firing in the VTA occurs only in dopamine neurons that are already spontaneously active [25]. Dopamine neurons that are inactive, presumably owing to GABA-mediated hyperpolarization, are unresponsive to activation of NMDA receptors. Because nonfiring dopamine neurons have a more hyperpolarized resting membrane potential, the absent NMDA-mediated response is probably a consequence of NMDA receptor

channel block by submillimolar concentrations of extracellular Mg^{2+} [42]. This suggests an interdependence of the GABA-mediated and glutamatergic VTA inputs; that is, only neurons not under GABA-mediated hyperpolarization are capable of entering a burst-firing mode in response to a glutamatergic input. Indeed, it has been demonstrated recently that the hippocampus can gate the activity states of dopamine neurons by decreasing ventral pallidal inhibition of their activity. Thus, by regulating the number of spontaneously active dopamine neurons, the hippocampus can determine the neurons that can be further modulated by excitatory inputs to induce a phasic burst response [27]. Hence, although distinct inputs to the VTA can regulate discrete activity states of dopamine neurons, these afferents also interact to regulate the responsiveness of dopamine neurons and its impact on both novelty and reward-directed behavior [28].

Compartmentalization of ventral striatal dopamine transmission

It is becoming increasingly apparent that dopamine transmission within the striatum is not a unitary phenomenon, but, instead, it might be segregated into dissociable compartments, each of which is regulated by different neural mechanisms. As alluded to above, burst firing of dopamine neurons is thought to mediate a fast-acting and spatially restricted 'phasic' signal. This mode of dopamine transmission induces a high-amplitude, transient signal, in which intrasynaptic dopamine concentrations are estimated to reach a low millimolar range (e.g. 1.6 mM in the NAc [43]) that might function rather selectively on dopamine receptors localized within or around the synapse (Figure 3). Importantly, phasic release of dopamine is expected to affect a relatively restricted number of postsynaptic neurons within the striatum, because diffusion of dopamine from the synapse is curtailed by reuptake mechanisms involved in eliminating dopamine from the synaptic cleft by the high-affinity dopamine transporter (DAT) [25]. The finding that a selective increase in PPTg-mediated burst firing of dopamine neurons, occurring without a change in the overall number of these cells that are active, does not evoke a discernable change in extrasynaptic dopamine levels within the NAc supports this hypothesis; however, if uptake is blocked, the same manipulation causes a dramatic increase in dopamine efflux. This finding indicates that a selective increase in burst firing of dopamine neurons induces a massive increase in dopamine release at the terminal level. However, under normal conditions, most of the dopamine released does not escape the synaptic cleft owing to reuptake by DAT.

In contrast to the phasic dopamine signal, extrasynaptic or 'tonic' dopamine transmission, resulting from spike activity, represents a dopamine pool in the extracellular space, the concentration of which changes on a much slower time course than transmission mediated by burst firing of dopamine neurons (seconds to minutes versus milliseconds, respectively). Changes in the dopamine concentration within this compartment are dependent on

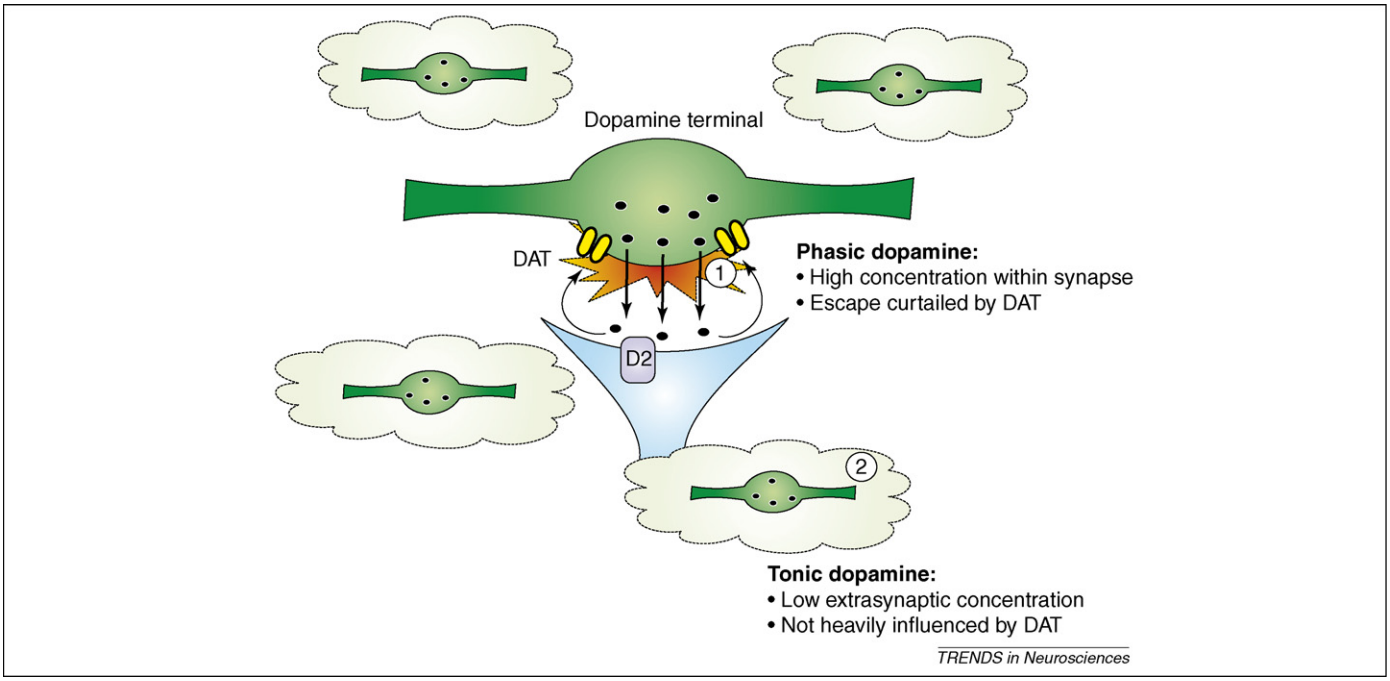

Figure 3. The dopamine input to the NAc exhibits a functional compartmentalization. Upon behaviorally salient stimulation, dopamine neurons emit a phasic burst of spikes. This leads to a massive release of dopamine into the synaptic cleft within the NAc (1). Dopamine levels within the synaptic cleft reach considerably high concentrations (estimated to be in the hundreds of micromolar range [43]), which should saturate postsynaptic D2 receptors that are preferentially localized within the synapse [44]. Most of the released dopamine is then rapidly removed from this spatially constrained compartment through reuptake into the terminal by the DAT before it can leave the synaptic cleft. Because dopamine within the cleft can saturate the D2 receptors, it is probable that this represents the compartment measured by raclopride displacement in imaging studies. By contrast, baseline slow, single-spike tonic activity of VTA dopamine neurons is responsible for the steady-state low-level (i.e, a concentration in the tens of nanomolar range) tonic dopamine present in the extracellular space of the NAc (2; represented by light green clouds). Dopamine in this compartment is not disproportionately affected by the DAT. Although tonic dopamine levels are only 0.01% of those estimated to be present in the synaptic cleft, it is still of sufficient concentration to stimulate the highly sensitive presynaptic D2 receptors present on afferent terminals. It is this dopamine compartment that is assessed by microdialysis measures [20,25].

tonic firing of dopamine neurons, rather than DAT activity. Thus, increases in the tonic activity of the dopamine neuron population through activation of the vSub result in consistent increases in extracellular dopamine levels in the NAc (Figure 3). However, blockade of dopamine reuptake does not alter the magnitude of change in the tonic dopamine level induced by disinhibition of nonfiring dopamine neurons. This indicates that, once dopamine diffuses away from the terminal, tonic dopamine levels are not heavily influenced by reuptake, and other mechanisms, such as enzymatic degradation, might regulate the clearance of dopamine from the extrasynaptic space. This organization is proposed to have an important role in the behavior function of this system, because each pathway controls a distinct compartment of dopamine transmission within the ventral striatum that interacts to control the balance between cortical and limbic drives of behavior.

Interaction between limbic and cortical inputs in the nucleus accumbens

The above data show that the dopamine system is functionally compartmentalized into two systems: a slow, tonic release of dopamine mediated by the population of spontaneously active dopamine neurons that maintains the low tonic concentration of dopamine in the extrasynaptic space, and a rapid, brief, high-amplitude phasic release of dopamine that is driven by behaviorally relevant burst firing of dopamine neurons. Indeed, because of the high concentration of intrasynaptic dopamine D2 receptors in the ventral striatum [44], it is probable that phasic dopamine transmission is reflected by raclopride displacement in imaging studies, whereas tonic dopamine transmission is selectively detected by microdialysis measures. Phasic changes in bursting of dopamine neurons occur in response to primary or conditioned rewarding stimuli and have been proposed to mediate a prediction error for anticipated rewards [19,45]. By its nature, fast-acting phasic dopamine transmission is expected to modulate the activity of only a subgroup of medium spiny neurons in the NAc. Thus, this mode of dopamine signaling might have a particularly important role during the early stages of reward-related associative learning, altering synaptic strengths of selected limbic striatal inputs to particular ensembles of NAc neurons [45,46]. By contrast, slower changes in the tonic levels of dopamine, regulated by the overall activity of the population of dopamine neurons, are more spatially distributed, modulating the activity of a large number of neurons in the ventral striatum, in addition to modulating presynaptic glutamatergic inputs from different limbic and cortical regions. Interactions between these tonic and phasic dopamine states are believed to potently modulate input selection and thus regulate the selection of the response in ambiguous situations to most effectively guide goal-directed behavior [47,48].

Both anatomic [49,50] and electrophysiological [51] studies have revealed that single neurons in the NAc receive convergent synaptic inputs from limbic structures, such as the vSub of the hippocampus, basolateral amygdala and PFC. Therefore, the NAc is positioned to integrate a substantial amount of information from these regions. Moreover, the dopamine system has a crucial role in regulating this integrative function. Data show that the NAc inputs coming from the limbic system and PFC are differentially regulated by dopamine receptor subtypes. Thus, D2 receptor stimulation was found to selectively attenuate the input from the medial PFC (mPFC) [52–54]; moreover, this attenuation is in a steady state, in that dopamine antagonists increase the input from the mPFC and D2 receptor agonists attenuate it. This input is also selectively affected by tonic dopamine transmission. Therefore, if the ventral pallidum is inactivated, which increases the number of firing dopamine neurons, there is a selective attenuation of the mPFC afferent drive of the NAc, without an effect on the input from the hippocampus vSub. By contrast, if the ventral pallidum is stimulated, tonic D2 receptor suppression of the mPFC input is diminished. These data demonstrate that changes in the activity of the population of dopamine neurons, which increases tonic dopamine levels in the NAc, selectively attenuate the afferent drive from the mPFC through D2 receptor stimulation (Figure 4).

By contrast, the rapid phasic dopamine system exerts its functional actions selectively on limbic system inputs. Thus, dopamine D1 receptor stimulation was found to increase the responsiveness of NAc neurons to inputs [53], specifically those arising from the vSub, without affecting inputs arising from the mPFC [54]. This system seems to depend on functional activation of the dopamine system, because D1 receptor antagonists do not have the opposite action in the anesthetized rat. The vSub inputs are selectively affected by phasic activation of the dopamine system; therefore, burst firing in dopamine neurons elicited by stimulation of PPTg glutamatergic afferents leads to a selective D1 receptor-mediated augmentation of vSub inputs to the NAc (Figure 4) [54]. In summary, increases in the dopamine input to the NAc mediate a shift in information flow away from mPFC control (through tonic D2 receptor-mediated attenuation of mPFC inputs), favoring limbic vSub control (through phasic D1 receptor-mediated augmentation of vSub afferents).

Behavioral significance of dopamine modulation of limbic and cortical inputs

These data demonstrate that tonic and phasic activation of the dopamine system can selectively modulate the PFC and limbic afferent interactions within the NAc, as evaluated by electrophysiological measures of neuronal pathway activation. However, does this translate into functional actions, with respect to the behavior of the animal? Such an interaction is revealed by examining the effects of manipulation of the dopamine system on goal-directed behavior believed to be mediated by the NAc [54]. To do this, rats were tested for their performance on a discrimination task, in which reaching a goal to obtain a reward is dependent on learning to respond to one cue, and then changing the task so that the rats had to ignore the original ‘correct’ cue and instead pay attention to another signal to determine the new correct choice. This paradigm enables the evaluation of both the ability to acquire a discrimination task and the ability to switch strategies once the initial discrimination is no longer valid

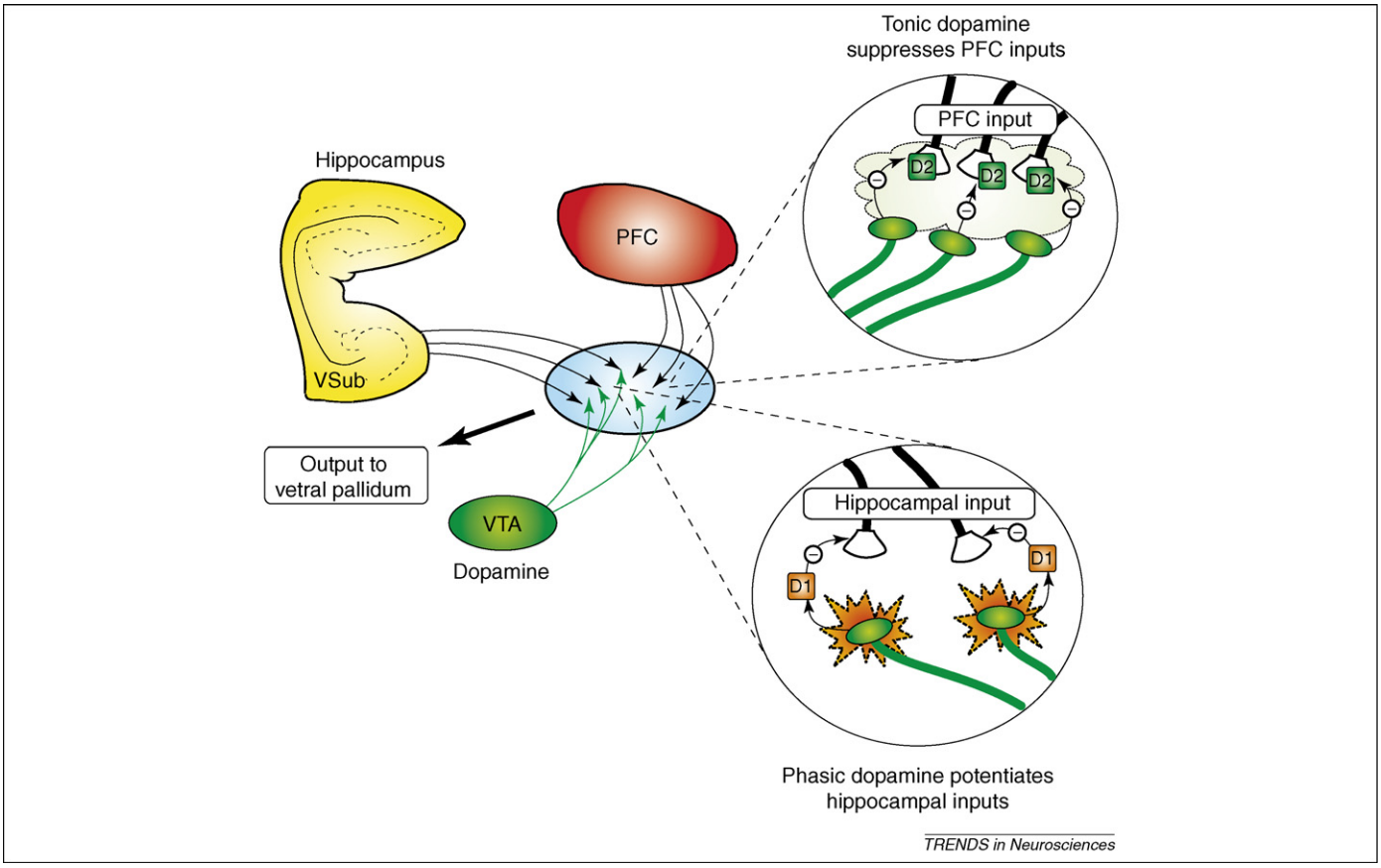

Figure 4. The NAc receives afferent inputs from several frontal cortical and limbic cortical regions, with excitatory glutamatergic afferents from these regions overlapping with a VTA dopamine input onto single neurons in this structure. Therefore, the NAc is positioned to integrate substantial amounts of information under the modulatory influence of the dopamine system for subsequent processing by output regions, such as the ventral pallidum. The input from the PFC is regulated by presynaptic D2 receptors, with D2 receptor stimulation inhibiting the ability of the PFC to influence NAc neurons. Presynaptic D2 receptor stimulation is dependent on extracellular dopamine (clouds) released by tonic dopamine neuron firing and is of sufficient sensitivity to be activated by the low tonic levels of extracellular dopamine present in the NAc extracellular milieu. By contrast, activation of D1 receptors by the high-amplitude, phasic dopamine signal can potentiate the drive of NAc neurons by inputs from the hippocampus vSub. As a consequence, an increase in tonic and phasic dopamine transmission inhibits the PFC drive and potentiates the vSub drive, effectively shifting the balance of information flow in favor of limbic inputs from the hippocampus [54]. By contrast, antipsychotic drug administration, by blocking dopamine receptors and inactivating dopamine neuron firing [62], would shift the balance of information flow in favor of a PFC predominance.

(i.e. show behavior flexibility), which together evaluate two interdependent means that drive effective goal-directed strategies. Then, each of the inputs to the NAc was neurochemically disconnected and the effects on task acquisition and behavior flexibility were evaluated.

Because the vSub input is modulated by D1 receptors, the influence of this input on the NAc was attenuated through a neurochemical disconnection, that is the vSub was inactivated unilaterally, whereas a D1 receptor antagonist was administered into the contralateral NAc. Under this condition, the rats were found to perform poorly in both parts of the task – they showed impairment in both the acquisition and the response-switching tasks. This is consistent with the function of the phasic dopamine system in using reward for learning a response strategy. By contrast, when the mPFC was disconnected (i.e. unilateral inactivation of the mPFC and administration of a D2 receptor agonist into the contralateral NAc), the rats performed the initial discrimination accurately but failed to switch strategies, exhibiting perseverance instead. Therefore, by increasing phasic and tonic dopamine transmission, the organism can continue to respond in a successful manner to achieve a goal, in addition to limiting the propensity to seek novel alternate solutions. However, taken to an extreme, such a focus can negatively affect the ability to achieve a desired goal, such as has been proposed to occur during pathologic states in this system.

Dopamine regulation of synaptic plasticity and its role in drug addiction

Drug addiction is characterized by the compulsive use of drugs of abuse, and substantial evidence suggests that disruption of the dopamine system in the NAc lies at the core of this condition [55,56]. Several studies have suggested that long-term alterations in dopamine-associated synaptic plasticity might be involved in the pathophysiology of drug addiction [57]. Indeed, with repetitive activation, afferent inputs to the NAc exhibit competitive synaptic plasticity within this structure. Thus, high-frequency tetanic stimulation of the vSub was found to produce long-term potentiation (LTP) of this afferent input to the NAc but long-term depression (LTD) of the PFC input to the NAc. By contrast, if a similar tetanic stimulation is subsequently applied to the PFC, LTP is induced in the PFC afferents to the NAc and LTD is induced in the vSub afferents. Therefore, the PFC and the vSub seem to compete for the control of information flow within the NAc. Moreover, increased stimulation by

dopamine tends to favor the vSub input, owing to a D1 receptor-dependent facilitation of this afferent pathway, with concomitant D2 receptor-dependent attenuation of the PFC input [58]. Thus, in the regulation of information flow within the NAc, a balance exists between the vSub limbic system and the PFC that depends on the recent history of activation (i.e. the pathway activated first wins), with dopamine shifting the balance in favor of the limbic system.

The competition between the vSub and the PFC has particular functional relevance in animals sensitized to psychostimulants. Thus, in rats that have been sensitized to cocaine, the balance of inputs to the NAc seems to exist in precisely the same state as that observed following tetanic stimulation of the vSub. Therefore, it seems that repeated cocaine treatment induces LTP in the vSub input pathway, while attenuating PFC control over this system. Moreover, this is reflected in the behavior of the animal: the cocaine-sensitized rats are not impaired in acquiring discrimination tasks but show powerful perseverative behavior if the goal is switched (i.e. a continued response to the original stimulus after it is no longer rewarded) [58]. Indeed, a similar type of disruption in the balance of the systems might occur after repeated L-DOPA administration in parkinsonian patients, whereby patients exhibit an impairment in probabilistic reversal learning that is correlated to the lack of NAc activation during the 'on' phase of treatment [59,60]. These data suggest that, in an individual taking a psychostimulant, there is an over-representation of limbic influence in the NAc and a disruption in the ability of the PFC to enable behavior flexibility. Such a condition could lock the individual into a state of perseverative drug-seeking behavior from which they cannot easily escape.

Concluding remarks

Studies of the regulation of limbic system function suggest that the balance between limbic and frontal cortical information inputs into the NAc is crucial for the normal regulation of goal-directed behavior. Furthermore, the dopamine system has a central role in maintaining this delicate equilibrium. Disruption of the stability of this system, either through pathologic states (e.g. pathology within the PFC) or pharmacologic intervention (e.g. drug abuse), is proposed to be a primary factor in the pathophysiology of major psychiatric conditions [61]. Indeed, the balance of inputs and how this affects regulation of dopamine neurons might form the pathophysiological basis for disorders of motivation and affect, and re-establishing this balance might be the most effective treatment strategy in alleviating these disturbances.

References

1 Hornykiewicz, O. (1962) [Dopamine (3-hydroxytyramine) in the central nervous system and its relation to the Parkinson syndrome in man.] *Dtsch. Med. Wochenschr.* 87, 1807–1810

2 Laruelle, M. and Abi-Dargham, A. (1999) Dopamine as the wind of psychotic fire: new evidence from brain imaging studies. *J. Psychopharmacol.* 13, 358–371

3 Grace, A.A. (1995) The tonic/phasic model of dopamine system regulation: its relevance for understanding how stimulant abuse can alter basal ganglia function. *Drug Alcohol Depend.* 37, 111–129

4 Bunney, B.S. *et al.* (1973) Dopaminergic neurons: Effect of antipsychotic drugs and amphetamine on single cell activity. *J. Pharmacol. Exp. Ther.* 185, 560–571

5 Hollerman, J.R. and Grace, A.A. (1990) The effects of dopamine-depleting brain lesions on the electrophysiological activity of rat substantia nigra dopamine neurons. *Brain Res.* 533, 203–212

6 Grace, A.A. and Bunney, B.S. (1980) Nigral dopamine neurons: intracellular recording and identification with L-dopa injection and histofluorescence. *Science* 210, 654–656

7 Grace, A.A. and Bunney, B.S. (1983) Intracellular and extracellular electrophysiology of nigral dopaminergic neurons–1. Identification and characterization. *Neuroscience* 10, 301–315

8 Grace, A.A. and Bunney, B.S. (1983) Intracellular and extracellular electrophysiology of nigral dopaminergic neurons–2. Action potential generating mechanisms and morphological correlates. *Neuroscience* 10, 317–331

9 Grace, A.A. (1990) Evidence for the functional compartmentalization of spike generating regions of rat midbrain dopamine neurons recorded *in vitro*. *Brain Res.* 524, 31–41

10 Ungless, M.A. *et al.* (2004) Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* 303, 2040–2042

11 Margolis, E.B. *et al.* (2006) The ventral tegmental area revisited: is there an electrophysiological marker for dopaminergic neurons? *J. Physiol.* 577, 907–924

12 Wang, L. and Pitts, D.K. (1994) Postnatal development of mesoaccumbens dopamine neurons in the rat: electrophysiological studies. *Brain Res. Dev. Brain Res.* 79, 19–28

13 Mereu, G. *et al.* (1997) Spontaneous bursting activity of dopaminergic neurons in midbrain slices from immagure rats: role of N-methyl-D-aspartate receptors. *Neuroscience* 77, 1029–1036

14 Hedner, T. and Lundborg, P. (1985) Development of dopamine autoreceptors in the postnatal rat brain. *J. Neural Transm.* 62, 53–63

15 Grace, A.A. and Bunney, B.S. (1984) The control of firing pattern in nigral dopamine neurons: single spike firing. *J. Neurosci.* 4, 2866–2876

16 Grace, A.A. and Bunney, B.S. (1984) The control of firing pattern in nigral dopamine neurons: burst firing. *J. Neurosci.* 4, 2877–2890

17 Grace, A.A. and Onn, S.P. (1989) Morphology and electrophysiological properties of immunocytochemically identified rat dopamine neurons recorded *in vitro*. *J. Neurosci.* 9, 3463–3481

18 Berridge, K.C. and Robinson, T.E. (1998) What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Brain Res. Rev.* 28, 309–369

19 Schultz, W. (1998) Predictive reward signal of dopamine neurons. *J. Neurophysiol.* 80, 1–27

20 Grace, A.A. (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* 41, 1–24

21 Bunney, B.S. and Grace, A.A. (1978) Acute and chronic haloperidol treatment: comparison of effects on nigral dopaminergic cell activity. *Life Sci.* 23, 1715–1727

22 Freeman, A.S. *et al.* (1985) Firing properties of substantia nigra dopaminergic neurons in freely moving rats. *Life Sci.* 36, 1983–1994

23 Grace, A.A. and Bunney, B.S. (1985) Opposing effects of striatonigral feedback pathways on midbrain dopamine cell activity. *Brain Res.* 333, 271–284

24 Floresco, S.B. *et al.* (2001) Glutamatergic afferents from the hippocampus to the nucleus accumbens regulate activity of ventral tegmental area dopamine neurons. *J. Neurosci.* 21, 4915–4922

25 Floresco, S.B. *et al.* (2003) Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat. Neurosci.* 6, 968–973

26 Tsai, C.T. *et al.* (1989) A comparison of the effects of electrical stimulation of the amygdala and hippocampus on subpallidal output neurons to the pedunculopontine nucleus. *Brain Res.* 494, 22–29

27 Lodge, D.J. and Grace, A.A. (2006) The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology* 31, 1356–1361

28 Lisman, J.E. and Grace, A.A. (2005) The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 46, 703–713

29 Chergui, K. *et al.* (1994) Subthalamic nucleus modulates burst firing of nigral dopamine neurones via NMDA receptors. *Neuroreport* 5, 1185–1188

30 Chergui, K. *et al.* (1993) Tonic activation of NMDA receptors causes spontaneous burst discharge of rat midbrain dopamine neurons *in vivo*. *Eur. J. Neurosci.* 5, 137–144
31 Overton, P. and Clark, D. (1992) Iontophoretically administered drugs acting at the N-methyl-D-aspartate receptor modulate burst firing in A9 dopamine neurons in the rat. *Synapse* 10, 131–140
32 Mercuri, N.B. *et al.* (1992) A voltage-clamp analysis of NMDA-induced responses on dopaminergic neurons of the rat substantia nigra zona compacta and ventral tegmental area. *Brain Res.* 593, 51–56
33 Seutin, V. *et al.* (1990) Evidence for the presence of N-methyl-D-aspartate receptors in the ventral tegmental area of the rat: an electrophysiological *in vitro* study. *Brain Res.* 514, 147–150
34 Wang, T. and French, E.D. (1993) L-glutamate excitation of A10 dopamine neurons is preferentially mediated by activation of NMDA receptors: extra- and intracellular electrophysiological studies in brain slices. *Brain Res.* 627, 299–306
35 Lodge, D.J. and Grace, A.A. (2006) The laterodorsal tegmentum is essential for burst firing of ventral tegmental area dopamine neurons. *Proc. Natl. Acad. Sci. U. S. A.* 103, 5167–5172
36 Mameli-Engvall, M. *et al.* (2006) Hierarchical control of dopamine neuron-firing patterns by nicotinic receptors. *Neuron* 50, 911–921
37 Geisler, S. and Zahm, D.S. (2005) Afferents of the ventral tegmental area in the rat-anatomical substratum for integrative functions. *J. Comp. Neurol.* 490, 270–294
38 Mena-Segovia, J. *et al.* (2004) Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? *Trends Neurosci.* 27, 585–588
39 Lokwan, S.J. *et al.* (1999) Stimulation of the pedunculopontine tegmental nucleus in the rat produces burst firing in A9 dopaminergic neurons. *Neuroscience* 92, 245–254
40 Pan, W.X. and Hyland, B.I. (2005) Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. *J. Neurosci.* 25, 4725–4732
41 Smith, I.D. and Grace, A.A. (1992) Role of the subthalamic nucleus in the regulation of nigral dopamine neuron activity. *Synapse* 12, 287–303
42 Mayer, M.L. *et al.* (1984) Voltage-dependent block by Mg2+ of NMDA responses in spinal cord neurones. *Nature* 309, 261–263
43 Garris, P.A. and Wightman, R.M. (1994) Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: an *in vivo* voltammetric study. *J. Neurosci.* 14, 442–450
44 Sesack, S.R. *et al.* (1994) Ultrastructural localization of D2 receptor-like immunoreactivity in midbrain dopamine neurons and their striatal targets. *J. Neurosci.* 14, 88–106
45 Schultz, W. and Dickinson, A. (2000) Neuronal coding of prediction errors. *Annu. Rev. Neurosci.* 23, 473–500
46 Parkinson, J.A. *et al.* (2002) Nucleus accumbens dopamine depletion impairs both acquisition and performance of an appetitive Pavlovian approach behaviour: implications for mesoaccumbens dopamine function. *Behav. Brain Res.* 137, 149–163
47 Floresco, S.B. *et al.* (2001) Modulation of hippocampal and amygdalar-evoked activity of nucleus accumbens neurons by dopamine: cellular mechanisms of input selection. *J. Neurosci.* 21, 2851–2860
48 Bratcher, N.A. *et al.* (2005) The role of dopamine in reinforcement: changes in reinforcement sensitivity induced by D1-type, D2-type, and nonselective dopamine receptor agonists. *J. Exp. Anal. Behav.* 84, 371–399
49 French, S.J. and Totterdell, S. (2002) Hippocampal and prefrontal cortical inputs monosynaptically converge with individual projection neurons of the nucleus accumbens. *J. Comp. Neurol.* 446, 151–165
50 French, S.J. and Totterdell, S. (2003) Individual nucleus accumbens-projection neurons receive both basolateral amygdala and ventral subicular afferents in rats. *Neuroscience* 119, 19–31
51 O'Donnell, P. and Grace, A.A. (1995) Synaptic interactions among excitatory afferents to nucleus accumbens neurons: hippocampal gating of prefrontal cortical input. *J. Neurosci.* 15, 3622–3639
52 O'Donnell, P. and Grace, A.A. (1994) Tonic D2-mediated attenuation of cortical excitation in nucleus accumbens neurons recorded *in vitro*. *Brain Res.* 634, 105–112
53 West, A.R. and Grace, A.A. (2002) Opposite influences of endogenous dopamine D1 and D2 receptor activation on activity states and electrophysiological properties of striatal neurons: studies combining *in vivo* intracellular recordings and reverse microdialysis. *J. Neurosci.* 22, 294–304
54 Goto, Y. and Grace, A.A. (2005) Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior. *Nat. Neurosci.* 8, 805–812
55 Volkow, N.D. *et al.* (2004) Dopamine in drug abuse and addiction: results from imaging studies and treatment implications. *Mol. Psychiatry* 9, 557–569
56 Everitt, B.J. and Wolf, M.E. (2002) Psychomotor stimulant addiction: a neural systems perspective. *J. Neurosci.* 22, 3312–3320
57 Hyman, S.E. *et al.* (2006) Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu. Rev. Neurosci.* 29, 565–598
58 Goto, Y. and Grace, A.A. (2005) Dopamine-dependent interactions between limbic and prefrontal cortical plasticity in the nucleus accumbens: disruption by cocaine sensitization. *Neuron* 47, 255–266
59 Cools, R. *et al.* (2001) Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain* 124, 2503–2512
60 Cools, R. *et al.* (2007) L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's Disease. *Neuropsychopharmacology* 32, 180–189
61 Grace, A.A. (2000) Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res. Brain Res. Rev.* 31, 330–341
62 Grace, A.A. *et al.* (1997) Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. *Trends Neurosci.* 20, 31–37