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An integrative theory of the phasic and tonic modes of dopamine modulation in the prefrontal cortex

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Abstract

This paper presents a model of both tonic and phasic dopamine (DA) effects on maintenance of working memory representations in the prefrontal cortex (PFC). The central hypothesis is that DA modulates the efficacy of inputs to prefrontal pyramidal neurons to prevent interferences for active maintenance. Phasic DA release, due to DA neurons discharges, acts at a short time-scale (a few seconds), while the tonic mode of DA release, independent of DA neurons firing, acts at a long time-scale (a few minutes). The overall effect of DA modulation is modeled as a threshold restricting incoming inputs arriving on PFC neurons. Phasic DA release temporary increases this threshold while tonic DA release progressively increases the basal level of this threshold. Thus, unlike the previous gating theory of phasic DA release, proposing that it facilitates incoming inputs at the time of their arrival, the effect of phasic DA release is supposed to restrict incoming inputs during a period of time after DA neuron discharges. The model links the cellular and behavioral levels during performance of a working memory task. It allows us to understand why a critical range of DA D1 receptors stimulation is required for optimal working memory performance and how D1 receptor agonists (respectively antagonists) increase perseverations (respectively distractability). Finally, the model leads to several testable predictions, including that the PFC regulates DA neurons firing rate to adapt to the delay of the task and that increase in tonic DA release may either improve or decrease performance, depending on the level of DA receptors stimulation at the beginning of the task.

Keywords: Dopamine; Inverted U-curve; D1 receptors; Working memory; Prefrontal cortex

1. Introduction

1.1. General concepts on neuromodulation

Artificial neural network dynamics are often studied independently of the influence of neuromodulation. However, it is well known that the activity of real neural populations can be modified by a number of neuromodulators originating in the forebrain. Monoaminergic and cholinergic neurotransmitter systems (including dopamine (DA), noradrenaline, serotonin and acetylcholine) project diffusely to a large number of brain regions. Particular parameters of the equations describing artificial neural networks can be considered as 'neuromodulatory' factors when they affect a group of neurons (property of diffusion) and change more slowly than variables describing the dynamics of the network. Such neuromodulatory parameters may have a broad variety of effects. They may change intrinsic properties of the neurons (e.g. input–output function), their afferent properties (e.g. strengthening some neural inputs rather than others) and/or their efferent properties (e.g. presynaptic modulation of release; Fellous & Linster, 1998). Precise computational models of the effect of neuromodulators on local cortical network are needed to provide better understanding of their precise computational influences on network dynamics.

Specific functions have been proposed for distinct neuromodulators. A general theory integrating their diverse functions and interactions is beyond the scope of this paper. Here, we will only consider the role of DA, which is diffused at the cortical level and in different extra-pyramidal and limbic structures, and that modulates information processing within and between cerebral structures (e.g. prefrontal cortex-striatum). The behavioral effect of this modulation is a modification of numerous cognitive, motor, emotional and motivational processes. The importance of DA modulation is revealed by the dysfunction of DA regulation, which includes

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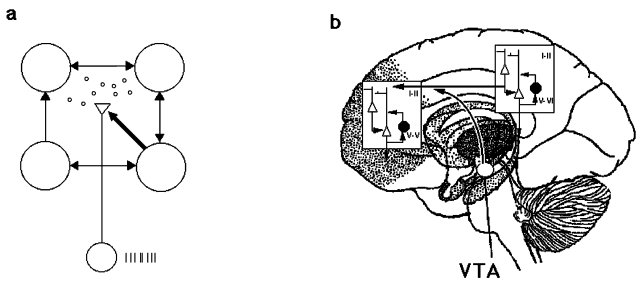

Fig. 1. (a) Intrinsic and extrinsic modes of neuromodulation on a neural network. Extrinsic mode: a neuron, external to the network, modulates the network properties by releasing a neuromodulator. Intrinsic mode: a neuron intrinsic to the network acts at the neuromodulatory neuron terminal (thick arrow), releasing the neuromodulator. (b) Schematic diagram showing that pyramidal neurons from the PFC receive dopaminergic projections from the VTA (extrinsic mode of modulation). These pyramidal neurons release glutamate that itself triggers release of DA from VTA neuron terminals (intrinsic mode of modulation, see Fig. 4). PFC pyramidal neurons receive inputs from long-range cortical areas and recurrent excitatory inputs from neighboring cortical columns.

drug seeking behavior and several dramatic diseases as schizophrenia and Parkinson's disease. At the cellular level, DA modifies the ionic properties and the metabolism of post-synaptic neurons. This modulation of neuronal ionic properties concerns changes of the size and shapes of action potential, of the firing rate and/or of the response to synaptic inputs. Dopaminergic neurons are often characterized in terms of a teaching signal for reinforcement learning (Contreras-Vidal & Schultz, 1999; Friston, Tononi, Reeke, Sporns, & Edelman, 1994; Montague, Dayan, & Sejnowski, 1996; Suri & Schultz, 2001). DA neurons responses transfer during learning from primary rewards to reward-predicting stimuli, thereby furnishing a reward prediction signal (see other articles in this issue about the role of DA in reinforcement learning).

An important factor in determining the post-synaptic effect of neuromodulators is their duration in the extra-synaptic space. Neuromodulators may either behave as hormones, being spatially widespread and possessing slow rates of recapture or they may be released locally and rapidly recaptured. Here, we propose that these two effects are simultaneously present for DA release in the prefrontal cortex (PFC), and are based on two distinct modes of release (phasic/tonic), influencing networks properties at different time-scales. The dichotomy between the phasic and the tonic modes of DA release parallels a distinction made between an extrinsic and an intrinsic mode of modulation (Katz, 1998). In the PFC, the source of the extrinsic modulation comes from dopaminergic neurons located in the ventral tegmental area (VTA), that release DA in a phasic fashion at a specific time of behavior. In contrast, the intrinsic mode of modulation comes from DA release induced by glutamatergic influence at PFC dopaminergic terminals, independently of VTA neurons firing (see Sections 2.2 and 2.3, and Fig. 1).

1.2. Dopaminergic modulation of the PFC during working memory tasks

Most DA models proposed theories of DA neurons firing (Contreras-Vidal & Schultz, 1999; Friston et al., 1994; Montague et al., 1996; Suri & Schultz, 2001) but remain silent regarding the post-synaptic effect of DA in the PFC during a cognitive task but see (Cohen, Braver, & O'Reilly, 1996; Durstewitz, Seamans, & Sejnowski, 2000). However, it is well known that the dopaminergic projection to the PFC exerts a profound influence on the regulation of working memory, the ability for retaining and manipulating information temporarily. Converging evidence from single-cell recordings and lesion studies indicate that the PFC plays a pivotal role in mediating working memory in animals (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 2001; Goldman-Rakic, 1995). One of the most widely used task to test working memory in animals is the delayed alternation task, which consists of alternating two responses (right and left) separated by a delay. This task is frequently used as a sensitive indicator of PFC dysfunction because deficit of its performance is observed both in monkeys with PFC lesions (Fuster, 1995; Jacobsen, 1935) and in rats with medial PFC lesions (Brito & Brito, 1990; Delatour & Gisquet-Verrier, 1996; Wortwein, Mogensen, & Divac, 1994). During the delayed alternation task, some PFC neurons are activated during the delay period, others during the delay and movement execution and others during the movement only (Carlson, Rama, Tanila, Linnankoski, & Mansikka, 1997; Niki, 1974a,b). Of particular importance for retention of the previous response and preparation of the next response are the neurons exhibiting sustained activity during the delay (Alexander, 1982; Fuster, 1973; Miller, Erickson, & Desimone, 1996a,b). A majority of the neurons responding during the delay period of the delayed alternation task are spatially selective, i.e. their discharge frequency is different during the delay between right-sided and left-sided trials (Carlson et al., 1997; Niki, 1974a,b).

Deficits of the delayed alternation task have been observed after pharmacological lesion of VTA neurons or of DA terminals in the PFC of monkeys (Brozoski, Brown, Rosvold, & Goldman, 1979) and rats (Bubser & Schmidt, 1990; Simon, 1981). More recent studies have more specifically revealed the importance of DA D1 receptors to regulate working memory in both the human and non-human primate PFC (Muller, von Cramon, & Pollmann, 1998; Murphy, Arnsten, Goldman-Rakic, & Roth, 1996; Sawaguchi & Goldman-Rakic, 1991, 1994; Williams & Goldman-Rakic, 1995). Intra-PFC infusion of D1 receptors agonists (SKF 81297) or antagonists (SCH 23390) impairs performance of the delayed alternation task in rats and monkeys (Arnsten, 1997; Murphy et al., 1996; Zahrt, Taylor, Mathew, & Arnsten, 1997). These results suggest

that the level of performance follows an inverted U-shape curve according to the level of DA D1 receptors stimulation (Arnsten, 1997; Zahrt et al., 1997).

1.3. Revisiting functional hypotheses of dopamine modulation in the prefrontal cortex

The effect of DA modulation in the PFC is complex and not fully understood. Several authors have proposed different functional models of the DA PFC effect to interpret the complex experimental literature. However, as the following brief review will show, these functional hypotheses need to be revisited to integrate recent biological data with more accuracy. Using an abstract class of networks (Parallel Distributed Processing models), Cohen, Servan-Schreiber and colleagues (Cohen & Servan-Schreiber, 1992; Cohen et al., 1996; Servan-Schreiber, Printz, & Cohen, 1990) have first proposed to link DA function to the performance of different cognitive tasks. For these authors, DA increases signal-to-noise ratio (gain parameter) of the sigmoid function of formal neurons, which would facilitate both excitatory and inhibitory inputs. However, in light of recent electrophysiological studies, such facilitation is unlikely to occur. In fact, in vivo data suggest that DA has more a general inhibitory function on PFC neuronal activity, with one of its primary effect being the modulation of excitatory inputs arriving on pyramidal neurons (Jedema & Moghddam, 1996; Yang & Seamans, 1996; Cepeda, 1992; Gao, Krimer, & Goldman-Rakic, 2001; Goldman-Rakic, Muly, & Williams, 2000). VTA stimulation decreases PFC neuron firing (Ferron, Thierry, Le Douarin, & Glowinski, 1984; Jay, Glowinski, & Thierry, 1995; Lewis & O'Donnell, 2000). This action is likely to occur from indirect action on GABAergic neurons that project to pyramidal cells (Ferron et al., 1984; Godbout, Mantz, Pirot, Glowinski, & Thierry, 1991; Pirot et al., 1992). Recent simulations of DA influence on intrinsic ionic and synaptic currents of PFC neurons led to a similar inhibitory functional role of DA in the context of working memory tasks performance (Durstewitz, Kelc, & Gunturkun, 1999; Durstewitz et al., 2000). This model proposed that DA reduces the impact of intervening stimuli on network activity, thereby increasing the robustness of representations encoding goal-related information via DA D1 receptors modulation.

The two classes of DA PFC models mentioned above (Cohen et al., 1996; Durstewitz et al., 1999) have considered that the effect of DA is time-independent, which can no longer be supported in light of classical electrophysiological data showing that DA neurons fire at specific times of behavior (e.g. reward predicting stimuli; Schultz, 1997; Schultz & Dickinson, 2000). To account for these results, recent theories of PFC phasic DA modulation have introduced a gating mechanism reflecting facilitation of incoming inputs at the precise time of their presentation (Braver, Barch, & Cohen, 1999). However, this gating theory does not appear to be biologically plausible. First, as noted previously, DA is unlikely to facilitate incoming inputs. Second, when a behaviorally significant stimulus induce VTA neurons to discharge, the DA consequently released in the PFC acts at post-synaptic sites after the stimulus that induce this VTA neurons firing (Gonon, 1997; Lewis & O'Donnell, 2000). Thus, DA may not be able to facilitate PFC inputs at the precise time of their arrival because the time necessary for a stimulus to induce VTA discharge (100–150 ms; Ljungberg, Apicella, & Schultz, 1991), added to the latency necessary for DA to act at post-synaptic sites (200 ms from VTA to the striatum; Hille, 1992; Gonon, 1997) is longer than the time necessary for a stimulus to reach the PFC (around 100 ms; Thorpe, Fize, & Marlot, 1996). A number of other arguments also confirm no fast PFC D1 receptors activation because D1 stimulation produces delayed and prolonged post-synaptic effects in the PFC (Seamans, Gorelova, Durstewitz, & Yang, 2001). Furthermore, DA uptake sites are scarce in the PFC and not located in the synaptic cleft. D1 receptors are also primarily localized extrasynaptically, further supporting the notion that D1-mediated neurotransmission is governed by volume transmission and laws of diffusion (Garris, Ciolkowski, Pastore & Wightman, 1994) (Fig. 2).

These neurophysiological data led us to propose that the effect of phasic DA release is to restrict, for a few seconds, excitatory inputs arriving on superficial layers, **after** DA neurons firing. This threshold function protects deep layers PFC pyramidal neurons from incoming noise (Dreher, 1999; Dreher, Guigon, & Burnod, 2002) (Fig. 3). This assumption of the function of phasic DA in the PFC is in accordance with the fact that, in vitro, DA restricts inputs arriving on apical dendrites of PFC pyramidal neurons by increasing the electronic distance between the distal and the proximal dendritic regions (Gorelova & Yang, 1997; Yang & Seamans, 1996; Zahrt et al., 1997). However, our previous DA PFC model did not take into account the functional role of tonic DA PFC release. Here, we extend our previous model to include a functional role of the tonic mode of DA release (see Section 2.3). We propose that the overall effect of PFC DA may be considered as a threshold restricting the inputs arriving on PFC pyramidal neurons. This restriction of inputs occurs at two different time scales: phasic DA release restricts excitatory inputs arriving on PFC pyramidal neurons for a few seconds while tonic DA release acts at the level of a few minutes or hours.

2. Assumptions of the model

The model is based on four functional hypotheses that are summarized in Fig. 4: architecture of the PFC network, phasic and tonic modes of DA release and regulation of DA release by the PFC.

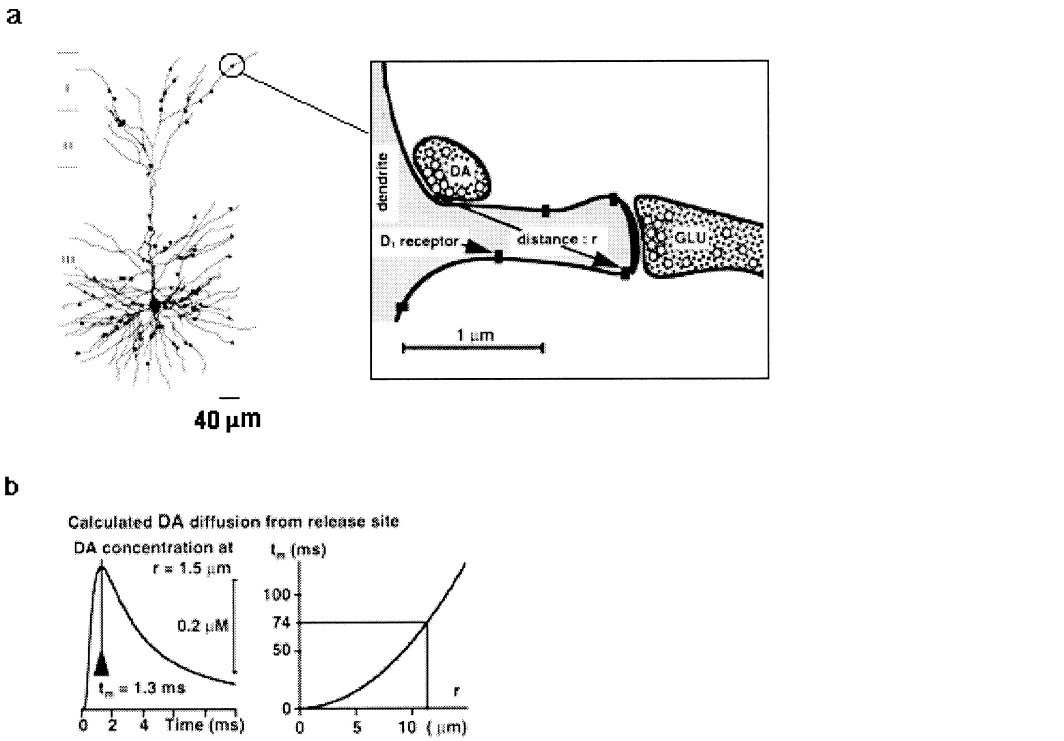

Fig. 2. (a) Left: a pyramidal neuron of PFC receives dopaminergic terminals on the dendritic tree, but not on the soma (adapted from Krimer et al. (1997)). Right: summary of morphological data concerning the localization of D1 dopaminergic receptors. Dendritic spine of a pyramidal neuron receiving a glutamatergic afferent and a dopaminergic terminal (adapted from Gonon (1997)). Synaptic clefts represent a fraction of the whole extracellular space that occupies 21% of the brain volume (Nicholson, 1985, 1995). (b) Left: DA concentration at a receptor site resulting from the exocytosis of only one DA vesicle in a release site located at a distance r (in the striatum). Right: the DA concentration reaches its maximum at a time t_m, which depends on the square of the distance (adapted from Gonon (1997)).

2.1. Architecture of the prefrontal cortex network

Deep layers PFC pyramidal cells are densely innervated by dopaminergic fibers (Berger, Gaspar, & Verney, 1991; Joyce, 1993). They are the major neuronal population expressing specific D1-receptor related protein (Smiley, Levey, Ciliax, & Goldman-Rakic, 1994). PFC connectivity on deep layers pyramidal neurons is organized in two principal information flows: (1) external inputs from long-distance areas arrive on superior layer (II–III) neurons and are integrated by the apical tree of these pyramidal neurons (Jones, 1984; Kuroda, Murakami, Kishi, & Price, 1995). Thus, the model will primarily consider DA influence at this site because synaptic integration of these inputs has a major role to induce pyramidal neurons firing; (2) inputs from neighboring cortical columns arrive on the deep layer and are integrated on basal dendrites and soma (Kritzer & Goldman-Rakic, 1995; Levitt, Lewis, Yoshioka, & Lund, 1993). In turn, deep-layers pyramidal neurons send glutamatergic efferents to the VTA (Taber, Das, & Fibiger, 1995).

The network architecture represents a local circuit of deep-layer PFC pyramidal cells connected in local excitatory recurrent networks via their basal dendrites, and receiving external inputs via their apical dendrites. DA also modulates GABAergic interneurons projecting to pyramidal cells (Penit-Soria, Audinat, & Crepel, 1987; Pirot et al., 1992). We will integrate indirectly this modulation in the model (see Section 3.1).

Hypothesis 1 (Architecture of PFC network). PFC connectivity on deep layers pyramidal neurons is organized in two principal information flows: external inputs from long-distance areas arrive on superior layer neurons while inputs from neighboring cortical columns arrive on the deep layer and are integrated on basal dendrites and soma.

2.2. Phasic mode of DA modulation

Hypothesis 2 (Function of phasic DA release during a cognitive task). The phasic function of DA PFC is to restrict inputs arriving to the PFC for a period of time **after** their presentation. We model this effect of phasic DA release as a threshold temporary restricting the external inputs arriving on apical dendrites of PFC pyramidal neurons. This is in sharp contrast with the classical gating theory that proposed that phasic DA release facilitates stimuli at their precise time of presentation (Braver et al., 1999).

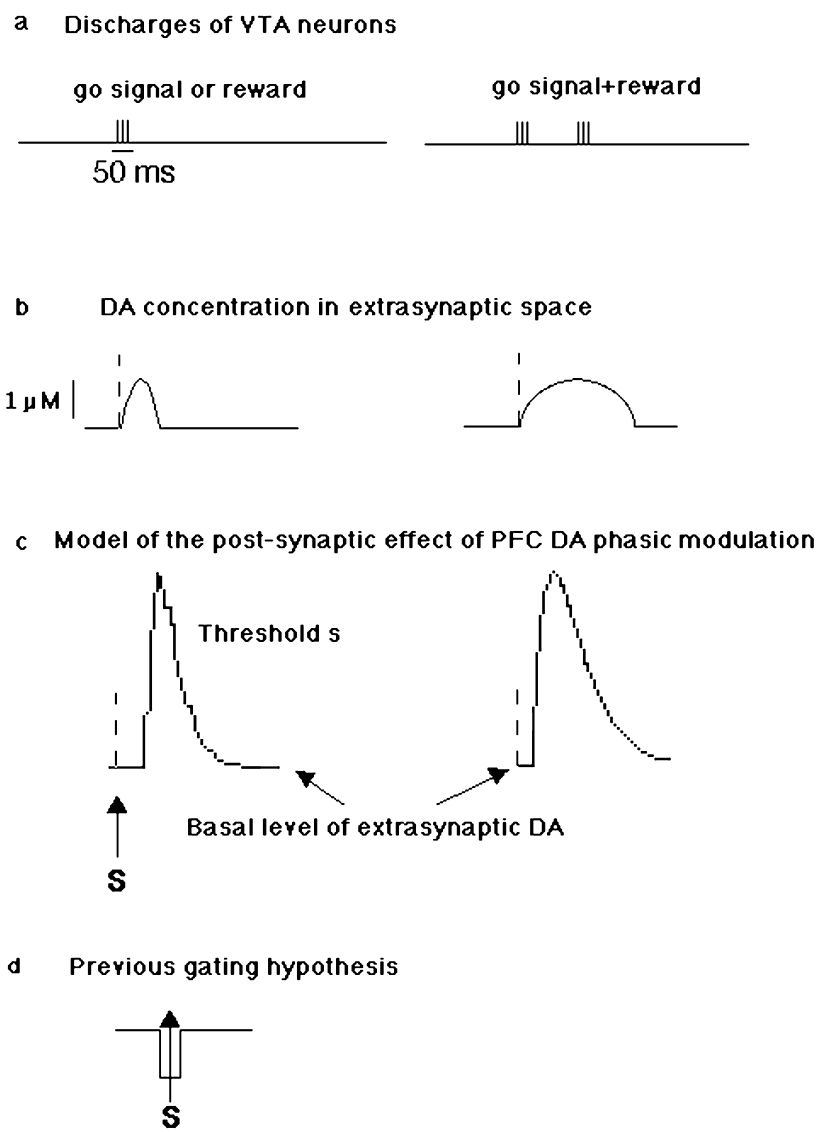

Fig. 3. (a) In the delayed alternation task, VTA neurons discharge occur for go-signal or for reward, which is delivered for a correct alternation (Ljungberg et al., 1991). Two different examples are displayed. Left: go-signal or reward alone. Right: go-signal followed by reward (correct trial). (b) Qualitative concentration of extrasynaptic DA in the PFC after these VTA neurons discharges. (c) Model of the post-synaptic effect of phasic DA release. The post-synaptic effect of phasic DA release is modeled as a temporary threshold $s(t)$ on inputs arriving on apical dendrites of deep layers pyramidal neurons. Two different durations of this threshold are considered to take into account VTA firing for correct and incorrect trials. Left: following an incorrect trial (go-signal alone), the duration of this threshold (modeled by an alpha-function) is supposed to last a few seconds. Right: following a correct trial, the threshold duration reflects the sum of the duration of the post-synaptic effect of DA delivered for the go-signal and the reward. (d) Schematic representation of the previous gating hypothesis proposing that DA facilitate incoming inputs at the precise time of their arrival (Braver et al., 1999).

2.3. Tonic mode of DA modulation

The existence of a tonic mode of DA release, independent of the firing of VTA neurons, has first been proposed in the striatum (Grace, 1991), and may be extended to the PFC, as suggested experimentally (Takahata & Moghaddam, 1998). Glutamate may be released by local networks of PFC pyramidal cells, by recurrent cortical loops from neighboring cortical areas or by glutamatergic projections from sub-cortical regions. All these glutamatergic afferents regulate the background level of extracellular PFC DA by acting at DA terminals. Dendritic spines of pyramidal neurons possess asymmetric synapses associated to glutamatergic inputs, which furnishes a possible functional architecture of DA–glutamate interactions (Smiley et al., 1994). The tonic mode of DA release in the PFC is consistent with the fact that homeostatic control mechanisms are far less efficient in the PFC than in the caudate/putamen and the nucleus accumbens (NAC); (Garris et al., 1994). The tonic mode of release occurs slowly, with a prolonged onset, delayed peak and extending duration, the entire process occurring over periods of minutes to hours (Gonon, 1997; Grace, 1991). The rapid reuptake and disgradation mechanisms of DA in extracellular flow do

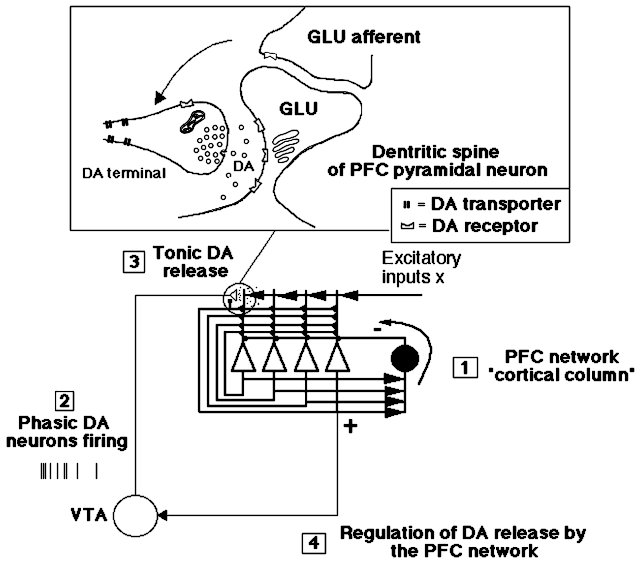

Fig. 4. The model is based on four hypotheses. Hypothesis 1: structure of the network. An excitatory recurrent network with inhibitory neurons and/or intrinsic neuronal properties can maintain sustained activities. Hypothesis 2: phasic DA is released at specific time of behavior, modulating the PFC network at a short time scale. Hypothesis 3: tonic mode of DA release: glutamatergic afferents can induce DA release at the terminal of VTA neurons without discharge of these DA neurons. Hypothesis 4: the PFC neurons controls firing of VTA neurons, leading to an adaptation of phasic DA release to the temporal structure of the task.

not occur with tonic DA as it does with phasic DA release. This may be due to presynaptic DA release occurring at extrasynaptic sites and/or to the low amplitude, slow time course of change in tonic DA levels, since the extracellular concentration of tonic DA is lower than the constant of capture of the uptake system (Grace, 1991). In contrast, the phasic DA release can diffuse for a short period of time a few μm around the DA terminal, but it is taken up so rapidly that it does not activate homeostatic compensatory mechanisms (Grace, 1991).

Tonic DA determines the basal level of DA receptor stimulation. A task particularly requesting the PFC (and thus triggering large activity of glutamatergic PFC pyramidal neuron populations) may thus release tonic DA in an important fashion. A significant increase of 25% of the extracellular level of DA was observed in the dorsolateral PFC of monkeys during the delayed alternation task as compared to the basal level of extracellular DA and to a control task not requiring working memory (Watanabe, Kodama, & Hikosaka, 1997). This observed increase of extracellular DA is likely to come from the tonic mode of DA modulation because glutamate, acting at DA terminals, is massively released by sustained activities of PFC pyramidal neurons and because phasic DA is rapidly recaptured. As we hypothesized that the general function of DA in the PFC is to restrict incoming inputs, a possible consequence of an increase of tonic DA release during a cognitive task may be to restrict inputs arriving on PFC network more importantly at the end of the task. We will test this functional role in our model by considering the behavioral consequence of a 25% increase of the basal level of DA during task performance.

Hypothesis 3 (Function of tonic DA release during a cognitive task). The role of tonic DA release during a cognitive task is to increase the basal level of DA receptors stimulation.

2.4. Regulation of DA release by the prefrontal cortex

The last important concept is that the PFC, which projects both directly and indirectly to the forebrain dopaminergic system, exerts profound control over general state as arousal, stress and mood (Robbins, 2000). It is thus likely that the PFC exerts a crucial regulation on VTA neurons firing during cognitive tasks. However, no specific function of this influence has yet been proposed. We will test the hypothesis that, during performance of a working memory task as the delayed alternation task, PFC control firing of VTA neurons in order that they adapt to the structure of the task (e.g. delay duration for the delayed alternation task).

Hypothesis 4 (Role of PFC regulation on DA neurons firing). The PFC controls firing of VTA neurons, leading to an adaptation of phasic DA release to the temporal structure of the task.

To summarize, we propose three functional hypotheses concerning the DA PFC interactions: (1) the general effect of DA is to restrict inputs arriving on the PFC; (2) this restriction of inputs occurs at two different time scales: phasic DA release restricts excitatory inputs arriving on PFC pyramidal neurons for a few seconds while tonic DA release acts at the level of a few minutes or hours; and (3) PFC controls firing of VTA neurons, leading phasic DA release to adapt to the temporal structure of the task (Fig. 4).

2.5. Goals of this study

The relation between the cellular effect of PFC DA receptor stimulation and the level of working memory performance remains poorly understood. The major goal of this study is to better understand this relation, based on the functional hypotheses of PFC DA proposed above. Previous DA PFC models did not combine the phasic and tonic modes of DA release (Braver et al., 1999; Cohen et al., 1996; Dreher, 1999; Dreher et al., 2002; Durstewitz et al., 1999). Here, we propose a general theory of DA modulation in the PFC that integrates these two modes of DA modulation. The model will show how these distinct modes of DA modulation relate to behavioral performance during the delayed alternation task.

Previous models of DA modulation in the PFC have been situated at a different level of abstraction, either using connectionist networks to link reduced DA PFC turnover to performance in various cognitive tasks (Braver et al., 1999; Cohen & Servan-Schreiber, 1992; Cohen et al., 1996; Servan-Schreiber et al., 1990) or biophysically detailed models of spiking neurons, linking the firing rate of PFC neurons to the change of their biophysical properties induced by variations of DA receptors stimulation (Durstewitz et al., 1999, 2000). Here, we chose an intermediary level of modeling that allows tractable mathematical understanding of the dynamical systems proposed.

3. Methods

3.1. Model of sustained activities

Pyramidal cells constitute the major portion of neurons with sustained activities and motor responses (Connors, Gutnick, & Prince, 1982; Fuster, 1973; Sawaguchi, Matsumura, & Kubota, 1990; Silva, Amitai, & Connors, 1991) whereas neurons in superficial layers are linked to the reception of sensory information (Sawaguchi et al., 1990). Sustained activities are found in numerous cortical and sub-cortical areas, suggesting the existence of general mechanisms for their generation. Both PFC and enthorinal cortex neurons have the particular ability to maintain sustained activities when distracting objects are presented during the delay (Miller et al., 1996a,b; Suzuki, Miller, & Desimone, 1997). This property is thus not specific to PFC neurons, unlike what was previously proposed (Durstewitz et al., 1999, 2000). It is true, however, that neither temporal cortex neurons (Miller et al., 1996a,b), nor posterior parietal cortex neurons (Constantinidis & Steinmetz, 1996; di Pellegrino & Wise, 1993) survive the presentation of intervening stimuli. The origins of sustained activities of pyramidal neurons have either been attributed to recurrent connections, consistent with the fact that they can be found at all stages of cortico–thalamo–cortical loops (Goldman-Rakic, 1995; Levitt et al., 1993) and/or to intrinsic neuronal mechanisms (ionic channels; Camperi & Wang, 1998; Delord, Klaassen, Burnod, Costalat, & Guigon, 1997; Marder, Abbott, Turrigiano, & Golowasch, 1996).

We model spatially selective delay activity by the mean discharge frequency y of a population of neurons coding anticipation of a right response by a high frequency of discharge (ON state) and the anticipation of a left response by a low frequency of discharge (OFF state) (Fig. 5). The opposite pattern of discharge would be embodied in a second population of neurons and will not be modeled here.

We use the following network to model these sustained activities:

$$\tau_y \frac{dy}{dt} = -\alpha y + \varphi_{\gamma\theta_1}(y) + I_{x,s} - z \quad (1)$$

$$\tau_z \frac{dz}{dt} = -\beta z + \varphi_{\Gamma\theta_2}(y) \quad (2)$$

where $\varphi_{ab}(u) = 1/(1 + \exp(-a(u - b)))$ and where θ_1 represents the threshold on basal dendrites, s is the threshold on apical dendrites (see Section 3.2), α and β are constants of passive decay, τ_y and τ_z are arbitrary time constants and γ and Γ correspond to the gain of sigmoid functions.

This network is able to switch ON and OFF sustained activities after a transitory excitatory input x. Eq. (1) describes the dynamic of the mean activity y of the network presented in Fig. 5(a). The variable y is equivalent to a frequency or to a probability of discharge of the neuronal population. Eq. (2) describes the dynamic of a slow variable z that can either be viewed as an intrinsic property of the neurons, such as the slowly inactivating potassium current (Delord, Klaassen, Burnod, & Guigon, 1996; Delord et al., 1997) or as feedback inhibition from inhibitory interneurons (Fig. 5(b)). Indeed, previous models have shown that transitory excitatory inputs may induce both transitions OFF → ON and ON → OFF when neurons possess a slowly inactivating potassium conductance, which is the case for pyramidal neurons of rat's frontal cortex (Delord et al., 1997; Hammond & Crépel, 1992). This mechanism is important because it allows the same excitatory input to induce both ON → OFF and OFF → ON transitions.

In Eq. (1), the first term $-\alpha y$ describes the passive decay of activity and insures stability of both states. The second term $\varphi_{\gamma\theta_1}(y)$ represents recurrent inputs on basal dendrites and insures sustained activities representing memory of the excitatory input that induced it. The term $I_{x,s}$, a non-zero constant if $x > s$ and 0 otherwise, represents the signal induced by an excitatory transitory input x arriving on apical dendrites, thresholded by s, the post-synaptic action of DA (described in Section 3.2). This term $I_{x,s}$ can induce transitions between stable states (ON → OFF or OFF → ON). Finally, the first term of Eq. (2) describes the passive decay of z, which allows its convergence, while the second term (sigmoïdal) describes the increase of z with the increase of y activity. Fig. 5(c) displays the phase plane analysis of this network.

3.2. Model of dopamine modulation in the prefrontal cortex

3.2.1. Model of the phasic mode of release

The effect of phasic DA release is to restrict, for a few seconds, excitatory inputs arriving on superficial layers, thereby protecting apical dendrites of deep layers PFC pyramidal neurons from incoming noise. As the exact duration of this restriction of inputs remains to be determined, the model will evaluate behavioral performance when this duration is or not adapted to the delay of the task. The phasic role of DA is modeled as a threshold temporarily restricting inputs arriving on apical dendrites of pyramidal neurons (Fig. 3). Formally, the post-synaptic effect of phasic

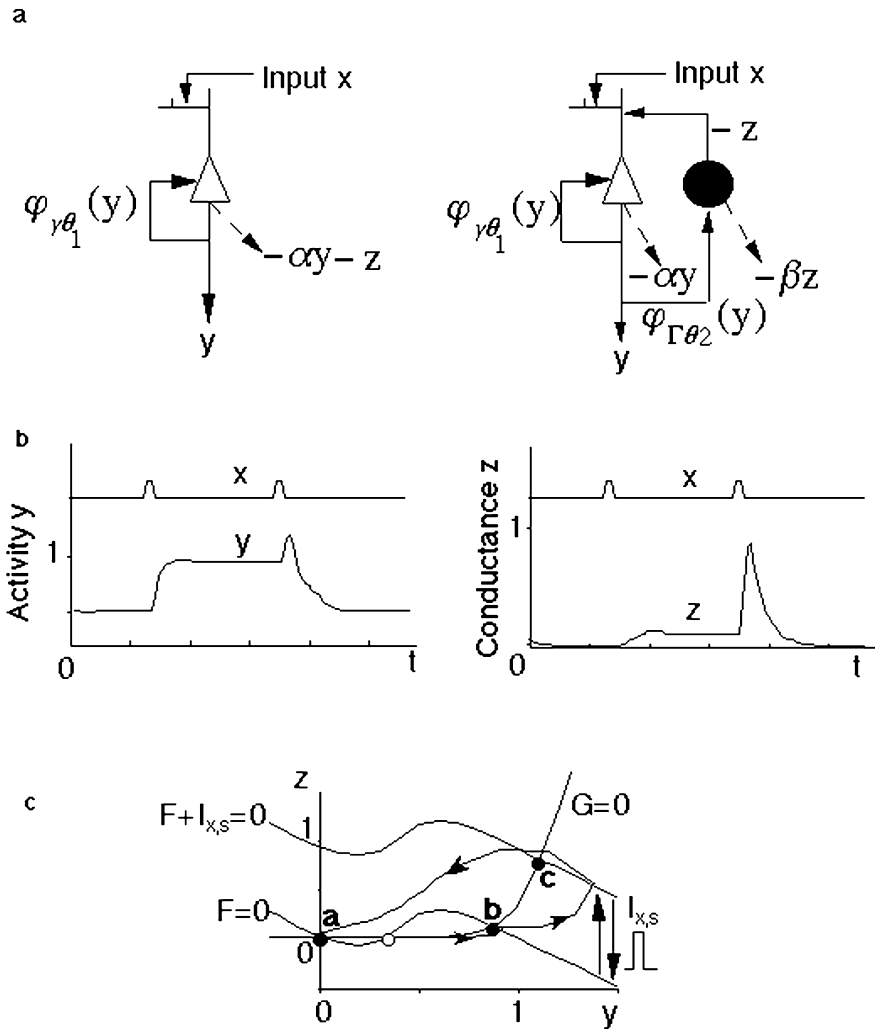

Fig. 5. (a) Structure of the PFC network model. Deep-layer pyramidal PFC neurons receive inputs from long-range cortical areas on superior layers and recurrent excitatory inputs from neighboring cortical columns on their basal dendrites. The mechanism that permits to switch OFF sustained activities of PFC pyramidal neurons can either be attributed to intrinsic neuronal properties, as the slowly inactivating potassium conductance $z(t)$, or to recurrent inhibitory neurons. (b) Left: The activity $y(t)$ of the network can be switched ON and OFF by transient excitatory inputs x arriving on superficial layers. Right: the conductance $z(t)$ is recruited at an intermediary level during the sustained activity of the neuron and increases rapidly with frequency y when a new excitatory input arrives during the discharge, which can induce an intrinsic inhibition, furnishing a mechanism to stop the discharge. This mechanism allows the same excitatory input x to induce both ON → OFF and OFF → ON transitions. (c) Trajectory of the phase point $(y(t), z(t))$ in the phase plane for two successive transient excitatory inputs $I_{x,s}$, respectively, inducing transitions OFF (stable state **a**) → ON (stable state **b**) and ON → OFF. Writing Eq. (1) as $F + I_{x,s} = 0$ and Eq. (2) as $G = 0$ (z-nullcline), allows to plot F and G in the phase plane. The transient input $I_{x,s}$ briefly translates the curve F, creating a temporary stable state **c** (intersection of $F + I_{x,s} = 0$ and $G = 0$). However, from the stable state **b** (ON), an appropriate duration $I_{x,s}$ does not induce the system to converge to **c**, but to converge back to the stable state **a** (OFF). This explains how the same excitatory input x induce both ON → OFF and OFF → ON transitions. Note that the coordinates of **c** explain that the second transitory input x briefly increase both y and z (Fig. 5(b)). $a \cong (0.0223, 0)$; $b \cong (0.8871, 0.1046)$, $y(0) = z(0) = 0$.

DA is given by:

$$s(t) = s_0 + k_i(t - t_i)\mathrm{e}^{-(t-t_i)/\tau_i}, \qquad t \geq t_i \tag{3}$$

In Eq. (3), s_0 corresponds to the basal level of DA receptor stimulation and the second term is the post-synaptic effect of phasic DA release (alpha function of amplitude k_i). It increases rapidly after each phasic DA release at time t_i and decays progressively with time constant τ_i. The threshold $s(t)$ can vary in two ways, either by a modification of the basal level of dopaminergic receptors stimulation s_0, or by a variation of phasic DA release. The basal level of DA D1 receptors stimulation is not modified by phasic DA release because phasic DA is rapidly recaptured (Parsons & Justice, 1992). However, this basal level of DA receptors stimulation may be modified by the tonic mode of DA release (see next paragraph).

3.2.2. Model of the tonic mode of release and of DA agonists/antagonists injection

3.2.2.1. Model of agonists/antagonists injection. D1 agonists/antagonists exert a long-lasting influence (several minutes or hours) on PFC pyramidal neurons (Gao et al.,

2001; Zahrt et al., 1997). As the influence of agonists/antagonists is long as compared to the time scale of the task, s_0 is supposed to be constant during task performance. Injection of DA D1 agonists and antagonists will be modeled by an increase (respectively decrease) of the basal level of DA receptors stimulation s_0.

3.2.2.2. Model of the tonic mode of DA release. In contrast to DA agonists or antagonists, tonic DA release progressively increases the basal level of D1 receptors stimulation during task performance. Thus, the level of DA receptors stimulation s_0 can no longer be considered to be constant. Rather, s_0 becomes a function of time that can be proposed, in first approximation, to be directly proportional to the extracellular level of DA concentration. This extracellular DA concentration, due to tonic DA release, can itself be modeled by a differential equation describing the difference between the rate of DA released and cleared (comprising uptake, reuptake and degradation; Garris et al., 1994; Wightman et al., 1988):

$$\mathrm{d[DA]}/\mathrm{d}t = -k[\mathrm{DA}] + [\mathrm{DA}].y \quad (4)$$

where [DA] is the concentration of extracellular DA, k is the rate of clearance, [DA].y is the rate of DA released by glutamatergic connections on DA terminals and y is the discharge frequency of PFC pyramidal prefrontal neurons. The rate of clearance $-k$[DA] (uptake, reuptake and degradation) fits to a first order process characterized by a constant k evaluated to be $0.5\ \mathrm{s}^{-1}$ for mPFC in the rat (Garris et al., 1994). This rate of DA clearance does not exceed 0.5 μM (Garris et al., 1994). DA terminal fields in different brain regions exhibit different mechanisms for governing extracellular DA levels. When uptake is normalized to tissue DA content in order to account for differences in DA terminal density, the normalized rate constants for uptake are similar in the mPFC, the caudate/putamen (CP) and the NAC. In contrast, relative release is similar in the NAC and CP but 10 times greater in the mPFC.

3.3. Model of the delayed alternation task

The monkey task is to depress an illuminated hold key for several seconds in order to darken it and to light two choice keys, then to press the correct key for that trial (e.g. the left) in order to obtain a reward. A single press on either choice key darkened both and relit the hold key, starting the next trial. A correct sequence is hold center, press left (reward), hold center, press right (reward), etc. (Fig. 6(a)). The network described previously is used to model execution of the delayed alternation task, which is supposed to be established after learning. The task is simulated in the following way. External inputs x, with fixed amplitude, representing the go-signals (light of the two choice keys) are presented during 40 ms every 5 s (delay interval). These go-signals induce a discharge of VTA neurons, whose terminals release DA, which in turn temporarily restrict inputs to the PFC network. In the optimal case, the go-signals exceed the s threshold, which induce a motor response corresponding to the memorized state and a transition between stable states.

3.3.1. Addition of noise to the network

The network presented previously performs the delayed alternation task without error (Fig. 6(b), left). In order to study the performance of the network in disrupted conditions when D1 agonists and antagonists are injected in the PFC, noise is added to the inputs (Fig. 6(b), right). This noise (duration of 40 ms) can be considered as internal fluctuations of the network or as being from external origin (distracting stimuli). It follows a Poisson process of fixed amplitude and of mean chosen in order to reach 80% of correct performance at the optimal level of D1 receptors stimulation, which corresponds to the level of performance achieved by rats after learning the task (Zahrt et al., 1997). This noise can induce undesirable transitions between two go-signals when exceeding the s threshold. An error can thus occur, corresponding to an absence of alternation. In such a case, the reward is not delivered and VTA neurons do not discharge at the time of reward delivery (Ljungberg et al., 1991).

3.3.2. Distinct threshold duration for correct/incorrect trials

After learning the delayed alternation task, VTA neurons discharge both after triggers and after rewards (Ljungberg et al., 1991). However, when an error occurs, reward is not delivered, and DA neurons do not fire (Ljungberg et al., 1991). It has to be noted that contrary to other delayed response tasks, DA released after reward delivery persists after over-training. This has been attributed to the fact that reward serves both as task reinforcer and as important stimulus for the continuous adaptation to the target in the next trial during the delayed alternation task (Ljungberg et al., 1991).

Two durations of post-synaptic effect of DA are considered for incorrect and correct alternations: (1) when an error occurs, reward is not delivered. Thus, DA released in the PFC is only induced by the go-signal. In this case, the duration of post-synaptic action is modeled by a short threshold *s(t)* on inputs (Fig. 3(c), left); (2) after a correct alternation, VTA neurons discharge both following reward and trigger (Ljungberg et al., 1991). In such successful trial, it can be assumed that the post-synaptic effect of these two successive release of DA, separated by 300–400 ms, can be modeled as one cumulative long threshold (Fig. 3(c), right). Two type sets of parameters k_i and τ_i are used to model these two situations of short and long durations of post-synaptic action of DA, corresponding, respectively, to a unique go-signal delivery and to the combination of go-signal and reward. Solving Eqs. (1) and (2) describing the behavior of the network is realized in the same time that performance is quantified, thereby determining whether the reward is delivered (Fig. 6(c)).

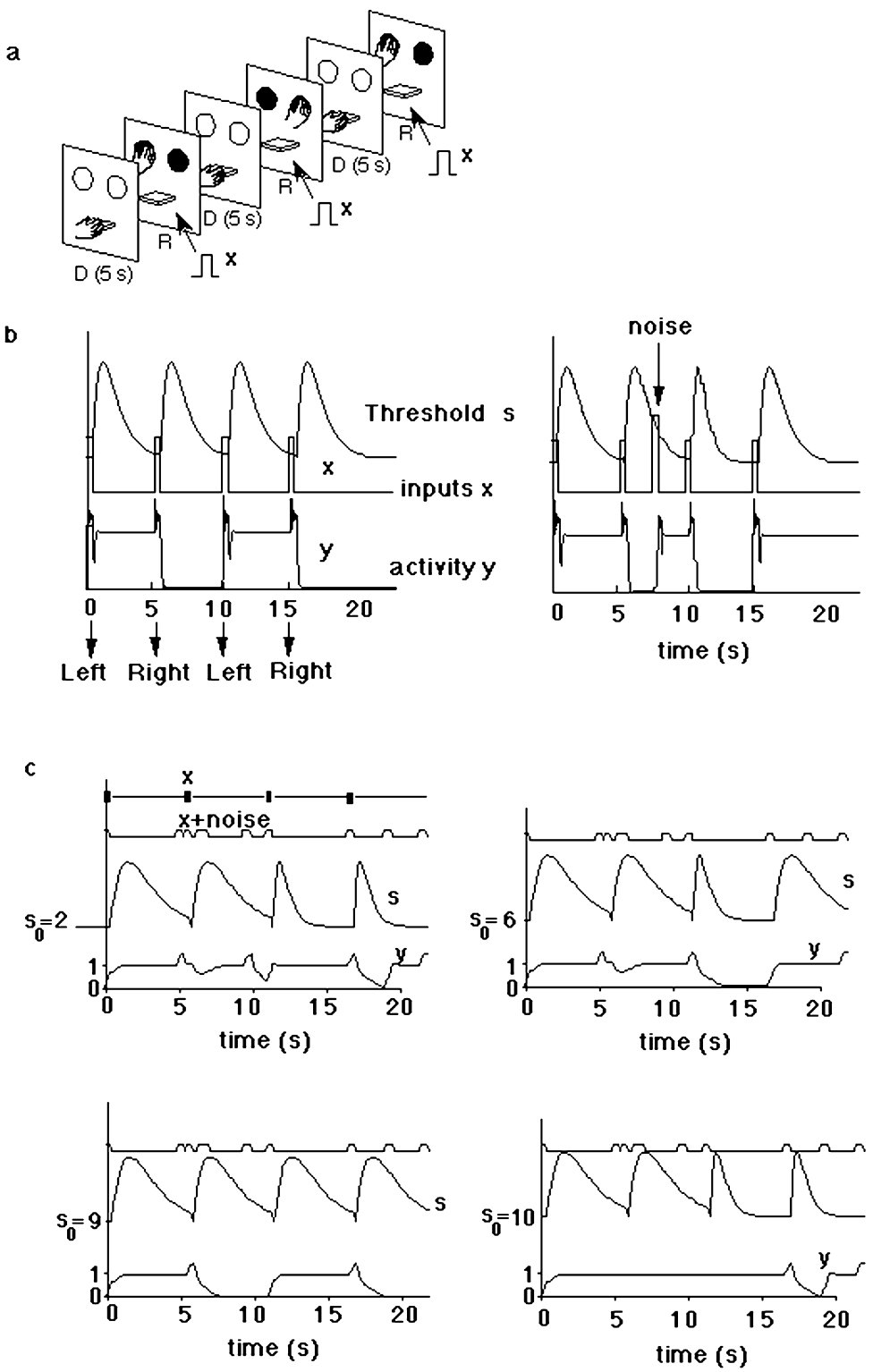

Fig. 6. (a) Structure of the delayed alternation task. Successive go-signals x (simultaneous apparition of the two circles) require to alternate between two responses (right and left) separated by a delay of 5 s. (b) Left: network activity $y(t)$ and time course of the post-synaptic effect of DA (temporary threshold s) in the PFC for successive transitory excitatory inputs x. Right: when noise is added to the system, unexpected transitions can occur before the next go-signal if the noise is higher than the temporary threshold. (c) Examples of activity $y(t)$ of the network when noise is added to the system and the basal level of DA D1 receptors stimulation is decreased ($s_0 = 2$) or increased ($s_0 = 9$) as compared to baseline ($s_0 = 6$). In order to evaluate performance of the network, sustained activities are considered in the OFF state if during more than half of the time between two movements, activity is inferior or equal to 0.5. An error is counted each time two successive stable states are repeated (e.g. ON–ON or OFF–OFF). For n intervals between two movements, there are $n - 1$ possible errors. The proportion of errors is the number of errors divided by $n - 1$ possible errors, and the percentage of success is $100(1 - k/(n - 1))$. Initiation of the evaluation of a correct alternation is done by always rewarding the first two movements.

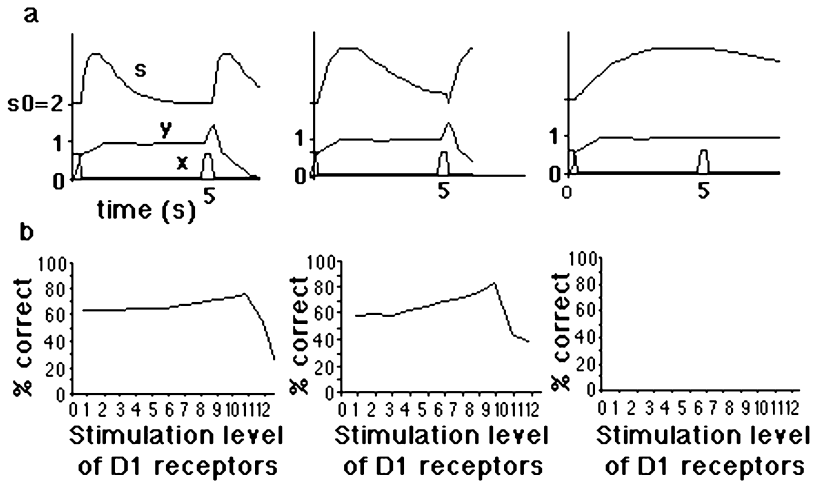

Fig. 7. (a) Activity $y(t)$ of the network and time course of the post-synaptic effect of DA (temporary threshold) in the PFC for two successive transitory excitatory inputs x in the case in which the time constant of the threshold is lower (left), adapted (middle) or higher (right) than the delay. (b) Network performance for increasing level of D1 receptors stimulation. Noise is distributed according to a Poisson process of mean 5 s.

4. Results

The architecture of the model distinguishes recurrent connections and long-distance inputs arriving on apical dendrites of pyramidal neurons. It integrates a combination of network properties and intrinsic properties of individual neurons, which allow transitory excitatory inputs to induce transitions between stable states. The network has two important features: (1) bistability, the network possess two stable states (ON and OFF) which stay fixed in the absence of external inputs and (2) the capacity to rapidly change between stable state with a transitory excitatory input. These two conflicting properties are important for updating representations within the PFC (Miller & Cohen, 2001).

4.1. Simulation 1: performance of the network with increased D1 receptors stimulation

The model takes into account both the short-lasting (phasic) and long-lasting (tonic) post-synaptic effect of DA modulation. As the exact duration of the post-synaptic effect of phasic DA release (temporary threshold) is currently unknown, the model evaluates the behavioral performance when this duration is or not adapted to the delay of the task. The injection of D1 agonists (respectively antagonists) is modeled as an increase (respectively decrease) of the basal level of dopaminergic D1 receptors stimulation. The performance of the network is tested during progressive increase of the basal level of DA D1 receptors stimulation when noise (external inputs or internal fluctuations) is added to the inputs (Fig. 7).

Fig. 7(b) (middle) represents the behavior of the network as a function of the level of D1 receptors stimulation when the time constant of the post-synaptic effect of DA is adapted to the delay. The performance changes with the level of D1 receptor stimulation according to an asymmetric U-curve. DA D1 antagonists induce a random behavior ($\sim$50% of success), corresponding to the fact that noise easily induce transitions between go-signals. For high level of D1 receptors stimulation (D1 agonists injection), performance drops below chance level, reflecting that the network remains in the same state for successive trials (perseverations) because the go-signals are restricted by the post-synaptic effect of DA. However, performance does not continue to drop abruptly for further increase in D1 receptors stimulation because when an error occurs, the absence of reward delivery reduces the duration of the temporary restriction of inputs, thereby allowing incoming noise and/or go-signals to switch between states.

Fig. 7(b) (left) shows the level of the network performance when the time constant of the threshold is lower than the delay. As noted previously, performance follows an inverted U-curve when D1 receptors stimulation increases. The optimal level of performance is lower and obtained for higher level of D1 receptors stimulation as compared to when the time constant of the threshold was adapted to the delay. Indeed, a lower time constant of the threshold reduces the duration of restriction of incoming inputs, making it more likely for noise to disrupt memory for a given level of D1 receptors stimulation. Importantly, performance falls abruptly below 50% correct after the optimal performance is reached, due to the fact that the temporary threshold no longer restrict go-signals for high level of receptors stimulation.

Finally, Fig. 7(b) (right) shows that when the time constant of the threshold is larger than the delay, all the inputs (go-signals and noise) are restricted. No transition between states is therefore possible, leading to a null level of performance.

In order to analyze the performance of the network more precisely, we also quantified perseverations. As the network performance only corresponds to experimental results

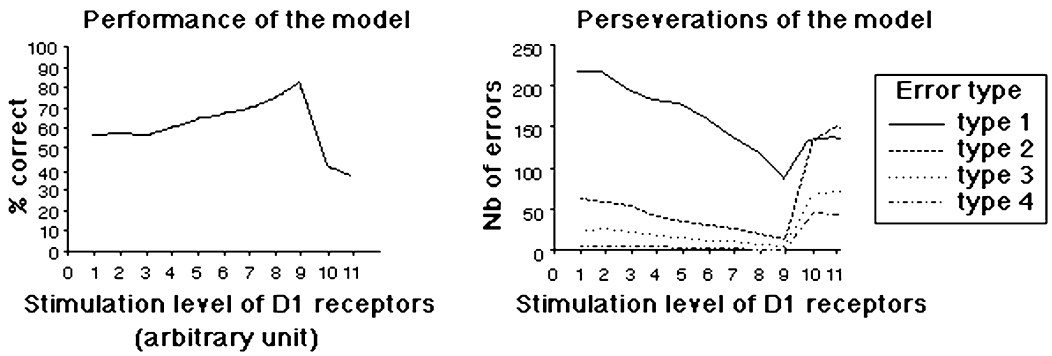

Fig. 8. Left: results of the simulated network performance for increasing level of D1 receptor stimulation when the time constant of the threshold is adapted to the duration of the delay. Right: number of different types of perseverations for n successive delays as a function of the level of D1 stimulation ($n = 1500$). Perseverations are quantified by counting two successive errors (e.g. ON–ON–ON–OFF is a succession of two errors). A perseveration of type 1 is the repetition of length 1 of the same activity (e.g. ON–ON). Noise is distributed according to a Poisson process of mean 5 s.

(inverted U-shape curve) when the time constant of the threshold is adjusted to the delay, we only quantified perseverations in this case (Fig. 8, right). At low level of D1 stimulation, the number of perseverations is high and then decreases with an increase of the level of D1 stimulation, until reaching a minimal level, which corresponds to the optimal level of performance. When D1 receptors stimulation increases further (for injection of D1 agonists), perseverations strongly increase. It is important to note the different nature of perseverations appearing for D1 antagonists and for D1 agonists. Perseverations present for D1 antagonists are due to the fact that the delayed alternation task only comprises two possible choices. Thus, as the noise easily induces transitions for low level of D1 receptor stimulation, there is a high probability to make an inopportune transition between two go-signals. This explains why so much perseverations of type 1 (repetition) are observed for D1 antagonists. If the choices were distributed not among two responses (right and left) but among n possible responses ($n > 2$), there would be only $1/n$ chance to make the same choice at each trial. Therefore, perseverations appearing for D1 antagonists are not the mark of a real behavior of perseveration but come from the inherent structure of the task. In contrast, the high number of true perseverations of the network (errors of type > 1) observed for D1 agonists are due to the fact that both distracters and go-signal cannot switch the current state. Long perseverations are thus observed, leading below 50% of correct performance.

4.2. Simulation 2: performance of the network with an increase of tonic DA release

We investigated the behavioral effect of an increase of 25% of the extracellular level of DA by tonic DA release during performance of the delayed alternation task (described in Eq. (4)). Fig. 9(a) represents the level of DA receptors stimulation, that is directly related to the extracellular level of DA due to tonic and phasic DA release. Fig. 9(b) displays two examples of the performance level, at the beginning of the task, and after an increase of 25% of the extracellular level of DA. The simulation shows that the performance level is either increased or decreased, according to the basal level of extracellular PFC DA at the beginning of the task. If the basal level of DA receptors stimulation is low, performance is improved. In contrast, if the basal level of DA receptor stimulation is optimal or too high, the performance level deteriorates. These two effects are simply explained by considering the inverted U-shape curve of performance when the basal level of D1 receptor stimulation s_0 varies in the arbitrary range [1,11] (Fig. 8, left). For example, if the basal level of DA receptors stimulation is $s_0 = 5$ at the beginning of the task (corresponding to a performance level of 65% correct), a 25% increase of s_0 leads to a value of 6.25, corresponding to a performance level of 70% correct. Similarly, if the value of s_0 was optimal ($s_0 = 9$) at the beginning of the task (corresponding to a performance level of 80% correct), a 25% increase of s_0 leads to a level of performance below 40%.

In conclusion, increasing the basal level of DA receptors stimulation during task performance, may either lead to a beneficial or a detrimental effect, according to the basal level of DA receptors stimulation at the beginning of the task and the relative increase of this basal level during task performance.

5. Discussion

Our model allows us to better understand the relation between the level of performance of the delayed alternation task and the cellular action of DA on a simple PFC neural network. It conciliates the short-term post-synaptic effect of phasic DA release and the long-time scale variation of the basal level of DA receptors stimulation occurring after tonic DA release. The model explains how phasic DA finely regulates inputs on prefrontal network and how the inverted U-curve of performance is obtained with an increase in the

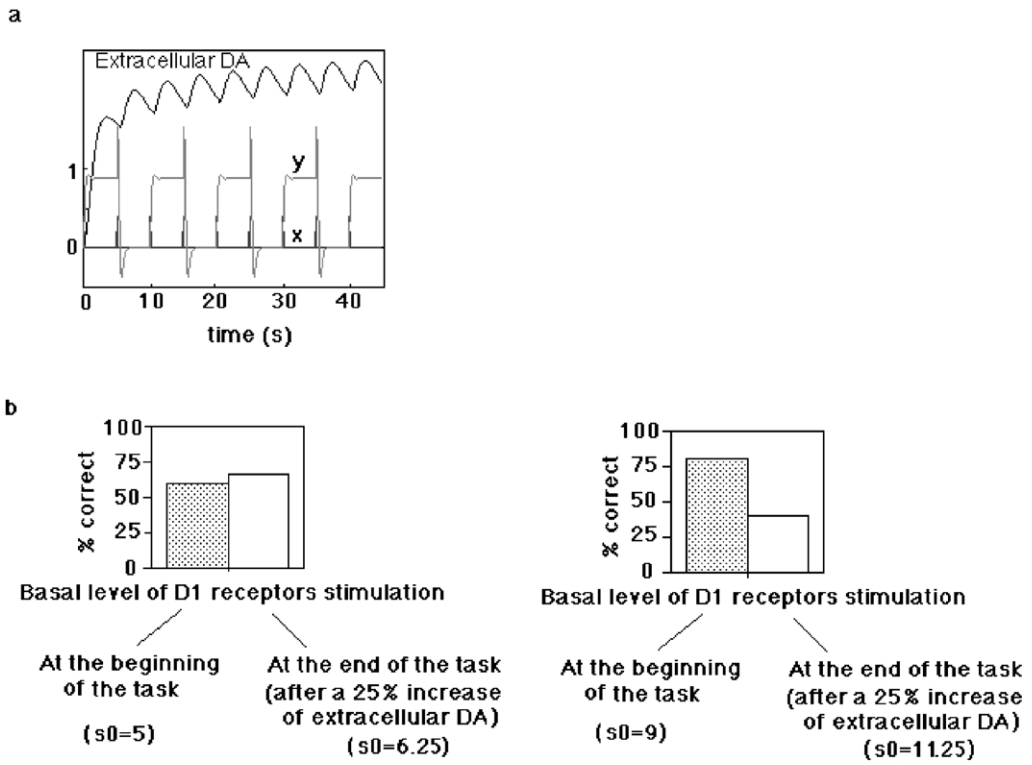

Fig. 9. (a) The upper curve represents the level of DA receptors stimulation, due to phasic DA release superimposed on the tonic DA release that increases logarithmically. The lower curve represents the activity y of the network for successive inputs x, with no noise disturbing the network. We model a 25% increase of the extracellular basal level of PFC DA by the tonic mode of release (following Eq. (4)). (b) Left: performance of the network at the beginning of the task ($s_0 = 5$, left column) and after a 25% increase of extracellular DA ($s_0 = 6.25$, right column) during 240 successive delays of 5 s. Right: performance of the network at the beginning of the task ($s_0 = 9$, left column) and after a 25% increase of extracellular DA ($s_0 = 11.25$, right column).

level of D1 receptors stimulation. As mentioned in the introduction, this inverted U-shape curve has been reported in experimental studies, indicating the existence of a certain level of D1 receptors stimulation for optimal working memory performance (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Arnsten, 1997; Murphy et al., 1996; Zahrt et al., 1997). Importantly, our model indicates that the inverted U-curve may only be obtained if the duration of the post-synaptic effect of DA is lower or adapted to the delay of the task (see Section 5.1.1).

The results of network simulation also show that the inverted U-curve of performance is not symmetric, which may be attributed to the fact that an identical dose of D1 agonists or antagonists does not have the same behavioral effect. In addition to the non-monotonic relationship between the behavioral performance and the level of D1 stimulation, the model makes qualitative predictions regarding the types of errors. For high level of D1 receptors stimulation, corresponding to D1 agonists injection, both go-signals and distracting stimuli were restricted, which leads the network to remain in the same state during successive trials. This prediction of increased perseverations with an increased level of D1 stimulation is confirmed by local injection of D1 agonists in rat's PFC (Zahrt et al., 1997). Our model also predicted that local PFC injection of D1 antagonists would lead to a chance level of performance, which is confirmed experimentally as the percentage of correct responses is close to 50% in rats after mPFC injection of D1 antagonists (Zahrt et al., 1997).

5.1. Phasic/tonic modes of dopamine release

5.1.1. Regulation of the duration of the post-synaptic effect of phasic DA

One important prediction of the model is that the post-synaptic duration of DA may be adjusted to the delay of the task. This may be possible if DA released after phasic VTA discharge is adapted to the delay duration, implying that the frequency of VTA discharges depends upon the delay of the task. This prediction is supported by a voltammetric study in rats under delayed reinforcement conditions, that showed that lever presses were followed by DA PFC signal increases that were time-locked to the delay duration (Richardson & Gratton, 1998). Adaptation of VTA discharges frequency to the delay is made possible by the close relationship between sustained activities and the time of VTA discharges. VTA neurons code the error of reward prediction (Montague et al., 1996; Schultz, 1997), and this signal, furnished to the PFC (Taber et al., 1995), is itself elaborated on the basis of reward prediction delivered by the PFC (Watanabe, 1996). Thus, PFC neurons, that show enhanced activity with increased desirability of an expected

reward (Leon & Shadlen, 1999; Tremblay & Schultz, 1999; Watanabe, 1996), are likely to dynamically regulate their own DA level. This validates our hypothesis (Hypothesis 4) that during performance of a cognitive task, PFC controls firing of VTA neurons, leading VTA discharges to adapt to the structure of the task (as the delay duration).

Current theories consider phasic DA as a teaching signal for reinforcement learning (Contreras-Vidal & Schultz, 1999; Friston et al., 1994; Montague et al., 1996; Suri & Schultz, 2001). Our proposed function of phasic DA modulation on information processing is compatible with this role of DA in learning. Phasic DA could, in the same time than protecting sustained activities from noise, form connections during novel situations. This learning role of DA, which is not accounted by our model, might be of primary importance to adapt the post-synaptic effect of DA after unexpected change of the task delay duration. Such delay variation should be associated with an increase of errors and lead to an adaptation of DA discharge frequency.

5.1.2. Role of the tonic mode of dopamine release

One important new aspect of this study is to model tonic DA as modulating the basal level of the threshold restricting inputs arriving to the PFC. Simulations of the model show that increasing tonic DA release of 25% from the beginning to the end of the task leads to different types of performance changes, depending upon the basal level of extracellular DA at the beginning of the task (Fig. 9). If the basal level of DA receptors stimulation is low, performance is improved, but performance deteriorates if the basal level of DA receptors stimulation is optimal or too high. Future experiments may test this prediction by dividing the course of an experiment in different stages, and compare performance between them. The fact that performance improvement depends upon the basal level of PFC extracellular DA is consistent with findings in healthy humans that report that DA agonists improve working memory performance only in subjects who have relatively low working-memory capacity at baseline, whereas in the subjects who have high working memory capacity at baseline, it worsened performance (Mattay et al., 2000). These various individual differences in the effects of DA agonists on working memory performance may be related to individual differences in DA function, as allelic variation of DA system genes (Egan et al., 2001).

Another possible functional hypothesis of tonic DA may be that, by its properties of slow and important diffusion, it modulates sites that DA released in a phasic way cannot reach. In particular, if dopaminergic receptors do exist on the soma of pyramidal neurons, tonic DA could have a specific role at this site. Indeed, as dopaminergic terminals innervate the whole dendritic tree (Krimer, Jakab, & Goldman-Rakic, 1997) but not the soma, and that DA diffuses around 40 μm around dopaminergic terminals in the PFC (Garris & Wightman, 1994), phasic DA cannot reach the soma, contrary to tonic DA. It would be possible to test this hypothesis in more detailed models of individual pyramidal neurons that include dendritic and somatic channels.

5.2. Comparison to previous models of prefrontal cortex DA modulation

Previous DA PFC models that have considered that DA increases signal-to-noise ratio in a time-independent fashion (Cohen & Servan-Schreiber, 1992; Cohen et al., 1996; Durstewitz et al., 1999), are insufficient to explain the U-curve of performance obtained in the delayed alternation task. According to these models, performance would increase monotonically with an increase of DA receptor stimulation until reaching an optimal level of performance, and would then fall abruptly to a null level of performance because of restriction of all go-signals. Similarly, the previous facilitating DA PFC gating theory (Braver et al., 1999), is by itself, insufficient to explain the inverted U-shape relationship between PFC D1 receptors stimulation and performance. In our model, it is the combination of DA D1 receptor stimulation, which increases the signal-to-noise ratio (basal level of D1 stimulation) and of phasic DA, which more specifically regulates activities at the time scale of the task that allows explaining the inverted U-curve of performance.

Importantly, the gating theory of DA at the time of stimuli presentation and our own theory make different predictions regarding the role of errors in learning. In our view, the absence of DA delivery following an error allows the updating of PFC representation (because the duration of the temporary threshold on the inputs is reduced), which may be useful to learn the correct behavior to be adopted. This is in accordance with the current view that behavioral learning depends on the coding of reward prediction error by DA neurons (Schultz & Dickinson, 2000; Waelti, Dickinson, & Schultz, 2001). In contrast, for Braver and Cohen, updating of representations is not done after each error but after phasic DA signal for reward or reward predicting stimuli (Braver et al., 1999). Thus, we believe our model adds an important piece to the puzzle by proposing a new theory of DA modulation that integrates the phasic and tonic mode of DA release in the PFC.

6. Conclusion

Our PFC network, which can maintain and stop sustained activities after transitory excitatory inputs, has shown how an increase in the level of DA D1 receptors stimulation leads to the inverted U-shape curve of performance obtained in the delayed alternation task. We have shown that supposing that the overall role of DA is to reduce inputs to pyramidal neurons is sufficient to explain the inverted U-curve of performance and the nature of errors (distraction, perseveration) observed during this task. Our model led to interpret

differently the reduction of performance for D1 antagonists and D1 agonists that could a priori seem similar when only considering the performance curve. The model has also shown that perseverations obtained for D1 agonists come from a defect to take pertinent stimuli into account, and that distractability is obtained for D1 antagonists.

The fundamental contribution of the model is to combine a functional role of phasic and tonic DA release in the PFC and to link the level of performance to the cellular action of DA in a neural network. These different time scales of DA modulation illustrate how fast and slow variables influence neural network dynamics. These results may be extended to larger class of neural networks and be useful in different domains. For example, artificial neural networks have proven useful in order that autonomous systems learn temporal sequences toward goal achievement (Banquet et al., 1997). This line of research has benefited from the study of the neurobiological structures involved in the temporal organization of behavior (e.g. rats foraging behavior in an unknown environment), and will probably also benefit from including the influence of neuromodulation on neural network dynamics. In particular, the idea that phasic DA modulation acts as a temporary threshold may find applications in different areas using artificial neural networks. To give only one final example, associative memories with dynamic thresholds prevent network dynamics to be trapped in a stable attractor state (Horn & Usher, 1991). Such mechanism has proven useful to increase the network sensitivity to new stimuli, allowing associative memories to correct input patterns.

Acknowledgments

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Appendix A. Dynamic of a recurrent unit in discreet time

The dynamic of a recurrent excitatory network can be model by a single recurrent unit based on the dynamic of a recurrent sigmoid function (Mc Auley & Stampfli, 1994). This approximation allows obtention of sustained activities in working memory tasks after stimulation by excitatory inputs (Mc Auley & Stampfli, 1994; Nakahara & Doya, 1998):

$$y(t+1) = \frac{1}{1+e^{-\gamma(y(t)-\theta)}} \qquad (\gamma \geq 0, \theta \in \mathbf{R}) \qquad \text{(A1)}$$

The behavior of the dynamic of this system (number of fixed points and stability) may be obtained by comparing $y(t+1)$ as a function of $y(t)$ for different values of the gain γ and the threshold θ (Fig. A1).

When the parameters γ and θ change, the dynamic of the system can bifurcate. A typical example of bifurcation is a saddle for which $y(t+1) = y(t)$ and $df/dy|_{y=y^*} = 1$ Fig. A1, case B and D, with y^* = fixed point).

Given the parameters (γ, θ), the number of fixed points can vary from 1 (case A, high fixed point; and case E, low point fixed), to 2 (case B, 1 low fixed unstable point and 1 high stable fixed point; case D, 1 low stable fixed and 1 high unstable fixed point), or to 3 (case C, 2 stable fixed points and 1 unstable).

The values of γ and θ for which equilibrium points y^* are tangents to the diagonal $y(t+1) = y(t)$ determine the bifurcation points in the parameter space:

$$\begin{cases} y^*(t+1) = y^*(t) \\ df/dy|_{y=y^*} = 1 \end{cases} \quad \text{for } 0 < y^* < 1$$

$$\begin{cases} \dfrac{1}{1+e^{-\gamma(y^*(t)-\theta)}} = y^*(t) \\ \dfrac{\gamma}{(1+e^{-\gamma(y^*(t)-\theta)})^2} e^{-\gamma(y^*(t)-\theta)} = 1 \end{cases}$$

$$\Leftrightarrow \begin{cases} \dfrac{1}{1+e^{-\gamma(y^*(t)-\theta)}} = y^*(t) \\ \gamma f(y^*)(1-f(y^*)) = 1 \end{cases}$$

$(0 < y^* < 1)$

We obtain for $(0 < y^* < 1)$:

$$\gamma = \frac{1}{y^*(1-y^*)}$$

$$\theta = y^*(1+(1-y^*)\ln((1-y^*)/y^*))$$

These two equations allow us to find the bifurcation curves of the saddle points when the values of the fixed points y^* vary between 0 and 1. Elimination of y^* in these two equations lead to:

$$\theta = \frac{1 \pm \sqrt{1-4/\gamma}}{2} + \frac{1}{\gamma}\ln\left(\frac{4}{\gamma(1 \pm \sqrt{1-4/\gamma})^2}\right) \quad \gamma \geq 4$$

This equation determinates θ as a function of γ and allows plotting the saddle nodes of bifurcation points in the parameters space (γ, θ) (Fig. A1). Inside the region defined by these borders, there are three fixed points (two attractors) and an unstable fixed point. Outside this region, there is only one attractor.

A.1. Limitation of the recurrent excitatory model

A dynamic system that is used to model goal-oriented behavior must be able to maintain information in a robust

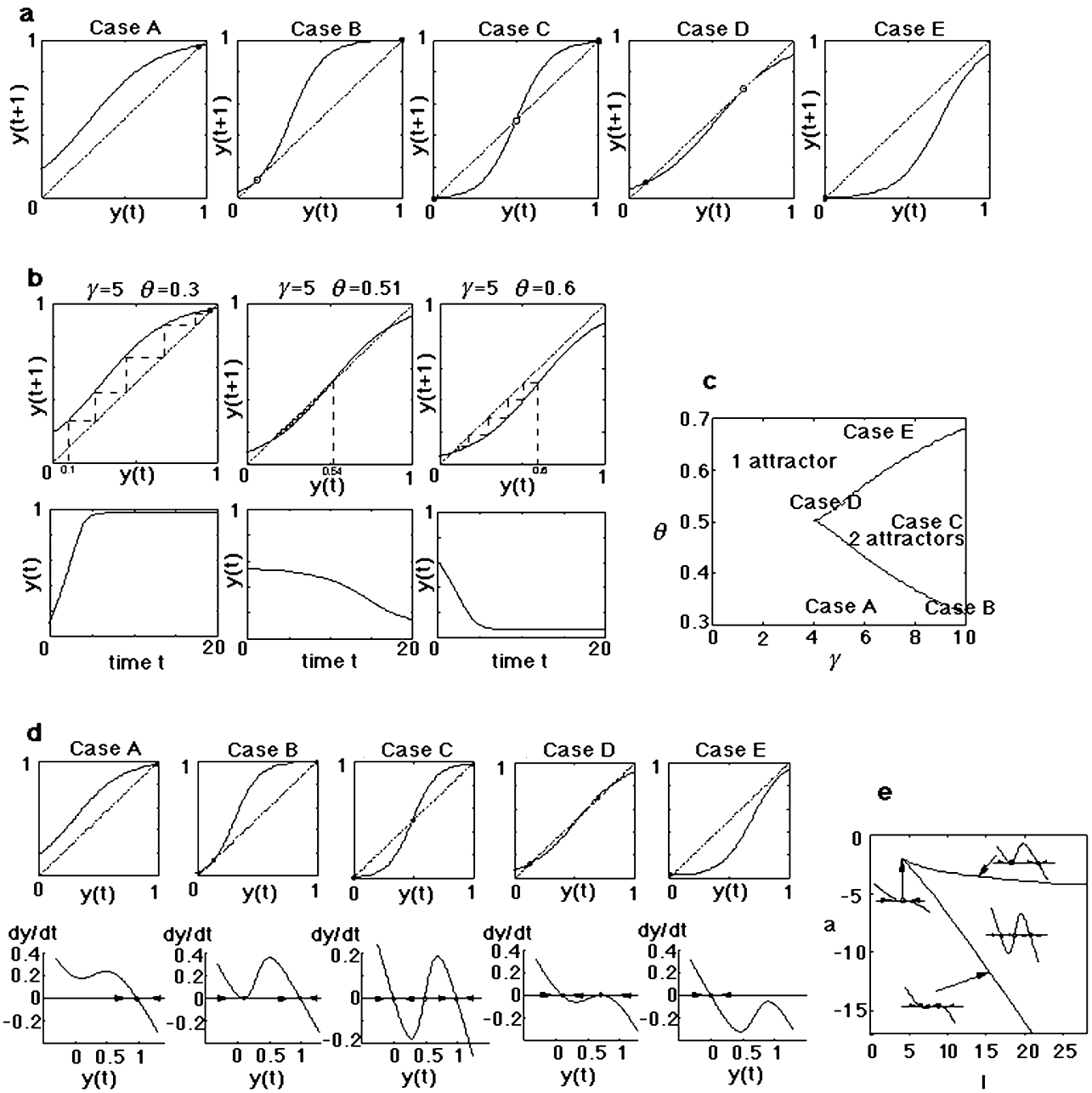

Fig. A1. (a) Diagram of transition state of the recurrent sigmoïd function for different values of the gain γ and the threshold θ. The fixed points are at the intersection of the sigmoïd and the line $y(t+1) = y(t)$. Stable fixed points are noted (•), the unstable fixed point is noted (○) and the saddle nodes of bifurcation are noted (◉). Case A: one stable high fixed point ($\gamma = 5$; $\theta = 0.3$); Case B: one high stable fixed point and a saddle node ($\gamma = 10$; $\theta = 0.3190$); Case C: two stable fixed points (high and low) and an unstable, fixed point ($\gamma = 10$; $\theta = 0.5$); Case D: a low fixed point and a saddle node ($\gamma = 5$; $\theta = 0.5311$); Case E: a low stable fixed point ($\gamma = 8$; $\theta = 0.7$). (b) Top: representation of $y(t+1)$ as a function of $y(t)$. Top: trajectory of $y(t)$ for ($\theta_1 < \theta = 0.3$, $\gamma = 5$ with $y(0) = 0.1$), ($\theta = 0.54 > \theta_2$, $\gamma = 5$ with $y(0) = 0.8$, middle figure) and ($\theta = 0.6 > \theta_2$, $\gamma = 5$, $y(0) = 0.6$ right figure). If $\gamma = 5$, the two values of θ for which there is a bifurcation are $\theta_1 = 0.4689$ and $\theta_2 = 0.5311$). Bottom: the dynamics of $y(t)$ as a function of time t shows that the system converges toward a stable state when $t \rightarrow +\infty$. (c) Bifurcation diagram showing the possible types of behavior (either one or two attractors) as parameters changes in the space (γ, θ). (d) The dynamics of the additive neuron (continuous time) can have one or two fixed points and a saddle node according to the values of the external input I. The parameters used to plot dy/dt as a function of $y(t)$ are those of the cases A–E of the model in discreet time. (e) Bifurcation diagram of the additive neuron. The region of stability is inside the scope. The point $(I, a) = (4, -2)$ is the point of bifurcation.

fashion and to possess rapid transitions between states to allow novel sensory cues to be stored in memory (Nakahara & Doya, 1998). These two properties have been proposed to be true for a recurrent sigmoid unit in which the parameters γ and θ of the sigmoid are chosen in such way than the intersection with $y(t+1) = y(t)$ requires a large number of steps to converge (Fig. A1(a), case $\gamma = 5,\ \theta = 0.51$) (Nakahara & Doya, 1998). In this case, the recurrent unit may stay in a false ON state for a number of time steps and switch to the low fixed point. This false ON state only appears to be an ON state because of slow convergence of the system (to a real OFF state). In fact, to be able to switch quickly between two reals, ON and OFF state, the system needs the property described previously in Eq. (2).

Appendix B. Model in continuous time

The model of the recurrent unit in discreet time can be written in continuous time as:

$$\mathrm{d}y_i/\mathrm{d}t = -y_i + f\left(I_i + \sum_{j=1}^{n} c_{ij}y_j\right) \tag{B1}$$

In Eq. (B1), y_i is the activity of the neuron i (probability of discharge), I_i is the external input to i, c_{ij} $(i \neq j)$ is the synaptic connection from the neuron j to the neuron i, c_{ii} is a feedback parameter and f is the sigmoid function: $f(x) = 1/(1+\mathrm{e}^{-x})$. The stable states are plotted as a function of the input (Fig. A1.d).

The conditions to have a supercritical pitchfork bifurcation are (noting $\mathrm{d}y/\mathrm{d}t = -y + f(ay+I) = F(y,a,p)$, $a \neq 0$ at I parameters):

Equilibrium: $y = f(ay+I)$.
Non-hyperbolicity of the equilibrium: $-1 + af'(ay+I) = 0$.
Non-zero second order term: $a^2f''(ay+I) \neq 0$. This condition is satisfied everywhere except at the inflexion point of f (i.e. at the origin). Thus, this condition can be written: $ay + I \neq 0$.
Transversality:

$$\begin{pmatrix} \dfrac{\partial F}{\partial I} \\ \dfrac{\partial F}{\partial a} \end{pmatrix} = \begin{pmatrix} f'(ay+I) \\ yf'(ay+I) \end{pmatrix} \neq 0$$

This condition is true for all finite values of y, a and I.

The first two equations allow to write explicitly a and I as a function of y, noticing that f and f' can be written:

$$f(x) = \frac{1}{1+\mathrm{e}^{-x}} = \frac{1+\mathrm{e}^{-x}-\mathrm{e}^{-x}}{1+\mathrm{e}^{-x}} = 1 - \mathrm{e}^{-x}f(x),$$

$$f'(x) = \frac{\mathrm{e}^{-x}}{(1+\mathrm{e}^{-x})^2} = \mathrm{e}^{-x}f^2(x) = (1-f(x))f(x)$$

$$\Rightarrow a = 1/(y(1-y)),$$

$$I = \ln(y/(1-y)) - 1/(1-y))$$

These equations define a parametric curve $0 < y < 1$ plotted in Fig. A1.d.

Appendix C. Parameters used in the simulations

$\alpha = 1,\ \beta = 0.5;\ \tau_y = 2,\ \tau_z = 1,\ \gamma = 10,\ \Gamma = 10,\ \theta_1 = 0.4,\ \theta_2 = 1.2$. Matlab was used to implement the model and run the simulations.

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