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The ability of the mesocortical dopamine system to operate in distinct temporal modes

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Abstract

Background—This review discusses evidence that cells in the mesocortical dopamine (DA) system influence information processing in target areas across three distinct temporal domains.

Discussions—Phasic bursting of midbrain DA neurons may provide temporally precise information about the mismatch between expected and actual rewards (prediction errors) that has been hypothesized to serve as a learning signal in efferent regions. However, because DA acts as a relatively slow modulator of cortical neurotransmission, it is unclear whether DA can indeed act to precisely transmit prediction errors to prefrontal cortex (PFC). In light of recent physiological and anatomical evidence, we propose that corelease of glutamate from DA and/or non-DA neurons in the VTA could serve to transmit this temporally precise signal. In contrast, DA acts in a protracted manner to provide spatially and temporally diffuse modulation of PFC pyramidal neurons and interneurons. This modulation occurs first via a relatively rapid depolarization of fast-spiking interneurons that acts on the order of seconds. This is followed by a more protracted modulation of a variety of other ionic currents on timescales of minutes to hours, which may bias the manner in which cortical networks process information. However, the prolonged actions of DA may be curtailed by counteracting influences, which likely include opposing actions at D1 and D2-like receptors that have been shown to be time-and concentration-dependent. In this way, the mesocortical DA system optimizes the characteristics of glutamate, GABA, and DA

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neurotransmission both within the midbrain and cortex to communicate temporally precise information and to modulate network activity patterns on prolonged timescales.

Keywords

Prefrontal cortex; Dopamine; VTA; Glutamate; D1; D2

Introduction

Midbrain dopamine (DA) neurons send projections to a variety of forebrain structures, forming a complex neuromodulatory system crucial for many cognitive processes and motor functions. Dysfunctions of this system underlie aspects of drug abuse and neuropsychiatric disorders, including schizophrenia and addiction (Phillips et al. 2003; Rompre and Wise 1989; Volkow et al. 2005; Winterer and Weinberger 2004). Often, pathologies that are associated with these disease states are manifested in aberrations of normal functions of the system such as working memory and reward processing (Winterer and Weinberger 2004; Abi-Dargham et al. 2002; Wise 2005; Ungless 2004). To combat these disorders, we need an understanding of the intricacies of the networks involved. Our current understanding of these processes are certain to change as we uncover the variety of signaling modalities that the mesocortical DA system may be able to employ. Likewise, our understanding of the inputs that activate the DA system has developed significantly in recent years. The present article will review aspects of DA signaling in PFC and highlight how the mesocortical DA system may affect information processing over various time scales in this area.

The most influential interpretation of the function of the DA system is the idea that the phasic activation/inactivation of DA neurons encodes a prediction error signal which is crucial for reinforcement learning. This theory suggests that DA neurons transmit information to efferent regions about discrepancies between predicted and actual reward magnitude, as well as the probability of forthcoming rewards (Schultz 1998a,b; Tobler et al. 2005). This theory highlights the precise temporal signaling demands placed on the DA system to effectively transmit these prediction error signals to target regions.

The PFC is postulated to be instrumental for a variety of temporally delimited executive functions such as trial-unique working memory and error detection (Goldman-Rakic 1995; Miller and Cohen 2001; VanVeen and Carter 2002). Many of these processes also require temporal precision in neural mappings of stimuli and rewards. For instance, working memory requires the active maintenance of a subset of stimuli that will be used to guide a correct forthcoming response. Upon completion of the response, the reward contingencies may change and their representations in working memory would have to be remapped. Accordingly, neurons in the PFC show sustained elevations in firing during delay periods that are specific for the previously encoded stimulus and its relationship to reward and when the location of the to-be-remembered stimulus changes, so does the delay-period activity of a given PFC neuron (Funahashi et al. 1989). Moreover, in humans, the error-related negativity (ERN) often observed on tasks involving conflict is an approximately 100–250 ms negativity in the event-related potential centered on the anterior cingulate region of the medial frontal cortex that reflects detection that an error was made based on a mismatch

between the actual and intended movement (VanVeen and Carter 2002). The ERN serves as an extremely fast internal signal of conflict that is present during situations when a perceived conflict arises immediately surrounding an incorrect response. Both working memory-related activity (Suri and Schultz 1999) and the ERN (Holroyd and Coles 2002) have been proposed to be influenced by phasic DA signaling. In fact, the ERN itself may be generated by phasic DA release associated with reward prediction errors (Holroyd and Coles 2002; Holroyd et al. 2003). If this is the case, then it is vital for DA release and its effects in PFC be temporally precise in onset and offset because if the DA signal is slow in onset and protracted, then it would be impossible for PFC neurons to accurately map the constantly changing associations between stimuli, reward, and responses (both intended and committed) to guide accurate responding in a trial unique manner.

However, when taking into account the physiological and biochemical properties of the mesocortical DA system, it becomes difficult to reconcile current theory with data that suggests that DA acts as a slow modulator of cellular and synaptic properties. While the firing patterns of DA neurons fit perfectly with the requirements of a prediction error signal, the duration and peak of DAs' effects in PFC alone appear too protracted to provide a relevant and timely bias on PFC networks to efficiently fill such a role, as will be discussed in detail later. On the other hand, recent evidence suggesting that DA neurons may corelease glutamate could reconcile many of the problems associated with the ability of mesocortical DA neurons to provide temporally precise information (Seamans and Yang 2004). In this review, we will focus on two main topics: (1) how DA modulates neurotransmission in the PFC to bias information processing in the network, and (2) how the mesocortical DA system is able to communicate temporally precise information. To this end, we will discuss evidence from the anatomy and physiology of the mesocortical DA system.

Basic anatomy of the DA system: volume transmission and extrasynaptic signaling

The dopaminergic innervation of the forebrain of mammals is constituted by a small number (~15,000–20,000 neurons on each side of the rat brain) of highly collateralized neurons residing in the ventral mesencephalon (Fallon and Loughlin 1995; Lindvall et al. 1984; Williams and Goldman-Rakic 1998). These mesencephalic cell groups are designated as A8, A9, and A10, according to the nomenclature of Dahlstrom and Fuxe (1964), and they generally correspond to the DA cells of the substantia nigra (SN, A9), ventral tegmental area (VTA, A10), and the retrorubral area (A8) (Berger et al. 1991; Porrino and Goldman-Rakic 1982; Williams and Goldman-Rakic 1998).

DA neurons show two predominant patterns of firing activity termed tonic and phasic (Grace 1991, 2000). Tonic activity consists of a regular spike firing pattern of ~1–6 Hz that DA neurons usually exhibit in the absence of salient stimuli (Grace and Bunney 1984b; Schultz et al. 1997). Tonic firing patterns maintain basal extracellular levels of DA in afferent regions, and can be affected by visceral stimuli that can moderately increase or decrease efferent DA levels to provide a "tone" on DA receptors (Grace 1991). These levels recorded using in vivo microdialysis are on the order of 0.3 to 15 nM in the striatum and PFC (Devoto

et al. 2001; Garris et al. 1993; Garris and Wightman 1994; Hernandez and Hoebel 1995; Hildebrand et al. 1998; Ihalainen et al. 1999; Izaki et al. 1998; Shoblock et al. 2003). Phasic activation of DA neurons increases their firing rates to ~20 Hz (Grace and Bunney 1984a; Kiyatkin and Zhukov 1988; Kiyatkin and Stein 1995), which results in significant and long-lasting increases in extracellular DA concentrations (Phillips et al. 2003; Williams and Millar 1990; Lavin et al. 2005). Changes in the firing rate of DA neurons can evoke a wide range of effects on efferent neurons by increasing or decreasing levels of DA (Phillips et al. 2003; Williams and Millar 1990; Lavin et al. 2005). We will examine the time course of DA modulation in PFC and attempt to reconcile this with changes in firing rates of DA neurons evoked by behaviorally salient stimuli.

The time course and local specificity of dopaminergic neurotransmission depends to a large extent on the regionally specific properties of uptake/breakdown of DA. In limbic and cortical regions such as the basolateral amygdala and PFC, DA clearance rates are slower than in the striatum (Cass and Gerhardt 1995; Garris et al. 1993; Garris and Wightman 1994). In the PFC, a 60 Hz/2 s stimulation evoked a maximal DA concentration of 2.4 μM and stimulation at lower frequencies (30 Hz/120 pulses) evoked ~200 nM (Garris et al. 1993). Decay of DA levels back to baseline in the PFC typically took longer than 5 s, while higher concentrations (1.2 μM) of exogenously applied DA decayed away over tens of seconds (Cass and Gerhardt 1995; Garris et al. 1993). Focal stimulation at 30 Hz/30 pulses evoked DA levels that reached 320 nM in PFC slices, and this decayed over a period greater than 5 s (Mundorf et al. 2001). Finally, in vivo we observed that a 20 Hz/2 s stimulation of the VTA evoked a 30–40 nM rise in DA that decayed back to baseline within a few seconds (Lavin et al. 2005). Because DA varicosities are fairly sparse in the PFC (10^6 per mm^3; Descarries et al. 1987), this concentration is rapidly depleted by radial diffusion, to nanomolar levels in the extrasynaptic space. Unlike in striatal regions, the PFC shows very low levels of DA transporter expression (Sesack et al. 1998) and the DA transporter accounts for only ~40% of DA uptake in the PFC, compared with ~95% in the striatum (Wayment et al. 2001). Rather, unlike in the striatum, a significant portion of DA uptake in the PFC is mediated by the norepinephrine transporter and catabolized enzymatically by catechol-*O*-methyltransferase and to a lesser degree monoamine oxidase (Bymaster et al. 2002; Cass and Gerhardt 1995; Moron et al. 2002; Wayment et al. 2001).

In the PFC of rats and primates, dopaminergic fibers make between 40–90% specialized contacts [~39% in the sulcus principalis of primates Smiley and Goldman-Rakic (1993); ~56% in the suprarhinal, and ~93% in the anteromedial PFC of rats, Seguela et al. (1988)]. The remaining axonal varicosities constitute unspecialized synaptic release sites and probably contribute to the actions of DA via volume transmission (Garris and Wightman 1994; Smiley and Goldman-Rakic 1993; Zoli et al. 1998).

In general, synapses of the central nervous system are classified as asymmetric (or type I), or symmetric (or type II), respectively, and these correspond to functional classes as well (Colonnier 1968; Gray 1959). Symmetric synapses are characterized by a darkening of both the pre- and postsynaptic side of the synapse, while asymmetric synapses are characterized by an intense darkening of the postsynaptic density (PSD) only (Colonnier 1968; Gray 1959). Asymmetric synapses are generally associated with glutamate transmission and

excitatory synaptic actions, while synapses with symmetric densifications of their membranes are implicated in inhibitory synaptic transmission.

Based on its physiological effects, DA is neither a classical excitatory nor inhibitory transmitter (Seamans and Yang 2004), and DA axons can form both symmetric and asymmetric synaptic contacts, although the latter ones clearly represent a minority: Asymmetric synapses have been found to constitute between as little as 3% and as much as 22% of the population of DA synapses. Part of this variability may stem from differences in methodology [see Smiley and Goldman-Rakic (1993) for a discussion of technical considerations], while other differences may depend on the area investigated. For example, in the rat medial PFC 84% of DA, synapses were characterized as symmetric and 16% as asymmetric, while in the ventro-orbital PFC 78% were found to be asymmetric and 22% asymmetric (Descarries et al. 1987; Seguela et al. 1988). For rat medial PFC, where much of the electrophysiological data has been collected characterizing the PFC DA system, an estimate of 16% (Seguela et al. 1988) would translate into ~150–200/mm^3 of asymmetric DA synapses out of 1315×10^3 DA varicosities/mm^3 reported for layer V (Descarries et al. 1987).

An important finding is that, in the striatum including the nucleus accumbens, most DA receptors can be found in the vicinity of glutamatergic asymmetric synapses, but are located at distant sites from a tyrosine-hydroxylase labeled DA synapse, further supporting the notion of volume transmission (Caille et al. 1996; Hara and Pickel 2005). A similar situation exists in PFC. Using mono and polyclonal antibodies directed at the C-terminal of the human D1 receptor, Smiley et al. (1994) found that D1 immunoreactivity was usually displaced to the side of the postsynaptic density of large asymmetric synapses that showed profiles not indicative of DA synapses. In fact, they report that none of the 21 synapses formed by tyrosine hydroxylase axons were labeled for D1 receptors. They conclude “that some or all cortical DA synapses do not utilize D1 receptors and that a substantial portion of D1 effects occur at sites other than synaptic specializations”. Likewise, Bergson et al. (1995) reported that D1 and D5 receptors are usually found on asymmetric synapses and not at DA synapses. As in the striatum, most D1 labeling was observed in spines and was typically displaced from the asymmetrical synapse. Most of the signal was observed in dendritic shafts, while only 5% of D5 labeling was found in spine heads. Likewise, most D2 immunogold labeling in dendrites and spines is associated with asymmetric synapses, but is found also outside the PSD at extrasynaptic and perisynaptic sites (Negyessy and Goldman-Rakic 2005). Collectively, these data indicate that D1 and D2 receptors are most often associated with asymmetric terminals, which are typically displaced from the PSD in the peri- or extrasynaptic space. In this way, DA is suited to modulate glutamate and GABA neurotransmission in a manner consistent with volume transmission.

Electrophysiological properties of PFC DA: understanding the classical “inhibitory” and “excitatory” effects of DA

There is a long history of studies showing that VTA activation or DA exert a predominately *inhibitory* effect on spontaneous firing of single pyramidal cells recorded extracellularly in

vivo (Bunney and Aghajanian 1976; Ferron et al. 1984; Godbout et al. 1991; Mantz et al. 1992; Mora et al. 1976; Pirot et al. 1992; Sesack and Bunney 1989; Tseng et al. 2006). Specifically, VTA stimulation tends to inhibit spontaneous firing of PFC neurons for a period of about 100–200 ms. Local iontophoretic application of DA also decreased the spontaneous firing of PFC neurons recorded extracellularly in vivo and this spike suppression was reduced by a D2, but generally not by a D1 antagonist (Parfitt et al. 1990; Pirot et al. 1992). Accordingly, D2 agonists were more effective than D1 agonists in replicating the DA-mediated inhibition of spontaneous firing (Thierry et al. 1998). However, Sesack and Bunney (1989) found that iontophoretic application of a D2 agonist directly onto single PFC neurons in vivo failed to mimic the DA-mediated firing suppression. Taken together, VTA stimulation or local DA application are capable of transiently inhibiting the spontaneous firing of PFC neurons although the DA receptor subtype involved is disputed.

In contrast to the effects on spontaneous firing recorded extracellularly, DA robustly increases the firing of PFC neurons evoked by intracellular current pulses both in vitro (Ceci et al. 1999; Henze et al. 2000; Lavin and Grace 2001; Penit-Soria et al. 1987; Yang and Seamans 1996; Shi et al. 1997; Wang and O'Donnell 2001), and in vivo (Lavin et al. 2005). Indeed, PFC neurons recorded intracellularly in vivo, VTA stimulation could both suppress spontaneous firing and enhance evoked firing (Lavin et al. 2005). The mechanisms underlying DA modulation of spontaneous firing in vivo and evoked firing by intracellular current pulses are somewhat different. Spontaneous firing in vivo involves a complex interplay of ionic currents. Computational models suggest that at low (spontaneous) levels of network activity, the DA-mediated increase in firing of interneurons (Gorelova et al. 2002; Kroener et al. 2006; Zhou and Hablitz 1999) and decreased glutamate release probability (Gao et al. 2001; Seamans et al. 2001a; Zhou and Hablitz 1999) dominate the D1-mediated effects, and cause a decrease of spontaneous firing in pyramidal cells. In contrast, firing evoked by somatic current injection (Lavin et al. 2005) is likely to depend to a larger degree on persistent Na^+ and slowly inactivating K^+ currents. By enhancing the former and diminishing the latter, D1 receptor activation increases firing evoked by intracellular current pulses (Dong et al. 2004; Dong and White 2003; Gorelova and Yang 2000; Henze et al. 2000; Yang and Seamans 1996). In addition, strong synaptic inputs driving PFC neurons to more depolarized levels will remove the voltage-dependent Mg^{2+} block of NMDA channels, amplifying the D1-mediated enhancement of NMDA receptors, establishing a positive feedback situation. Thus, the net enhancing effect of DA would be much more dramatic in strong activity situations such as persistent activity states (Goldman-Rakic 1995; Durstewitz et al. 2000a; Wang and O'Donnell 2001; Durstewitz and Seamans 2002). D1-mediated effects lead to an enhancement of sustained recurrent network inputs, while the effects of weaker or brief inputs are usually diminished (Seamans et al. 2001a; Durstewitz and Seamans 2002). The DA modulation of the currents involved in these effects is very protracted but collectively their combined effect can be thought of as a form of increased signal-to-noise ratio (Winterer and Weinberger 2004), favoring sustained and high-rate at the expense of transient or low-rate inputs.

Unlike the protracted effects of DA on NMDA, Na^+, and K^+ currents in pyramidal neurons that lead to the effects described above, DA appears to quickly and transiently depolarize interneurons. DA has been shown to selectively depolarize fast-spiking interneurons, yet has

little effect on other subtypes of interneurons (Gorelova et al. 2002; Kroener et al. 2006). The depolarization and increased excitability of fast-spiking interneurons is mediated solely by D1 receptors in some studies (Gorelova et al. 2002; Kroener et al. 2006) but also includes D2 receptors in others (Tseng and O'Donnell 2004). Surprisingly, the depolarization of FS interneurons and the simultaneous increase in interneuronal excitability by DA occur on different time scales. For the same application of DA and in the same interneuron, the depolarization lasted for less than 10 min, while the increase in evoked firing lasted >40 min (Gorelova et al. 2002; Seamans and Yang 2004; Kroener et al. 2006). Because these two actions depend on DA modulation of different K^+ currents in interneurons (Gorelova et al. 2002; Wu and Hablitz 2005), these data raise the interesting possibility that DA can act through the same receptor to modulate different ionic currents on different time scales to produce the different durations of changes in neuronal excitability vs membrane depolarization. Unlike the slower changes in evoked excitability, the depolarization of interneurons that can be observed with the focal pressure application of DA occurs within seconds of DA application (Fig. 1). However, the *exact* time frame of this depolarization is not clear due to technical constraints when using focal pressure application, such as the diffusional properties of the brain slice and variability in the placement of the pressure application pipette relative to the cell being recorded. However, at least in the brain slice preparation, this potent and relatively short-lived effect of DA on fast spiking interneurons is not observed for the DA modulation of a variety of intrinsic and synaptic currents in PFC pyramidal and interneurons (Gorelova et al. 2002; Gonzalez-Burgos et al. 2005; Gulledge and Jaffe 2001; Henze et al. 2000; Seamans et al. 2001a,b;Yang and Seamans 1996).

Fast-spiking interneurons that are the targets of this DA modulation synapse near the spike initiation zone of pyramidal neurons and directly regulate their spike initiation and timing (Szabadics et al. 2006; Tamas et al. 2000). Thus, a synchronous DA-mediated depolarization of fast-spiking interneurons might be a highly effective way to quickly shut off pyramidal neuron activity, and this could contribute to the transient inhibition in spontaneous firing after VTA stimulation or DA iontophoresis discussed above. Accordingly, Pirot et al. (1992) showed that the GABA antagonist bicuculline blocked the iontophoretic DA and VTA-mediated inhibition of spontaneous firing in 57 and 51% of cells, respectively. Moreover, a D2 antagonist reduced the DA-mediated and VTA stimulation induced inhibition of spontaneous firing in PFC in 89 and 54% of cells, respectively. Furthermore, depleting DA stores by pretreatment with α-methly-p-tyrosine reduced the number of cells inhibited by VTA stimulation to 39% and in this subset of cells the VTA-induced inhibition was no longer influenced by sulpiride (a D2 antagonist), but was blocked by bicuculline (Pirot et al. 1992). Thus, there is both a DA-dependent activation of local GABAergic interneurons and direct inhibition of PFC neurons through GABAergic neurons.

The direct effect of GABAergic interneurons by VTA stimulation may relate to potentially unique properties of the DA system. The feed-forward activation of PFC interneurons by DA neurons is reflected in the EPSP–IPSP sequences evoked by VTA stimulation in PFC pyramidal neurons recorded intracellularly in vivo (Fig. 1; Lavin et al. 2005; Lewis and O'Donnell 2000; Mercuri et al. 1985; Seamans et al. 2003; Tseng et al. 2006). The EPSP–IPSP sequence potently inhibits PFC firing for the duration of the IPSP (~200 ms) and likely accounts for much of the described fast inhibition of spontaneous firing of PFC neurons after

VTA stimulation in in vivo single unit recordings (Bunney and Aghajanian 1976; Ferron et al. 1984; Godbout et al. 1991; Mora et al. 1976; Pirot et al. 1992). The mechanisms responsible for generating this EPSP–IPSP sequence will be discussed in more detail below.

Collectively, these data suggest that the fast excitation of local interneurons and a VTA-induced IPSP contribute to the classic observation of a brief reduction in spontaneous firing of PFC neurons. On the other hand, modulation of intrinsic and NMDA synaptic currents by DA contribute to the enhancement in current–pulse evoked excitability as well as the amplification of sustained recurrent or particularly strong depolarizing inputs. In this way, diverse effects of the DA system act through a variety of seemingly unrelated mechanisms and on multiple time scales to both transiently inhibit spontaneous firing, while enhancing the efficacy of depolarizing inputs over prolonged time scales.

Beyond DA: the nature of the EPSP–IPSP in the VTA-PFC pathway

As noted above, stimulation of the VTA evokes an EPSP– IPSP sequence in PFC neurons recorded intracellularly in vivo, or in field recordings from the PFC (Fig. 1; Lavin et al. 2005). One of the first reports of VTA-induced EPSPs in PFC was given by Mercuri et al. (1985). In this study, a fast monosynaptic EPSP was recorded in the PFC of rats when the medial forebrain bundle was stimulated. Similar studies have observed evoked EPSPs in the striatum after electrical stimulation of the substantia nigra (Guyenet and Aghajanian 1978; Hull et al. 1973; Kocsis and Kitai 1977; Preston et al. 1981). Kocsis and Kitai (1977) observed a fast EPSP evoked in the caudate nucleus when the SN was stimulated. In addition to the fast-evoked EPSP, the authors also reported the presence of a slower EPSP. This slow EPSP was blocked by simultaneous orthodromic stimulation (collision), thus suggesting that it was an antidromic response. However, the fast excitatory response was maintained and may have been carried by DAergic fibers. Thus, these studies were instrumental in suggesting an excitatory role for DA neurons.

Recent studies have sought to elucidate the mechanisms that mediate these fast excitatory responses using in vivo recordings. Lavin et al. (2005) found that when the VTA was stimulated pharmacologically or electrically, an excitatory event was recorded using both field potential recordings and intracellular recordings in PFC. These responses were blocked by a glutamate antagonists, but not by DA antagonists. However, when the VTA was unilaterally lesioned with 6-hydroxydopamine, the fast-response evoked by the VTA stimulation was abolished in the hemisphere ipsilateral to the lesion, while excitatory responses in the contralateral hemisphere remained intact, collectively suggesting that it was mediated by release of glutamate from DA neurons and not antidromic activation of descending PFC-VTA fibers or fibers passing by the VTA. However, a surprising result from our characterization of the fast EPSP evoked by VTA stimulation was that the onset latency of the response seemed to be faster than what is commonly reported for DA axons (Lavin et al. 2005). DA axons in the rat are unmyelinated; thus, implying that propagation of action potentials through the axon will be rather slow compared to a myelinated axon (Siggins 1978; Chang et al. 1981). Based on antidromic activation, the conduction velocity reported for VTA-cortical fibers ranges between 0.55 and 11.5 m/s (Deniau et al. 1980; Thierry et al. 1980). The fast conduction (11.5 m/s) fibers are unaffected by 6OHDA lesions and are likely

myelinated non-DA fibers (Glowinski et al. 1984; Thierry et al. 1980). The lower conduction value of 0.55 m/s for unmyelinated mesolimbic DA fibers is similar to the 0.58 m/s reported for nigrostriatal DA fibers (Guyenet and Aghajanian 1978). The predicted onset latency for a pathway of this length from the VTA to PFC (not accounting for synaptic delays) is expected to be between 9.5 and 18 ms. However, VTA stimulation often evoked a field or intracellular EPSP with onset latencies faster than these values (Lavin et al. 2005; Fig. 1). Therefore, such fast conduction velocities continue to represent a potential problem for the idea that the EPSP is generated by DA neurons.

Because conduction velocities are usually calculated based on antidromic activation, EPSP latency estimates are only correct if one assumes that conduction velocities are equivalent in both the ortho- and antidromic direction. DA neurons have atypical morphological features that may influence their assumed conduction velocities (Gauthier et al. 1999; Hausser et al. 1995; Prensa and Parent 2001; Preston et al. 1981; Tepper et al. 1987). One feature of the DA neuron is that often the axon of the DA neuron originates from the apical dendrite (Prensa and Parent 2001; Tepper et al. 1987). The somata of DA neurons are typically 20–30 μm in diameter with three to six primary dendrites emanating from it. The primary dendrites extend for about 20–40 μm before bifurcating into secondary dendrites (Prensa and Parent 2001). Often, the axon branches from a primary dendrite within 40 μm of the soma (Gauthier et al. 1999; Prensa and Parent 2001; Tepper et al. 1987). However, it has been observed that the axon can be as far as 250 μm from the soma (Hausser et al. 1995; Fig. 2). Furthermore, in DA neurons there seems to be heterogeneity within the make-up of the axon itself, with at least two different types of axons being evident in singleneuron tracings (Prensa and Parent 2001). These two types of DA axons project to different postsynaptic targets and they are characterized by different apparent diameters and properties, and presumably different conduction velocities (Prensa and Parent 2001).

In DA neurons, where the axon arises from the dendrite, it could be that action potentials are initiated first in the dendrites (or axon initial segment located on the dendrite) from where they pass directly into the small diameter, low capacitance, high input resistance axon, bypassing the soma. It has been shown in motorneurons that axons can be fired independently of the soma or initial segment (Gogan et al. 1983), and in pyramidal cells spike initiation most often occurs in the axon initial segment (Colbert and Johnston 1996). However, with antidromic spike initiation, the spikes would have to propagate from low (axon) to high (dendritic stem, soma) capacitance/low input resistance regions, resulting in a higher likelihood of failures and potential delays. Hence, the dynamic of the action potential propagation may differ for antidromic and orthodromic propagation, thus leading to different transmission delays for the two directions. Indirect support for this hypothesis was found in an elegant study performed by Hausser et al. (1995) that suggests that the flow of current to initiate an action potential in DA neurons may go from the dendrites to the axon and then to the soma, rather than from the dendrites to the soma, and then finally the axon. Given that the site of action potential initiation is in the axon just beyond the initial segment (Colbert and Johnston 1996), a dendrite that gives rise to an axon may be in a position to bring the axon to threshold and circumvent the soma altogether, a possibility that Hausser and coworkers termed “the privileged dendrite” (Hausser et al. 1995). In the case of a DA neuron, antidromic activation would involve the soma because this is the site sampled in

extracellular single unit recordings. In contrast, a stimulating electrode need not activate the soma orthodromically. Therefore, conduction velocity asymmetries may be pronounced in the case of DA neurons, making it difficult to compare conduction velocities using different techniques. A resolution of this issue awaits future investigations.

Assuming that it is actually DA neurons that are responsible for the fast EPSPs then it supports the idea of glutamate corelease by DA neurons (Sulzer et al. 1998). DA neurons in culture are capable of making excitatory synapses utilizing glutamate as a cotransmitter (Dal Bo et al. 2004; Sulzer et al. 1998). Because neurons grown in culture often lack their usual postsynaptic targets, they frequently form synaptic connections with themselves, at a rate much higher than what occurs in the intact brain (Bekkers 1998). These autapses allow for the study of pre- and postsynaptic mechanisms that govern neurotransmitter release in the same cell. In this preparation, it was found that DA neurons form excitatory autapses that release glutamate (Sulzer et al. 1998). Furthermore, it was shown that DA neurons in culture and in vivo also contain vesicular glutamate transporter 2 (VGluT 2), a protein that is responsible for packaging glutamate into vesicles (Dal Bo et al. 2004). A possible confound of these studies are dedifferentiation processes known to occur in culture that potentially could lead to an aberrant release phenotype, which may not truly represent a process found in vivo. However, evidence for VGluT2 expression has also been found in acute midbrain preparations as well (Hur and Zaborszky 2005).

In a quantitative analysis of VGluT2 expression in VTA (A10), Kawano et al. (2006) reported that 19% of the total TH-labeled neurons also expressed mRNA for VGLUT2, yet, remarkably, such signal was largely absent in A8 and A9. The percentage was as high as 52.7% in the rostral linear nucleus (RLi) of the VTA which is a rostral midline nuclei projecting preferentially to PFC and limbic regions (Swanson 1982). Accordingly, VTA neurons expressing VGluT2 mRNA were retrogradely labeled from PFC (Hur & Zaborszky 2005). However, almost half of the neurons in VGluT2-rich areas of VTA expressed mRNA for VGluT2 but were TH-. It was suggested that these glutamatergic non-DA VTA neurons may be the myelinated high conduction velocity fibers originally described by Thierry et al. (1980) (Kawano et al. 2006). Therefore, this represents another possible explanation for the observed fast onset latencies we observed (Lavin et al. 2005). These fast EPSPs may then merge with slower onset EPSPs arising from corelease of glutamate from nonmyelinated DA neurons. It is likely that both DA and non-DA subtypes of VTA neurons were recorded in behavioral physiology experiments because they cannot be dissociated electrophysiologically (Margolis et al. 2006).

Using a unique brain slice preparation that left the VTA-NAcc projection intact, Chuhma et al. (2004) found that electrical or pharmacological stimulation of the VTA could evoke a fast glutamate-mediated response in the NAcc. Furthermore, this study showed that the fast response after VTA activation was modulated by the D2 agonist quinpirole. This indicates that D2 receptors, which are located presynaptic in the SN/VTA, are able to modulate the release of glutamate from DA neurons (Meador-Woodruff et al. 1989; Sesack et al. 1994). Taken together, these data support the notion that DA neurons can provide a fast excitatory signal via corelease of glutamate, and that DA itself is acting as a neuromodulatory influence.

However, several issues with this interpretation remain. One of them, discussed above, relates to the fast onset latencies of EPSPs from putatively unmyelinated DA axons. Furthermore, several studies found evidence for a third population of neurons in the VTA, which are not considered to be GABA or DA cells, and that in theory could mediate these excitatory events (Margolis et al. 2006; Ungless et al. 2004). Another issue is the fact that only a small portion of DA positive fibers to the PFC makes asymmetric synapses indicative of glutamate (see above). However, because in the EM studies discussed above DA immunoreactivity was used to detect DA axons, these data may underestimate the number of asymmetric synapses, if some axon terminals from DA neurons contain glutamate, while others only contain DA (Sulzer et al. 1998). A much high proportion of VGLUT2/TH+ terminals exhibit synaptic specializations than for singly labeled TH+ terminals (Berube-Carriere et al. 2006). Furthermore, asymmetrical synapse profiles may not always reflect an accurate assessment of glutamatergic release sites (Kaneko and Fujiyama 2002) as suggested by recent findings based on the location of VGluTs (Fremeau et al. 2002, 2004; Gras et al. 2002; Schafer et al. 2002). Surprisingly, several studies have shown that synapses that express VGluT3 often have symmetric profiles (Fremeau et al. 2002; Gras et al. 2002; Herzog et al. 2004). Furthermore, VGluT3 has been isolated in neurons that also expressed other neurotransmitters traditionally not thought to participate in excitatory neurotransmission, such as serotonin, GABA, and acetylcholine (Hioki et al. 2004; Schafer et al. 2002). Yet, data that supports the expression of VGluT3 in DA neurons is tenuous, with studies finding that VGluT3 and Tyrosine Hydroxylase (TH) do not show clear colocalization (Fremeau et al. 2002; Gras et al. 2002). However, there have been reports of colocalization of VGluT3 and the vesicular monoamine transporter-2 (VMAT2). Furthermore, it appears that the VGluT3 protein is expressed in the VTA; however, reports are still conflicting concerning the expression of VGluT3 mRNA in the VTA (Fremeau et al. 2002; Herzog et al. 2004). Thus, although the fine details of VGluT3 expression are pending, these data indicate that we must reevaluate what we consider a unique marker of glutamatergic synapses. Therefore, while certain issues related to DA/glutamate corelease persist, it remains a viable option for fast neurotransmission in the mesocortical system.

Functional signaling in the mesocortical pathway

Midbrain dopaminergic neurons exhibit a phasic burst of action potentials immediately after *unexpected* salient events, which include sudden novel stimuli (Ljungberg et al. 1992; Schultz and Romo 1990), and primary rewards (Ljungberg et al. 1992; Schultz et al. 1993a,b; Ungless et al. 2004). During the learning phase of a classical conditioning task, reward-related activation of DA neurons first occurs in response to the (unexpected) primary reward (the unconditioned stimulus, US). If the US is paired with a conditioned stimulus (CS), activation of DA neurons “shifts” to the occurrence of the CS (Ljungberg et al. 1992; Schultz et al. 1993a,b; Schultz 1998a,b). Both phasic responses to the CS and US undergo task-dependent modulation in firing rate (Tobler et al. 2005; Schultz 1998a,b). The initial response to the CS is graded reflecting the probability and salience associated with the cue. The more rewarding and the more probable the delivery of the reward becomes, the more DA neurons will respond to the CS (Fiorillo et al. 2003; Tobler et al. 2005). In contrast, the later US-associated response appears to exhibit phasic activation only for rewards that are

not predicted with high certainty, and the magnitude of the phasic response increases as the predictability decreases (Fiorillo et al. 2003). Furthermore, if the value of the US turns out to be less than expected or aversive, a phasic cessation of tonic firing is observed (Ljungberg et al. 1992; Schultz et al. 1993a,b; Schultz 1998b, 2002 for review; Ungless et al. 2004). This phasic suppression may also scale with the reward predictability, such that when the reward did not occur on trials with high predictability, a greater suppression can be seen (Fiorillo et al. 2003). Thus, the CS-associated phasic activation is directly related to reward predictability, while the US-associated phasic activation is inversely related. This suggests that through phasic modulations in firing rate, DA neurons initially encode an expectancy of forthcoming rewards based on how accurate a CS proved to be in predicting the US. The subsequent phasic US-associated response then encodes how much better or worse the US turned out to be, relative to what was expected based on preceding stimuli, i.e., it encodes a prediction error. Although it is unclear whether DA neurons themselves compute explicit reward expectancies, DA neurons do appear to provide feedback about such expectations.

The phasic activation of DA neurons could serve as a teaching signal, instructing target areas to modify their synaptic connections such that predictive links between CS and US accurately reflect reward value, magnitude, and likelihood (Dayan et al. 2000; Fiorillo et al. 2003; Schultz 2002). Thus, the underlying idea is that surprise (prediction mismatch) drives the associative learning process, and if a stimulus is no longer surprising (i.e., it is accurately predicted by a preceding stimulus) then DA is not released because synaptic connections do not need to be modulated. Indeed DA neurons fit predictions of formal learning models as they exhibit the nontrivial blocking phenomenon, in that they do not show phasic activation in response to a second CS when it is paired with an established CS that by itself accurately predicts reward (Waelti et al. 2001). Thus, in summary, although the DA system may subserve different functions on different time scales (Schultz 2002), the prediction error theory posits that a critical function of the phasic DA signal is to create or modify associations of stimuli according to violations of expectations.

A minority of DA neurons also exhibit sustained activations in the interval between the CS and the US during trials in which the reward predictability is low. Fiorillo et al. (2003) have suggested that this sustained firing pattern codes reward uncertainty because the sustained response was largest for (1) stimuli that predicted reward 50% of the time, or (2) for stimuli that predicted two rewards, which were most different from each other in valence (i.e., small to large). Therefore, if a CS tells the animal to expect an event with an uncertain outcome, sustained DA neuron activity intervenes between the CS and the outcome. In this way, DA neurons may provide a sustained attentional signal to target areas in situations with uncertain outcomes. These authors suggest that this type of uncertainty is rewarding in itself and leads to the learning about stimuli or actions that are good predictors of reward. In a similar vein, Redgrave et al. (1999) proposed that DA release is responsible for reallocating attentional and behavioral resources, alerting the organism that a new or salient stimulus is present. Again, both groups (Fiorillo et al. 2003; Schultz 2002; Redgrave et al. 1999) have highlighted that even in the context of DA-associated attentional processes the ultimate function of the DA signal is still linked to the formation of associations. As the consistent interpretation of these data is that the activity of dopaminergic neurons provides an essential

signal for reinforcement learning (Schultz 1998a,b; c.f. also Montague et al. 1996), the question is then whether we really need DA to learn reward associations.

DA receptor antagonists have been shown to impair acquisition of conditioned place preference (Duarte et al. 2003; Spyraki et al. 1982) and Pavlovian approach behavior (Di Ciano et al. 2001). However, recent studies employing mice genetically engineered to lack DA have greatly refined the role of DA in reinforcement learning. DA-deficient mice do not perform a learned task and even stop eating in the absence of L-dopa or caffeine, highlighting the importance of DA in motivation. Yet, when temporarily taken off L-dopa, these mice nevertheless prefer a sucrose solution to water, suggesting that the circuitries, which mediate food preference, are intact in mice unable to make DA (Cannon and Palmiter 2003). Similarly, DA-deficient mice are able to learn reward associations in an appetitive T-maze task (Robinson et al. 2005) and conditioned place preference (Cannon and Patel 2006). DA-deficient mice also exhibit conditioned place preference to morphine, suggesting that DA is not required for making predictions or associations with cues previously paired with reward (Hnasko et al. 2005). Conversely, mice with chronically elevated extracellular levels of DA produced by knockdown of the DA transporter show no effects in Pavlovian and operant learning for reward, even though this manipulation significantly enhances the tendency to work for a food reward (Cagniard et al. 2006). These studies suggest that DA per se is not required for associative learning about reward or the accurate processing of reward itself. Rather, they are more consistent with the idea that DA is instrumental in pursuing and focusing the behavior on current goals and shielding them from distraction (Durstewitz et al. 1999, 2000a; Salamone et al. 2005; Cannon and Palmiter 2003; Denenberg et al. 2004; Heusner et al. 2003; Hnasko et al. 2005; Sotak et al. 2005).

It should be noted that DA-deficient mice or DA transporter knockdown mice may express compensatory mechanisms to counteract potential effects on associative learning, which could make it difficult to reconcile these data with earlier studies that showed a role of DA in associative learning related to reward. Yet, there are additional issues related to the physiological properties of the mesocorticolimbic DA system that place constraints on what the system is capable of in terms of modulating precise associations. If DA signals are to enable correct predictive links between a CS and the US, then they must be tightly associated with the occurrence of the stimuli, so that stimuli that follow the US in time get not mislabeled as predictors. Similarly, the synaptic changes supposed to encode the predictive link need to be specific for this CS–US combination and should not represent an indiscernible temporal integral across many different subsequent US with differing reward values, magnitudes, and likelihoods.

Again, the firing properties of DA neurons seem to fit the prediction error scheme perfectly, yet temporally constrained messages are not effectively transmitted by DA. DA release is often slow and prolonged, and DA effects on target neurons in PFC usually develop over a protracted timecourse, lasting for tens of minutes. Simply put, the postsynaptic effects of DA in PFC neurons lack temporal precision in their onset and in their offset. Microdialysis studies show that behaviorally relevant events, whether they be appetitive or aversive, increase PFC DA levels slowly and for prolonged periods (Phillips et al. 2004; Feenstra and Botterblom 1996; Di Chiara et al. 1999). Similarly, the presentation of a CS associated with

cocaine elevates levels of DA in the striatum for ~5 s as assessed using fast-scan cyclic voltammetry (Phillips et al. 2003). In the PFC, we observed that the response to a similar brief ~4 s release of DA exerts extremely protracted postsynaptic effects. Stimulation of the VTA at 20 Hz/2 s evoked a ~4 s rise in DA in PFC measured using fast-scan cyclic voltammetry, but this phasic rise in DA produced a change in the evoked excitability of PFC neurons that developed over a 10-to 15-min period and often lasted over an hour in vivo (Lavin et al. 2005). In the same cells, spontaneous firing was decreased for many minutes, similar to what has been reported using extracellular single unit recordings (Au-Young et al. 1999). This phenomenon of slowly developing and protracted effects is mimicked by application of DA or its selective receptor agonists in vitro on a variety of ionic currents in PFC neurons and in a variety of preparations (Yang 2000; Umemiya and Raymond 1997; Cameron and Williams 1993; Huang and Kandel 1995; Gribkoff and Ashe 1984; Seamans et al. 2001a,b; Trantham-Davidson et al. 2004; Seamans and Yang 2004; Gorelova et al. 2002; Gorelova and Yang 2000; Chen and Yang 2002; Urban et al. 2002; Gonzalez-Burgos et al. 2005; Henze et al. 2000; Kroener et al. 2006; Gorelova et al. 2002; Gulledge and Jaffe 2001; Wang and O'Donnell 2001; Fitch et al. 2006; Matsuda et al. 2006; Yang and Chen 2005; Young and Yang 2005; Yang and Seamans 1996; Floresco et al. 2001a,b; Cheer et al. 2005). Although the mechanisms that underlie this slow modulation are not entirely clear and it remains possible that eventually a fast acting DA effect will be discovered, given the current state of knowledge, the sluggish and protracted effects of DA appear to represent the predominate mode of action of DA on target neurons in the PFC.

How could DA provide sufficiently specific information to the PFC about the predictive link between a CS and a reward, if its effects are so slow to develop and lingering and the effects of even a phasic release of DA may last tens of minutes? A prediction error signal must have two essential properties: (1) It should be retrospective in the sense that only stimulus associations preceding the to-be-predicted event in time are influenced by the prediction error signal because by definition, only these can be temporal predictors of the subsequent reward. Hence, this hypothesis requires that *both* the onset and the offset of the prediction error signal are sufficiently fast such that stimuli occurring later, *after* the actual rewarding event, are not mislabeled as potential predictors of the event. (2) There must be some mechanism that ensures that different prediction error signals are not integrated over extended periods of time in such a manner that they, for instance, simply cancel each other out. For instance, a rewarding plus a subsequent punishing event may not simply sum up to make a neutral event—the animal may still want to seek out the former while avoiding the latter. Moreover, it may be important that neutral stimuli following the specific US do not get mislabeled as to-be-predicted rewards, simply because the prediction error signal is active for too long. Hence, for this condition to be fulfilled, once again either the initial physical carrier of the prediction error signal (DA) must have a sufficiently quick offset, or the molecular and physiological processes initiated by DA must be terminated or desensitize sufficiently rapid. Thus, this requirement would imply that the cellular processes that translate the prediction error signal into synaptic changes are effectively sensitive only to changes in DA concentration, not DA concentration itself.

From the previous discussion, we review a wealth of evidence suggesting that DA has a very slow decaying time course, much too slow to provide a sufficiently rapid termination of the

prediction error signal. This necessitates that the postsynaptic cell must somehow be able to terminate DA effects shortly after the release event occurs. However, a mechanism that is calibrated to detect only changes in DA concentration, besides the fact that evidence for it is currently lacking, will only have a limited operational range. Hence, the fact that DA itself lingers around for so long and decays only very slowly especially in PFC, is certainly not helpful for such a mechanism either, as it bears the risk that the operational range is quickly exceeded by piling up reward signals. Furthermore, many if not all of the DA-induced cellular processes have a very slow offset time themselves, independent of the presence of DA. For instance, D1-induced changes in $GABA_A$ currents could persist for tens of minutes after washout of the agonist (Seamans et al. 2001a,b). Putting this together, it seems unlikely that the DA-induced cascade has sufficiently rapid offset times or desensitization properties that would prevent prolonged temporal integration of prediction error signals.

As reviewed here, the buildup of DA in extracellular space is itself not very rapid. Furthermore, DA exerts all of its postsynaptic effects through metabotropic, G-protein-coupled receptors in PFC, with many of the subsequent molecular processes having time constants in the range of seconds to minutes (Bhalla and Iyengar 1999; Greengard 2001; Nishi et al. 2002, 2005). In fact, it takes many seconds to minutes for the expression of DA-induced changes in the properties of voltage-gated or synaptic channels.

To summarize, both the onset and offset times of the processes associated with DA release seem too slow to support the signaling properties required for an effective prediction error signal. Because the onset of the signal is at least seconds too slow, stimuli subsequent to the to-be-predicted event could be falsely labeled as predictors, if DA carries this signaling burden. Moreover, because DA offset is too slow, prediction error signals could be integrated across time such that different events with different reward signs and magnitudes would be confounded, and no clear predictive links could be efficiently formed. Because DA release is spatially diffuse and receptors are extrasynaptic it furthermore implies that many if not most synapses are affected by a DA release event. This may pose no problem for a reinforcement theory as long as DA onset and offset signals were sufficiently fast. However, because this is not the case, the anatomy and kinetics of the PFC DA system probably rule out any potential solution based on tight spatial specificity.

As we have argued here and previously, corelease of glutamate from DA neurons could be one mechanism that provides an alternative solution to this dilemma (Lavin et al. 2005; Seamans and Yang 2004). It is tempting to speculate that glutamate is able to carry the burden of fast reward processing. This may occur through the convergence of glutamate released by DA and non-DA VTA neurons with other excitatory inputs in the cortex and basal ganglia to trigger the formation of specific predictive links to reward related stimuli. However, DA may help to maintain the representation of the initial predicting stimulus (Durstewitz et al. 2000a,b), even in the face of distraction, such that the associative link across time can be formed. It follows that mice that are DA deficient are still able to make reward related associations, but they may not be as effective at processing reward-related information as their wild type counterparts.

Putative roles for the three modes of the mesocortical dopamine system

If corelease occurs, it would be perfectly suited to transmit the temporally precise information encoded by bursting activity of DA neurons. Glutamate release onto pyramidal neurons and interneurons is extremely efficient at activating or inactivating neurons on precise millisecond timescales. In contrast, as argued above, DA is not well suited for this task. Therefore, we argue that the fastest processing timescale of the DA system is on the order of milliseconds and is subserved by release of glutamate (Fig. 1a). We propose that glutamate may carry the temporally precise signal encoded by DA neuron firing that is critical for a prediction error signal (Schultz 2002).

Upon activating D1 receptors on fast spiking interneurons, a variety of ionic currents are modulated in a protracted manner (Gorelova et al. 2002; Seamans and Yang 2004); however, the modulation of currents that produce membrane depolarizations occur on the order of seconds (Fig. 1). Gorelova et al. (2002) showed that the DA-mediated depolarization of fast spiking interneurons occurred through modulation of a leak current, while the increase in excitability to depolarizing current pulses occurred via modulation of inwardly rectifying and slowing inactivating K^+ currents. Although all three currents are targeted by DA D1 receptors, it is only this fast depolarization via modulation of a leak current that is capable of activating fast-spiking interneurons directly because DA modulation of the other currents only serves to increase the excitability to subsequent inputs.

Fast-spiking interneurons are capable of precisely timing the firing of pyramidal neurons as spikes reliably occur at the offset of IPSPs (Cobb et al. 1995; Tamas et al. 2000; Fricker and Miles 2001). Because spike-timing dependent plasticity strongly relies on precise timing of action potentials (Bi and Poo 1998), DA-mediated depolarization of interneurons may augment this process. While speculative, the phasic activation of interneurons could increase the temporal precision of spiking in pyramidal neurons and thus ensure that pre and postsynaptic spikes fall in the ~10 ms window necessary for synaptic strengthening or depression (Bi and Poo 1998). This modulation of interneurons could facilitate a putative role for DA in regulating associative strength between synapses as discussed above. Its role would not be to strengthen synapses directly or to provide specific reward-related information. Rather, by briefly activating fast-spiking interneurons temporal precision in neural firing of target neurons would be amplified for a brief interval surrounding a phasic DA release event. However, the reverse is also possible as DA-mediated activation of fast spiking interneurons could shut down activity in PFC briefly and thereby hinder the formation of synaptic associations. Indeed, most evidence supports this latter view because the oft reported brief inhibition in firing of PFC neurons recorded extracellularly by VTA stimulation or DA iontophoresis is blocked by a GABAergic antagonist (Pirot et al. 1992). Moreover, the spatial tuning of working memory fields in behaving primates is abolished by a GABAergic antagonist and enhanced by low doses of a D1 receptor antagonist presumably by removing the D1-mediated modulation of interneuron activity (Williams and Goldman-Rakic 1995; Goldman-Rakic et al. 2000).

This relatively fast modulation of FS interneurons, together with the feedforward inhibition of prefrontal cells through the EPSP–IPSP may serve as a stop signal that could help to shut

off further input to the PFC from other brain regions in situations where a biologically significant event just occurred, and the stimuli preceding it have to be maintained and shielded from distraction to allow for the predictive links to be formed.

Finally, the slowest and most commonly observed mode of DA modulation in PFC occurs on the order of minutes to hours (Fig. 1c). This type of long-lasting modulation has been observed for a variety of currents via both D1 and D2 receptors (Dong et al. 2004; Gao et al. 2001; Gao and Goldman-Rakic 2003; Gorelova et al. 2002; Gorelova and Yang 2000; Gulledge and Jaffe 2001; Henze et al. 2000; Seamans and Yang 2004; Seamans et al. 2001a,b; Trantham-Davidson et al. 2004; Yang and Seamans 1996). Many of these currents, including NMDA and K^+ currents, are critical to associational models of synaptic memory. Although seemingly diverse, computational models of the D1-mediated modulations suggest that they converge on a single function, which is to make networks of PFC neurons more robust to distraction and noise (Compte et al. 2000; Durstewitz et al. 2000a,b; Durstewitz and Seamans 2002). Simulated D1-mediated modulation leads to a deepening and widening of the basins of attraction of working memory states of the network, while simultaneously decreasing background activity. This phenomenon has been described as an increase in signal to noise or an increase in cortical efficiency (Winterer and Weinberger 2004). It is advantageous when a single goal state must be maintained in the face of distractors.

In contrast, D2 receptor activation often has opposing effects on ionic currents to D1 receptor activation (Seamans et al. 2001b; Trantham-Davidson et al. 2004; Zheng et al. 1999) and as a result has an opposing effect on PFC networks, making them less robust to distraction and noise. The upside of this type of modulation is that the networks are much more flexible in incorporating new inputs and in dealing with more items nearly simultaneously (Durstewitz et al. 2000a,b). As a result, D2 receptor activation may provide a resetting mechanism allowing working memory buffers to incorporate new information. Moreover, D2-mediated effects on a given postsynaptic current tend to be somewhat briefer than D1-mediated effects (Seamans et al. 2001b).

It must be emphasized, that although these effects last “minutes to hours” (Fig. 1c) this is only true when the system is left unperturbed, as is the case in both the acute brain slice preparation and the in vivo anesthetized preparation. It is possible that no single effect is so protracted in an intact awake brain. Preferential D1 vs D2 modulation in PFC occurs at different DA concentrations (Trantham-Davidson et al. 2004) and as a result they may have truncating influences on each other when activated by natural variations in DA levels. Even the peak D1 mediated effect can be reversed by application of a D2 agonist and vice versa (Seamans et al. 2001b). This indicates that DA mediated effects need not be locked in for minutes to hours, but can be reversed under the appropriate conditions, although even these reversing effects take seconds to minutes to set in and are too slow to address the issues raised above. Thus, in vivo, as the animal is exploring its environment, VTA cell activity may exhibit stimulus-dependent variations that result in variations in PFC DA levels. Although the variations may not be highly temporally precise or spatially localized due to the properties of the PFC DA system, the variations may continually cross the threshold for preferential D1 vs D2 receptor activation. As a result, PFC networks will dynamically switch between the two theorized states, constantly incorporating new information (D2) and then

locking it in robustly (D1). Likewise, other neuromodulatory systems could also potentially reverse the effects of DA on a given current. Hence, most of the DA modulation of PFC neurons may in fact only be long-lasting *if* nothing happens to reverse or counteract their effects. Potentially, in different situations, each current could be in a different state of modulation depending on the relative D1 vs D2 receptor activation. In this way, the state of the PFC may be in flux at any given moment. In the context of Fig. 1c, if any combination of red and green arrows could be present at any given time, the staggering richness and complexity of DA signaling becomes apparent. This richness of neuromodulation may be a key component that underlies complex cognitive processes mediated by the PFC.

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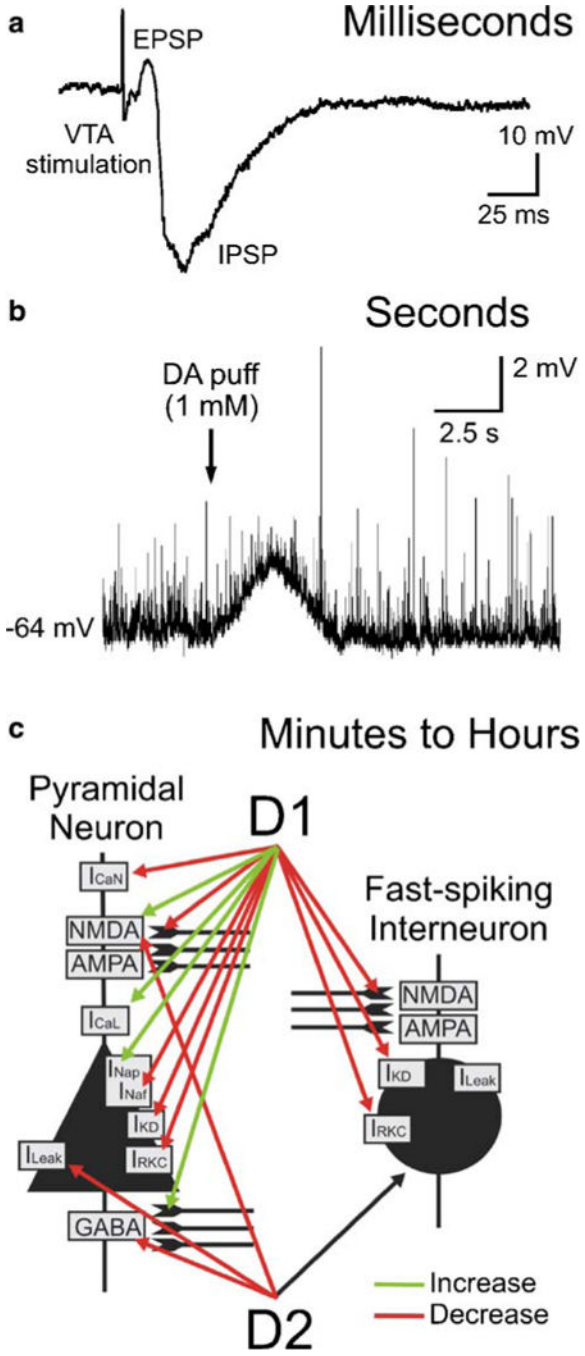

Fig. 1.

Orders of magnitude in the observed time course following dopamine (DA) application or VTA stimulation. **a** A very fast EPSP–IPSP sequence can be recorded in prefrontal cortical cells after stimulation of the VTA in-vivo. The EPSP is evoked with a latency on the order of milliseconds and is thought to be the result of corelease of glutamate from dopamine cells in the VTA. **b** Depolarization of a fast-spiking interneuron by DA in the prefrontal cortex in vitro. Local pressure application of DA leads to depolarization and repolarization of the membrane potential that seems to follow the diffusion of the drug in the slice on the

timescale of seconds (Kroener and Seamans, unpublished observations). **c** Modulation of a variety of intrinsic and synaptic currents by DA has been shown to occur over minutes and hours both in vivo and in vitro. Activation of D1- and D2-type receptors occurs in both pyramidal cells and interneurons, adding to DA's ability to modulate network behavior. The time course and direction of some of the effects indicated in the diagram have been shown to be concentration- and receptor-specific. It is assumed that in vivo the very long lasting effects that have been reported in experimental settings can be curtailed by fluctuating levels of extracellular DA and opposing effects at the different DA receptors that result from it. See text for details

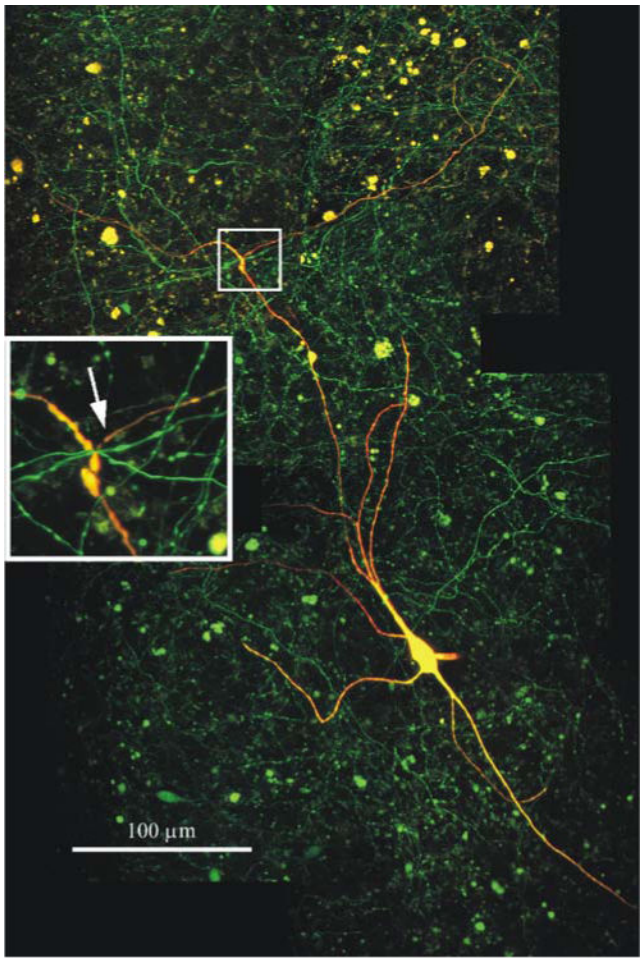

Fig. 2.

Anatomy of a dopaminergic VTA neuron, illustrating the distal dendritic location from which the axon can originate. Composite confocal images of a VTA neuron recorded in a coronal brain slice of a transgenic mouse expressing green fluorescent protein under the control of the TH gene promoter (TH-GFP+). The green cell was filled with a red dye (Alexa 594) during the recording, resulting in a yellow signal in the merged image. The *insert* represents a magnified view of the white square in the main picture. The *arrow* points where the axon (on the *right*) branches off the dendrite