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THE ROLE OF DOPAMINE IN THE MAINTENANCE OF WORKING MEMORY IN PREFRONTAL CORTEX NEURONS: INPUT-DRIVEN VERSUS INTERNALLY-DRIVEN NETWORKS

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How do organisms select and organize relevant sensory input in working memory (WM) in order to deal with constantly changing environmental cues? Once information has been stored in WM, how is it protected from and altered by the continuous stream of sensory input and internally generated planning? The present study proposes a novel role for dopamine (DA) in the maintenance of WM in the prefrontal cortex (Pfc) neurons that begins to address these issues. In particular, *DA* mediates the alternation of the Pfc network between input-driven and internally-driven states, which in turn drives WM updates and storage. A biologically inspired neural network model of Pfc is formulated to provide a link between the mechanisms of state switching and the biophysical properties of Pfc neurons. This model belongs to the recurrent competitive fields[33] class of dynamical systems which have been extensively mathematically characterized and exhibit the two functional states of interest: input-driven and internally-driven. This hypothesis was tested with two working memory tasks of increasing difficulty: a simple working memory task and a delayed alternation task. The results suggest that optimal WM storage in spite of noise is achieved with a phasic *DA* input followed by a lower *DA* sustained activity. Hypo and hyper-dopaminergic activity that alter this ideal pattern lead to increased distractibility from non-relevant pattern and prolonged perseverations on presented patterns, respectively.

Keywords: Recurrent networks; dopamine; prefrontal cortex; working memory; cognitive control.

1. Introduction

The link between working memory (WM), cognitive control, and prefrontal cortex (Pfc) functioning has been an active topics of research in cognitive science.[27,45–47,51] Cognitive control is the process of selecting contextually relevant information and organizing these representations to achieve the organism's behavioral goals. Cognitive control has been linked to the ability to maintain goal-related information in WM, and neuropsychological and neurophysiologic studies have provided strong evidence in favor of an involvement of Pfc in active maintenance of information in WM.[8,62] WM is impaired in human subjects with lesions in the frontal cortex, and particularly the dorsolateral Pfc.[22,6] Pfc ablation in non-human primates has been shown to cause impairments in tasks requiring WM.[5,28] Such deficits are also common in rats with lesions to the medial Pfc, the rodent equivalent of the dorsolateral Pfc in primates.[42]

Pfc has been shown to be involved in tasks that use a delayed-response paradigm. In these kinds of

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tasks, performance is linked to the ability of the animal to maintain information over some temporal delay in order to release a response at a later point in time, often facing the presentation of several distracters interleaved between the to-be-stored cue and the release of an action (Refs. 25, 32, 43 and 68). Neurons in Pfc exhibit stimulus-specific, sustained activation during performance of these tasks, whereas lesions to Pfc impair their correct execution (for reviews: see Refs. 15, 32 and 48). These results are corroborated by neuroimaging studies, where Pfc activity has been shown to increase as memory load increases[7] and to be sustained over the entire delay interval.[14]

Miller and colleagues[69] have provided direct evidence for the ability of Pfc to maintain information in the face of interference. While cue-related information was held in both Pfc and infero-temporal cortex (IT) after the presentation of the stimulus, subsequent presentations of distracters obliterated the activity in IT, while the pattern in Pfc was maintained until a match (target presentation) occurred. Not surprisingly, Pfc damage has been associated with increased distractibility and perseveration.[16]

Pfc is also a target structure of dopaminergic (DAergic) innervation, and a linkage has been suggested between an imbalanced DAergic system, a poor Pfc activation and some key symptoms of neurological and psychiatric diseases.[29] Converging evidence suggests that DAergic projections to the Pfc modulate both attention and WM processes that may be related to either insufficient or excessive dopamine activity specific to the DAergic D_1 receptor mechanism.[11]

The action of *DA* in spatial WM has also been investigated. Both primate and rodent studies have highlighted the role of dopaminergic receptors in the maintenance of activity in Pfc neurons during a task that implies some delay between the cue and the response. In particular, DAergic midbrain neurons become active[54] and *DA* levels in the Pfc increase[63] during WM performance. Blockade of the subtype D_1 of *DA* receptors in Pfc (Refs. 52, 53 and 55) and *DA* depletion in Pfc[70,71] are correlated with WM deficits. At the same time, *DA* agonists enhance delay task performance (Refs. 2 and 72). Over the past decades, in vivo and in vitro studies have suggested a more articulated picture by showing the differential influence of stimulation from the D_1 and D_2 subtypes of dopamine receptors on Pfc activity (Refs. 6, 66 and 73–76).

The relationship between *DA* receptor stimulation, WM and some neurological and psychiatric deficits has been a focus of interest in psychopathology. In a review paper, Lidow *et al.*[44] summarize the evidence supporting a precise link between antipsychotic drugs, D_1 and D_2 receptors, Pfc activation and some major features of schizophrenia, one of the major psychiatric diseases that have been linked to an imbalanced DAergic transmission. Evidence from both physiological and behavioral studies suggests that normal cognitive performance is achieved with a restricted range of D_1 receptors activation.[31]

Goldman-Rakic and her colleagues have proposed a descriptive model trying to capture the relationship between D_1 receptor stimulation, pyramidal neurons and gamma-aminobutyric acid (GABAergic) interneurons activation, and WM performance.[31] The relative activation of pyramidal, excitatory neurons and inhibitory interneurons is important in shaping the resulting activation pattern in a neural population. Goldman-Rakic and colleagues suggest that, at an optimal level of *DA* stimulation, glutamatergic (pyramidal) neurons activation is enhanced more than the activation of inhibitory interneurons. At low levels of *DA*the absence of modulation does not allow any activation to be stored in WM. At high D_1 activation, D_1 receptors in pyramidal neurons will saturate while GABAergic interneurons will still be able to increase their firing rate, causing an overall decrease in activation and no WM storage.

Despite decades of studies on the nature of the action of *DA* in Pfc, the exact mechanism and, more importantly, the behavioral and computational function of the innervation of Pfc from the DAergic nucleus ventral tegmental area (VTA) is still elusive. Studies aimed at determining the excitatory or the inhibitory influence of *DA* in Pfc neurons have led to controversial results.[30] Durstewitz and Seamans[18] propose a detailed computational model incorporating numerous biophysical and electrophysiological data on the presumed role of *DA* in Pfc neuron functioning. Their simulations show that *DA* acts on several Pfc membrane currents (Na++, K+,

Ca++), with the net effect of enhancing delay-active neurons and reducing the impact of intervening stimuli, therefore determining a shift between a resting state and a high memory state, defined as the average firing rate of the Pfc field. A simplified phase plane analysis of such a system shows how *DA* can widen the distance between the two critical points that describe the two states, thereby making it more difficult to switch between low and high memory states in the presence of *DA*. The Durstewitz and Seamans[18] model is one of the most sophisticated computational model in terms of biophysical details simultaneously implemented in a single simulation. However, the authors do not simulate a behavioral task, nor do they systematically vary the magnitude of the DAergic innervation to determine its effect on the behavior of the network. Thus, based on this model, it is not possible to determine whether Pfc can preserve its activity in the face of interference in a behavioral task.

On the other hand, Braver and Cohen[8] place emphasis on behavioral control in order to demonstrate the ability of a simple model to incorporate interactions between the DAergic system and Pfc in order to perform tasks known to involve WM load. Unlike the model by Durstewitz and Seamans,[18] Braver and Cohen[8] model the macroscopic functional features that the network should express in order to control behavior. This work focuses on the most prominent behavioral impairment in schizophrenia, namely the loss of cognitive control. This involves impairment in attention, WM and behavioral inhibition.[44] The authors suggest a possible role for *DA* as a gate for Pfc, determining the maintenance or the update of goal-related information based on the phasic DAergic signal controlled by VTA. Indeed, the proposal of *DA* as exerting a general gating function with respect to distal input is a recurring theme in the modeling literature[17,57,77] and is also emerging with increasing insistence in the neurophysiological community.[18,74] However, the exact mechanisms of this gate are still under debate, with the main issue being the status of the gate, namely whether the gate is normally closed or open, and therefore whether the action of *DA* is to open or close the prefrontal gate. In Braver and Cohen's[8] model, *DA* controls the update of information in Pfc. A DAergic spike allows the input synchronized with this spike to enter Pfc and to be stored in WM. In the absence of DAergic modulation, the Pfc gate is therefore closed, allowing reverberation of activation, protection from interference, and storage in WM. The competitive, recurrent network implemented in this study has been used to simulate the continuous performance task,[12] an experimental setting in which a WM load is required in order to store sensory representations. Despite the encouraging results, the computational analysis of the system does not allow for a formal characterization of the behavior of the network. Furthermore, the model only allows inputs which are synchronized with a VTA DAergic spike to enter Pfc for WM storage. The specular view, as pointed out by Dreher and Burnod,[17] is more plausible (see discussion below).

The work by Dreher and Burnod[17] seems to take advantage of the strengths of Durstewitz and Seamans[18] and Braver and Cohen[8] in terms of neurobiological details incorporated in the model and the link between behavior and simulation results. Dreher and Burnod[17] have chosen to limit the study to a two-population system in order to fully characterize the system dynamics and, with some simplifying assumptions, to remain able to simulate a non-trivial WM task, the delayed alternation task (DaAT). When DaAT is used in animal studies, the animal must alternate between two different responses (e.g., right/left button press) separated by a delay. Both rats[9] and monkeys[26] are impaired in this DaAT when they have Pfc lesions. Dreher and Burnod's[17] focus is on the subset of Pfc neurons that show sustained activity during the delay between right-sided and left-sided trials from the same animal studies. DaAT is sensitive to VTA DAergic innervations and direct infusions of D_1 agonists and antagonists in Pfc impair behavioral performance.[3] Dreher and Burnod's[17] model is built on the assumption that *DA* reduces the impact of intervening stimuli on network activity through D_1 stimulation. This proposal is in disagreement with the one by Braver and Cohen,[8] in which *DA* modulation is proposed to facilitate incoming inputs at the precise time of their presentation. Dreher and Burnod[17] propose that *DA* is unlikely to play this role, for two different reasons: (1) *DA* presumably has an inhibitory effect on Pfc neurons; and (2) when the DAergic VTA neurons fire, *DA* released by their terminals in Pfc requires some time before influencing

the post-synaptic cell (100–150 msec for VTA neurons to fire, plus some other time for *DA* to act at the post-synaptic site −200 msec observed in the striatum, Seamans *et al.*[56]). This time is greater than the time necessary for a stimulus to reach Pfc. Thus, Dreher and Burnod[17] propose that the role of DAergic transmission is to momentarily *isolate* Pfc neurons activated by an input from a previous cortical area, in particular input to Pfc neuron's apical dendrites. This would be achieved by increasing a threshold, defined as the electrotonic distance between the dendrite and the proximal dendritic regions.

The network simulated by Dreher and Burnod[17] reflects an inverted "U" function between behavioral performance and levels of *DA* stimulation; low or high levels of *DA* increase errors in the task. The hypothesis of *DA* as acting on the input to apical dendrites of Pfc cells is supported by neurophysiological data (see Ref. 65). However, the scale of Dreher and Burnod's[17] simulation does not allow to clarify whether the demonstrated properties it would be scalable in a more complex and realistic model of Pfc.

Reid and Willshaw[50] analyze the role of *DA* in forming delay cell ensembles responsible for the kind of activation seen in physiological recordings of Pfc in WM tasks. They propose that *DA* acts primarily on layer 3 cells by reducing firing threshold and allowing synchronous activation in the cell ensemble. Reid and Willshaw[50] propose that *DA* has two major roles with regard to layer 3 activation dynamics: *decrease* in the firing threshold via its action on proximal dendrites/soma (amplification of recurrent connection within layer 3) and *increase* in firing threshold in distal dendrites (isolation of layer 3 from distal input). Thus, *DA* has an effect in synchronizing and lowering the threshold for reverberation of activity in layer 3, as well as isolating layer 3 cells from other inputs that might reset working memory. In Reid and Willshaw's[50] model, underactivity in D_1 receptors causes the disruption in the coherent firing of layer 3 cells and a reduction in the gating preserving delay ensembles from being influenced by (potentially) non-pertinent information. On the other hand, overactivity of D_1 receptors would cause over-gating of layer 3 cells. Similarly to Braver and Cohen's,[8] Reid and Willshaw's model assumes that *DA* is necessary for Pfc input to be processed at all. This model is therefore subject to the same critiques to the Braver and Cohen's model: since DAergic action in Pfc is delayed with respect to the arrival of sensory input to Pfc, *DA* might not be able to open the Pfc gate in a timely manner for storing the correct information.

The aim of the present work is thus to clarify, within a realistic but still simple and mathematically tractable computational model, the possible roles played by *DA* in maintaining WM information in Pfc neurons. In the first part we describe the mathematical and computational foundations of the work. Two tasks with different levels of difficulty are then simulated in order to test the ability of the model to perform a WM task, which requires storage of information over time in spite of intervening distracters.

2. Input Driven versus Internally Driven Networks

Storage of information in Pfc requires maintenance of pattern of activation across an extensive network of cortical neurons. When groups of interconnected neurons become capable of self-sustaining their activity through repetitive, reverberatory excitation,[37] they form cell assemblies. Examples of neural networks models capable of preserving patterns of activation through time are Hopfield's network[39] and the Boltzmann machine.[1] Recurrent artificial neural networks models can be regarded as the closest mathematical analogous of Hebb's cell assembly theory of cortical associative memory. A particularly mathematically well-characterized subset of recurrent networks is recurrent competitive fields.[33,34] Grossberg[33] explained with the use of RCFs how arbitrary activation patterns can be stored in WM in a population of neurons that obey biologically plausible membrane equations. RCF have been characterized mathematically by later studies[13] in an effort to define the conditions, parameters and architecture that allow a given activation pattern to be stored without major distortions in WM. RCF are therefore particularly suitable for being employed as a putative Pfc network which, given certain conditions, is able to store an arbitrary WM pattern once its external input is turned off. RCF, and recurrent networks in general, are complex dynamical systems that can exhibit a plethora of different network behaviors, ranging from the formation of stable

activation patterns to chaos. Even when the recurrent field is considered in isolation, namely when any external input source is turned off (as, for instance, in the presence of a pharmacological gate), it is nontrivial to define the conditions upon which a stable activation pattern can be achieved, and what sort of deformation would be eventually applied to the to-be-stored pattern.

In order to demonstrate that a dynamical system of the complexity of a RCF has a stable solution, an energy function or Liapunov function can be constructed for that system. The existence of a Liapunov function guarantees that the system would converge to a set of stable points or limit cycles and, therefore, would not exhibit a chaotic or unpredictable behavior.[59] Cohen and Grossberg[13] have formally analyzed a general class of biologically inspired, competitive, recurrent neural networks, proving that given certain conditions these networks converge to a global, stable solution (units' activations do not oscillate or overshoot to – or + ∞) for any choice of parameters. An example of a RCF which obeys the Cohen-Grossberg theorem[13] of global pattern formation and absolute stability of the activation pattern is the two-node network illustrated in Fig. 1 which is governed by Eqs. (1) and (2):

$$\frac{d}{dt}x_1 = -x_1 + f(x_1) - x_1[f(x_1) + f(x_2)], \qquad (1)$$

and

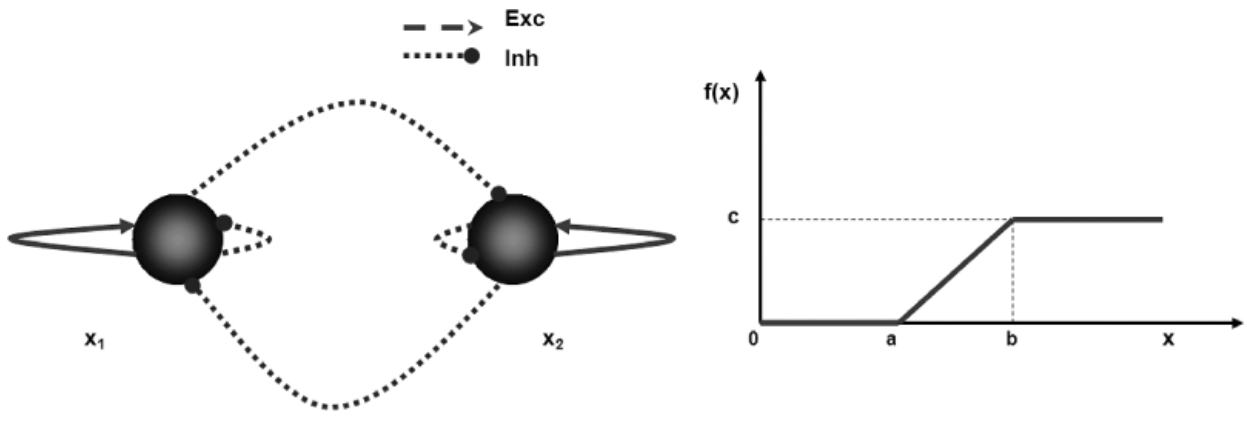
$$\frac{d}{dt}x_2 = -x_2 + f(x_2) - x_2[f(x_1) + f(x_2)], \qquad (2)$$

where x_1 and x_2 are the activation values of the nodes, -x_1 describes a leak term, $f(x)$ is the self excitatory term, and $x_1[f(x_1) + f(x_2)]$ is the inhibitory term from both neurons. Equations (1) and (2) describe a simplified model of neuron's membrane potential.[33] The activation function $f(x)$ is defined by Eq. (3) and plotted in Fig. 1:

$$f(x) = \begin{cases} 0 & \text{when } 0 \le x < a \\ \dfrac{c}{b-a}(x-a) & \text{when } a \le x \le b \\ c & \text{when } b < x \end{cases} \qquad (3)$$

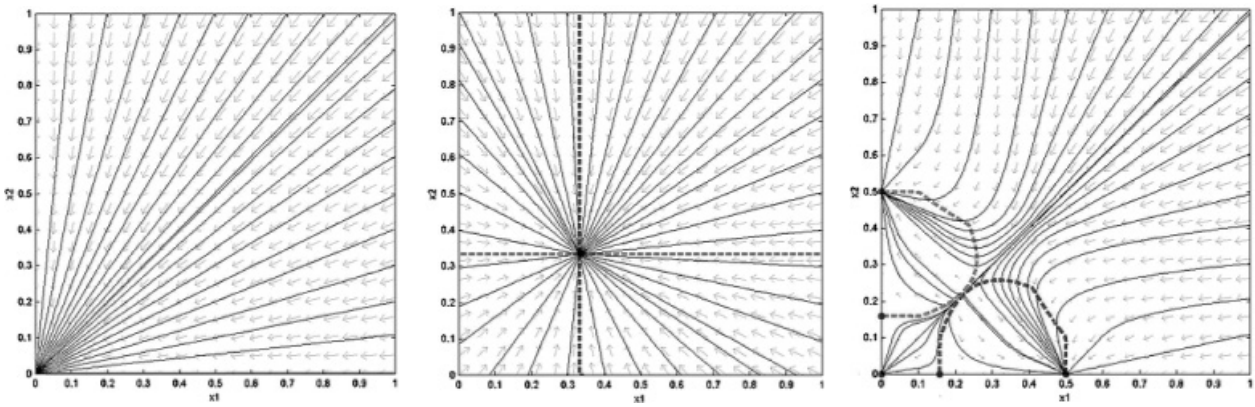
The parameters a, b, and c of the function are constrained to non-negative values, and their choice determines the behavior of the system. In fact, the choice of these parameters determines the shape of the signal function, namely the input/output mapping of the artificial neuron. For instance, $a > 1$ allows only input pattern greater than 1 to enter the linear part of the signal function and therefore being considered for storage in WM. Likewise, $a \cong b$ determines a steep and short linear section of $f(x)$. Various combination of a, b and c determine a family of very different mappings.

This network can be more easily characterized in isolation, that is, by assuming that external input is turned on only briefly in order to generate activation pattern in the field, and is off otherwise. Although chaos can be ruled out as an admissible behavior of such system, it remains to be determined what is the fate of the input pattern, namely what would be the activation pattern emerging as a result of the



(a) (b)

Fig. 1. (a) The recurrent competitive two-node network has self-exciting connections that help store a pattern in WM, and inhibitory connections within and between units. (b) The piecewise activation function $f(x)$.



(a) (b) (c)

Fig. 2. The phase plane describes the behavior of the two neurons' activation (x_1 and x_2) in three examples of the many admissible systems obtained by varying the values of the parameters a, b, and c in the signal function $f(x)$ defined in Eq. (3). The choice of the parameters of the function $f(x)$ affects the shape of the signal function and the resulting behavior of the system, exemplified in the phase portrait. The light gray arrows in each phase portrait show the local direction of the change in the activation pattern, the dashed lines show the nullclines (points in which one of the derivative is zero), and the dots show the critical points (either stable points or saddles). In (a), the activation of the network converges to a state in which the two nodes have zero activation, no matter what the initial conditions are (uniformization of the pattern). In (b) the activation converges to a non-zero symmetrical value, whereas in (c) a binary "choice" network is implemented, in which one of the network wins the competition for WM storage unless both activations collapse to zero. Notice that only in c) $a > 0$.

interaction in the two-node network. This is particularly important if we assume that the pattern of activation reaching Pfc carries some important information.

A convenient way to visualize and study the behavior of low-dimensional systems such as the one described in Eqs. (1), (2), and (3) is through the use of phase plane analysis. Figure 2 illustrates how the activation of the two nodes varies with respect to each other as a function of parameter choice, in particular the shape of the signal function. The choice of the parameters in Fig. 2 emphasizes the very different families of behavior that can be obtained by varying the shape of the signal function. Depending from the choice of parameters, the network can either quench, or suppress, the WM pattern (Fig. 2(a)), converge to a uniform, stable solution (Fig. 2(b)), or implement a choice network in which only one unit preserves its activity in WM (Fig. 2(c)). Figure 2 shows how the choice of the parameters of in Eq. (3) greatly affects the dynamics of the system, suggesting that neuromodulatory, unspecific input might be able to switch the behavior of the network from one functional state to the other by acting on the input/output mapping. This concept is related to a long-held hypothesis suggesting that *DA* and other catecholamines exert their action by modulating target neuron responses, for instance by increasing their signal-to-noise ratio.[21] In particular, *DA* effects have been cited as responsible to the change in the slope (or gain) of the sigmoid shaped input–output activation function of model neurons.[20,57] In a symmetric system like the one described in Eqs. (1), (2), and (3), an unspecific activation (e.g., a neuromodulatory input) can move x_1 and x_2 into different regions of the phase plane and determine, for instance, the storage of information or its suppression, as well as acting to amplify recurrent connections and isolate the network from external sources of stimulation. The proposal of this work is that *DA* actually subserves the latter role.

3. A Computational Model of the Delayed Alternation Task: Role of Dopamine in Working Memory

The architecture of the model is shown in Fig. 3. The network consists of 10 pyramidal (excitatory) neurons and 10 (inhibitory) interneurons. A pyramidal node, simulating a Pfc neuron, receives input from previous cortical stages, VTA DAergic innervations,

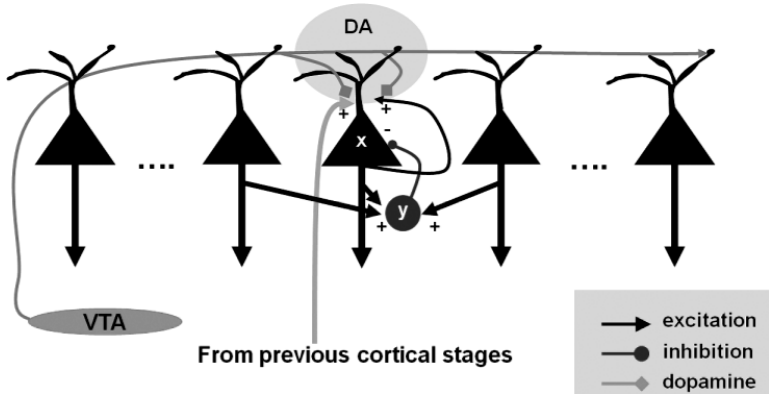


Fig. 3. The model: every pyramidal neuron (x) receives input from a previous cortical stage and interacts with the neighboring pyramidal cells through a population of inhibitory interneurons (y). A DAergic projection (shaded gray area) from VTA modulates the effectiveness of the input from previous cortical stages to the pyramidal neurons, as well as the efficiency of their recurrent connections.

recurrent excitation, and intracortical inhibition. The equations describing the dynamics of the excitatory (x) and inhibitory (y) nodes are:

$$\frac{dx_i}{dt} = -Ax_i + (B - x_i)[I_i \cdot (1 - DA) + F \cdot DA \cdot f(x_i)] - (x_i + C) \sum_{j=-1}^{1} y_{i+j}, \quad (4)$$

and

$$\frac{dy_i}{dt} = -Ay_i + (B - y_i) \left[\sum_{j=-1}^{1} x_{i+j} \right] - (y_i + C) f(y_i), \quad (5)$$

where

$$f(h) = \frac{h^2}{0.25 + h^2}, \quad (6)$$

and x_i and y_i are the units' activation, where $i = 1, 2, \ldots, 10$, I_i is the bottom-up input to the cell, $f(x_i)$ and $f(y_i)$ are the recurrent excitatory and inhibitory inputs, respectively, A and B and C are the decay rate, the excitatory and the inhibitory saturation point, respectively. As observed experimentally,[23] a sigmoid $f(h)$ signal function defined defines the feedback input/output relationship in the network. In Eq. (6), h is the activation of the node and F is a constant. In Eq. (4), $0 \leq DA \leq 1$. In all simulations, $A = 1, B = 1, C = 0.2, F = 10$. The choice of parameters A, B, C and F was such as to ensure desired functional properties in the RCF networks. In particular, $B = 1$ and $C = 0.2$ ensure that activations is bounded between 1 and -0.2. This parameter choice account for the fact that the maximum cell excitation during a spike is higher than the inhibition, as measured with respect to resting potential, which in an RCF is conventionally set to $x_i = 0$. Finally, $F = 10$ allows amplification of the DA innervations and the feedback function $f(x_i)$ with respect to the external input. This value of F was empirically derived by trial and error, until a robust storage of activation was achieved. As shown in Eq. (4), DA has a double effect on the RCF excitatory neurons. On the one hand, it isolates the network from external (distal) input through the term $(1 - DA)$ such that a high DAergic signal would bias Pfc activation mode from externally-driven to internally-driven (recurrent mode). On the other hand, DA is assumed to amplify recurrent connections through the term $DA \cdot f(x_i)$, facilitating WM storage. The computational model described in Eqs. (4)–(6) belongs to a class of well-studied biologically-inspired network equations which exhibit desirable computational properties, like resistance to saturation, preservation of the relative magnitude of the input with respect to varying level of total input energy, and the ability to store activation in WM when recurrent connections are included.[33,36,2] Furthermore, Eqs. (4)–(6) satisfy the constraints of the Cohen-Grossberg theorem,[13] which studies the conditions under which recurrent neural networks are stable. The network implemented in this study will eventually converge to some stable point, and there will be at most a countable

number of such stable points, therefore excluding chaotic dynamics.

4. Results

The network is tested in two tasks involving different degrees of WM load. The first set of simulations, described in Fig. 4, involves a simple WM (sWM) task in which a stimulus, a spatial pattern of activation instantiated in the network from a previous cortical stage, is maintained until a new stimulus arrives in Pfc and resets its activation. In the sWM task the inter-stimulus interval (ISI) is 1100 msec (where

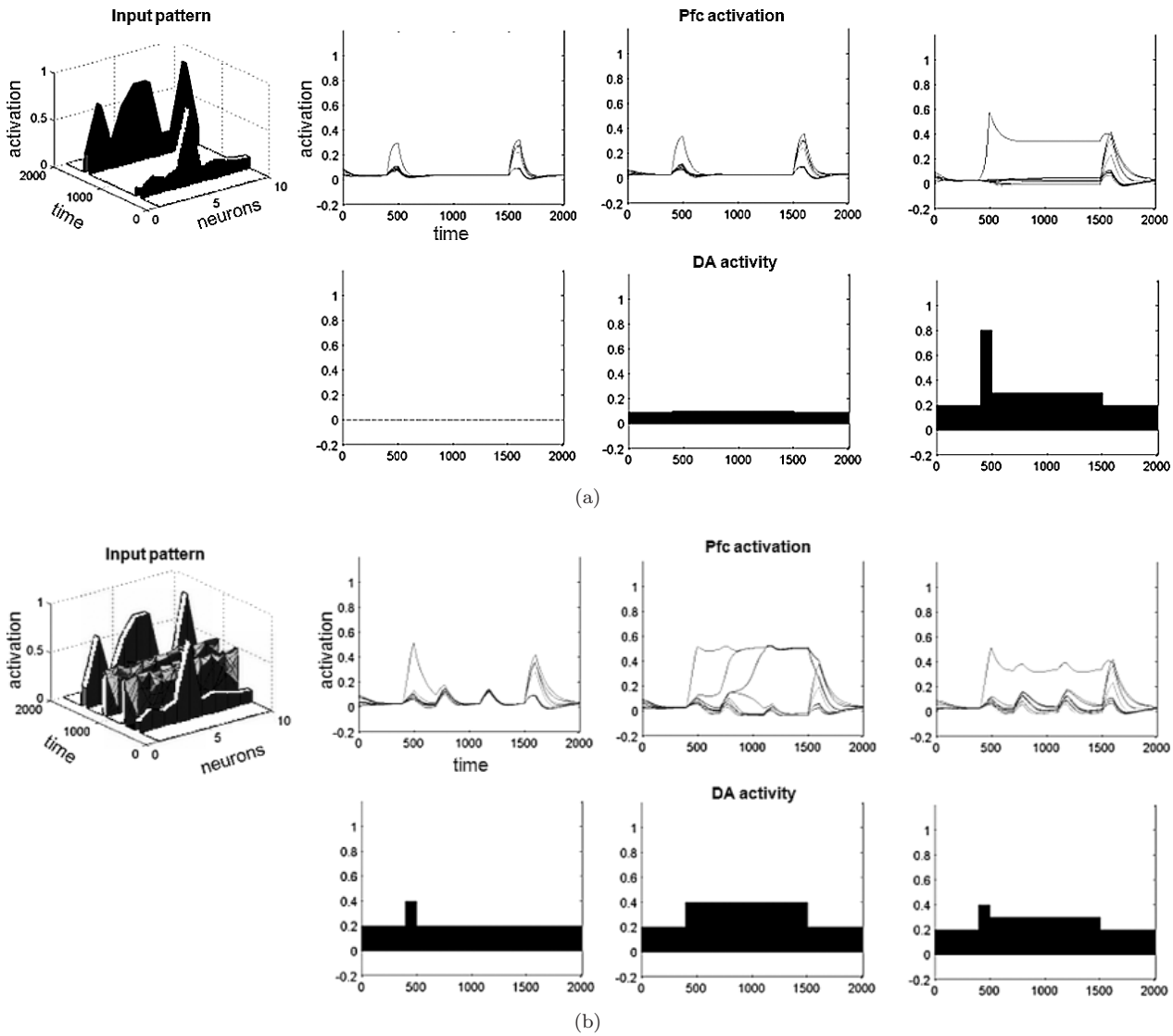


Fig. 4. Activation traces represent the activation of different excitatory neurons. (a) sWM task. The input pattern (top, left) is presented to the Pfc network for 2000 msec. The top rows show the activation of the pyramidal neuron x over for variable levels of DAergic activity (bottom row). Notice how *DA* regulates the storage of activation in WM, as well as the formation of a spatial pattern in the Pfc field. Lack of DAergic activity prevents the storage of activation in WM, whereas a phasic DAergic input followed by a tonic baseline is optimal for WM storage. (b) sWM task in the presence of noise. The input pattern is represented in the left inset. The 50-msec-noise interferes with the WM pattern that decays due to the absence of a tonic *DA* baseline (left panels). A hyperactive tonic DAergic input causes the loss of the pattern (middle panels). This effect is mainly due to the multiplicative effect of *DA* on self-excitation and to the intrinsic dynamics of the on-center/off-surround architecture. An initial phasic-tonic DAergic transmission prevents noise to disrupt the pattern (right panels).

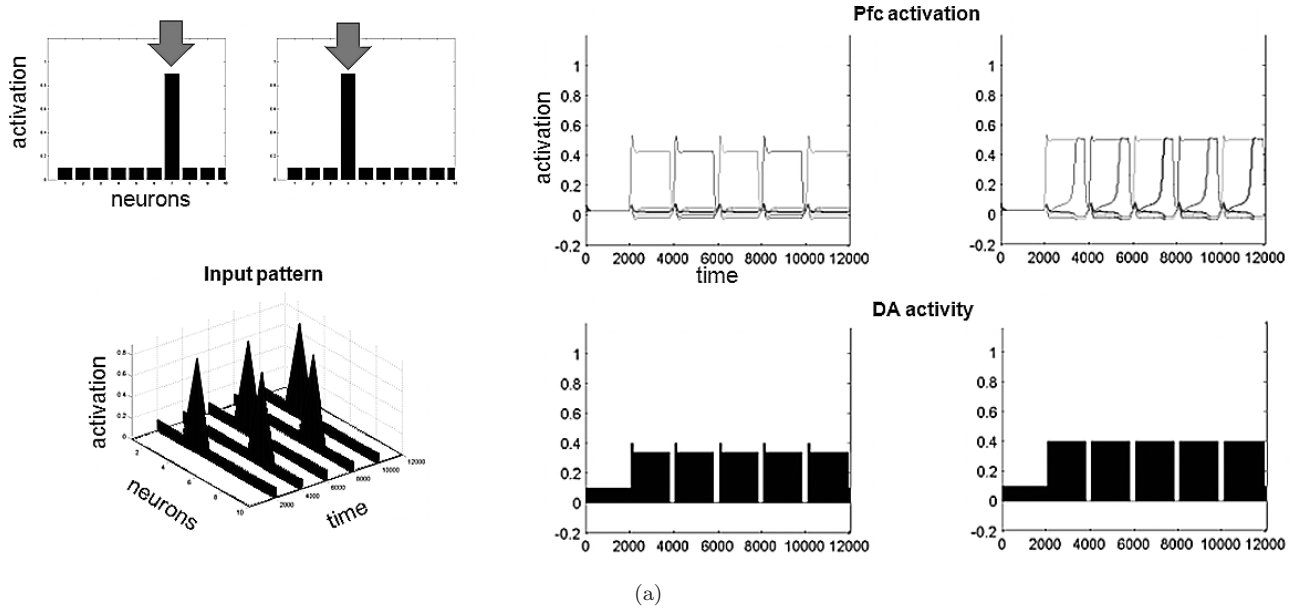
1 msec = 1 time step), while both stimuli are presented for 50 msec. The network is simulated with variable DAergic innervation parameters and in the presence of noise during the active maintenance of WM.

Figure 5 shows the network performance in the Delayed Alternation Task (DaAT). This task, described previously and simulated by Dreher and Burnod,[17] is more demanding than the sWM task. At each moment in time, the subject should alternate between left and right responses in order to obtain a reward. A delay is interposed between the execution of the movement direction that leads to the delivery of the reward, requiring the subject to temporarily store the previous movement in WM throughout the delay in order to execute the correct alternation. The DaAT requires that the input trace, in this simulations a 50 msec activation pattern, should precisely alternate at each trial, and the activation pattern should be prevented from being corrupted or decay throughout the entire duration of the task. Furthermore, the robustness of the WM network has to be tested in the presence of noise during the delay interval, mirroring the fact that although sensory and associative cortical stages which provide input to the Pfc can be continuously updated by new information, the Pfc should preserve important activation patterns even though its distal input changes over time. In the delay interval, the network has to rely exclusively on its reverberatory activity and the DAergic input in order to preserve the activation pattern in WM. Noise consists of 50-msec-bursts of random input ranging from 0 to 0.4 (see figures for details). The injection of noise as input to the network is motivated by the assumption that sensory information is continuously processed by previous cortical stages. This input reaches Pfc and affects its processing via the term $I_i \cdot (1 - DA)$, where $0 \leq I_i \leq 0.4$. The choice of this level of noise, which is smaller than the behaviorally relevant input reaching Pfc, is motivated by the hypothesis that selective attentional mechanisms might operate upstream in brain areas inputting Pfc to help selectively suppress irrelevant sensory information. Other sources of noise, such as internal membrane potential fluctuation, random delays in connectivity, and other forms of variability were not investigated in this study, since the focus of the investigation was to characterize the ability to maintain relevant signals in Pfc in spite of the presence of distracters (noise). Each simulation runs for 12,000 simulated milliseconds, with 5 alternations between left/right responses in each run.

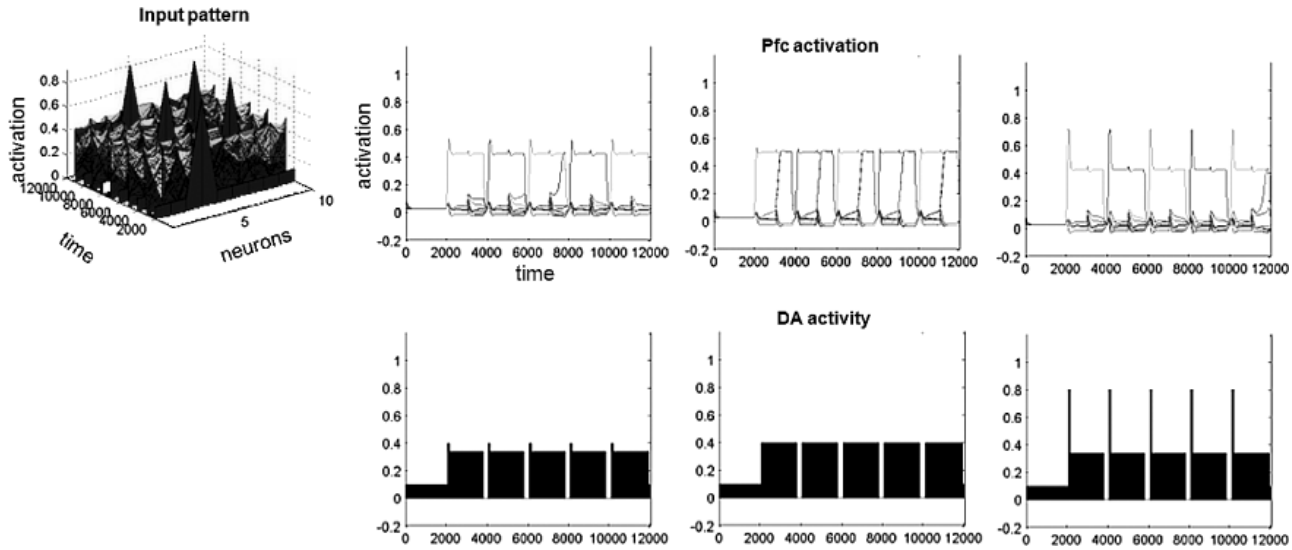
4.1. *The simple working memory task*

The network simulated in this study is designed to implement a competition within the Pfc field due to the choice of the sigmoid feedback function.[33] The optimum activation pattern would consist of one or a limited number of active units (soft winner-take-all behavior) surrounded by a population of inhibited units. Inhibition is mediated by projections from the winning unit(s) to a kernel of interneurons, which in turn inhibit neighboring pyramidal cells. The behavior of each neuron is determined by the equilibrium between its excitatory and inhibitory inputs, the neuron's recurrent signal function, as well by the level of DAergic innervation common to all units. The relationship between the level of DAergic innervation and the behavior of the system is highly nonlinear. Varying the amount of DAergic stimulation, all other things being equal, switches the behavior of the network between a no memory state (no maintenance of WM), a WM state, and a corrupted state (multiple units active in WM). A robust WM storage prevents other stimuli from entering Pfc, preserving the instated WM pattern and preventing interference. Figure 4 summarizes the qualitative behavior of the network for the sWM task. Each plot shows the input pattern, the activation of the field of 10 pyramidal prefrontal neurons for 2000 time steps (top panels), and the related DAergic innervation level (bottom panels). Varying the degree of DAergic input to the field has dramatic consequences on the resultant activation pattern. Low DAergic innervation does not allow the input pattern to be stored in WM (Fig. 4(a), left panels). Intermediate, tonic levels of *DA* allow moderate WM storage (Fig. 4(a), middle panels), whereas higher levels of DA, both phasic and tonic, determine the storage of the pattern (Fig. 4(a), right panels).

Noise can be ignored when DAergic levels are too low (Fig. 4(b), left panels), or determine the corruption of WM when *DA* levels are high enough (Fig. 4(b), middle panels). This effect can be understood in light of the fact that *DA* not only gates external input, but also amplifies recurrent activation (Eq. (4)). High levels of *DA* amplify recurrent



(a)



(b)

Fig. 5. (a) DaAT task. The alternation in the pattern to be stored is achieved by alternating the active Pfc unit (left). Optimal DAergic innervation allows a correct alternation of left/right response (left panels). Notice that two units correctly alternate in the competition for WM storage. Tonic DAergic hyperactivity, as illustrated in the plots immediately below PFC units activation, causes interference in the pattern storage (right panels): in the final 200 msec before the response is generated, one of the units increases its activation and matches the "correct" unit's activation. This can potentially lead to a behavioral error. (b) DaAT task despite the presence of noise. The input pattern is presented on the left inset. Optimal DAergic input allows the correct execution of the task despite the presence of noise (left panels). Notice that an error might occur in the third trial. Tonic DAergic hyperactivity disrupts the performance in the noisy condition (central panels). Tonic and Phasic DA: in a difficult, noisy task, increasing the phasic level of *DA* can be beneficial to the storage of the target in WM (right panels).

activation, and the sigmoid signal function can eventually cause activity of cells with initial small values to grow. Since the DAergic signal varies between 0 and 1, many possible combinations of gating/WM storage are possible, depending also on the balance between excitation and inhibition. A phasic DAergic spike at the beginning of the trial can prevent noise from entering the system (Fig. 4(b), right panels), and thus avoiding the corruption of the relevant WM pattern. Finally, in this task the model shows that a hyper-DAergic state maintains information in WM, but that the maintained patterns are corrupted by spurious neurons interfering with the task-relevant representation. The prediction of an increase Pfc activation in states of hyper-DAergic transmission is consistent with recent neurophysiological data.[4]

4.2. *The delayed alternation task*

In the DaAT (Fig. 5(a)), optimal model behavior can be achieved by a phasic DAergic spike followed by tonic input (Fig. 5(a), left panels), whereas tonic DAergic hyperactivity can cause the corruption of the WM pattern (Fig. 5(a), right panels). The network is robust against noise (Fig. 5(b), left panels), although DAergic tonic hyperactivity would cause noise to corrupt the WM pattern (Fig. 5(b), middle panels). Finally, even in this tonic hyperactive state, DAergic phasic signal can bias the WM pattern, thus preventing noise corruption of the already instated activation (Fig. 5(b), right panels).

In order to quantitatively characterize the goodness of WM storage for any given task and DAergic innervation, the cosine of the angle between the input pattern vector to be stored and the Pfc neurons activation vector after a given delay were calculated. The results, summarized in Table 1, support the qualitative results that can be inferred from the graphs.

Figure 6 illustrates the effect of time jitter in the arrival of the DAergic spike with respect to the arrival of the input stimulation to Pfc in the DaAT task. Simulations show that a variation of $+/-10$ ms and $+/-50$ ms produce no qualitative change in network behavior.

Figure 7 provides a qualitative summary of the main results of the simulations. An inverted U relationship is found between level of DAergic stimulation and the resulting WM storage. Low DA does not allow WM storage, since the term $DA \cdot f(x_i)$ silences the recurrent connections of the network. High DA prevents bottom-up input from previous cortical stages (continuous line) to modify Pfc activation through the term $(1 - DA)$, whereas recurrent connections (dashed line) are amplified through the term $DA \cdot f(x_i)$. This is a high-WM state, in which the input pattern is preserved through time. Excessive DAergic innervation can cause spurious patterns to be formed, e.g., units that should loose the competition with the winning node become active and degrade the WM pattern.

5. Discussion

The model proposed herein begins to address how do organisms store relevant input in working WM, and how WM is protected from and altered by the continuous stream of sensory input and internally

Table 1. Cosine of the angle between input to be stored in WM and Pfc activation vectors for variable DA innervations ($DA = 0.1, 0.5$, and 1 for low, medium and high levels, respectively). High values represent good storage in WM. For the sWM task, the input vector is sampled at time $t = 450$, and the activation of Pfc is sampled at time $t = 1000$. For the DaAT task, the input vector is sampled at time $t = 2000$, and the activation of Pfc is sampled at time $t = 3500$.

Task	Dopamine Level		
	Low	Medium	High
sWM	0.76	0.88	0.73
	Low tonic		High tonic
DaAT (no noise)	0.96		0.64
	Low tonic	High tonic	High tonic + high phasic
DaAT (noise)	0.93	0.64	0.95

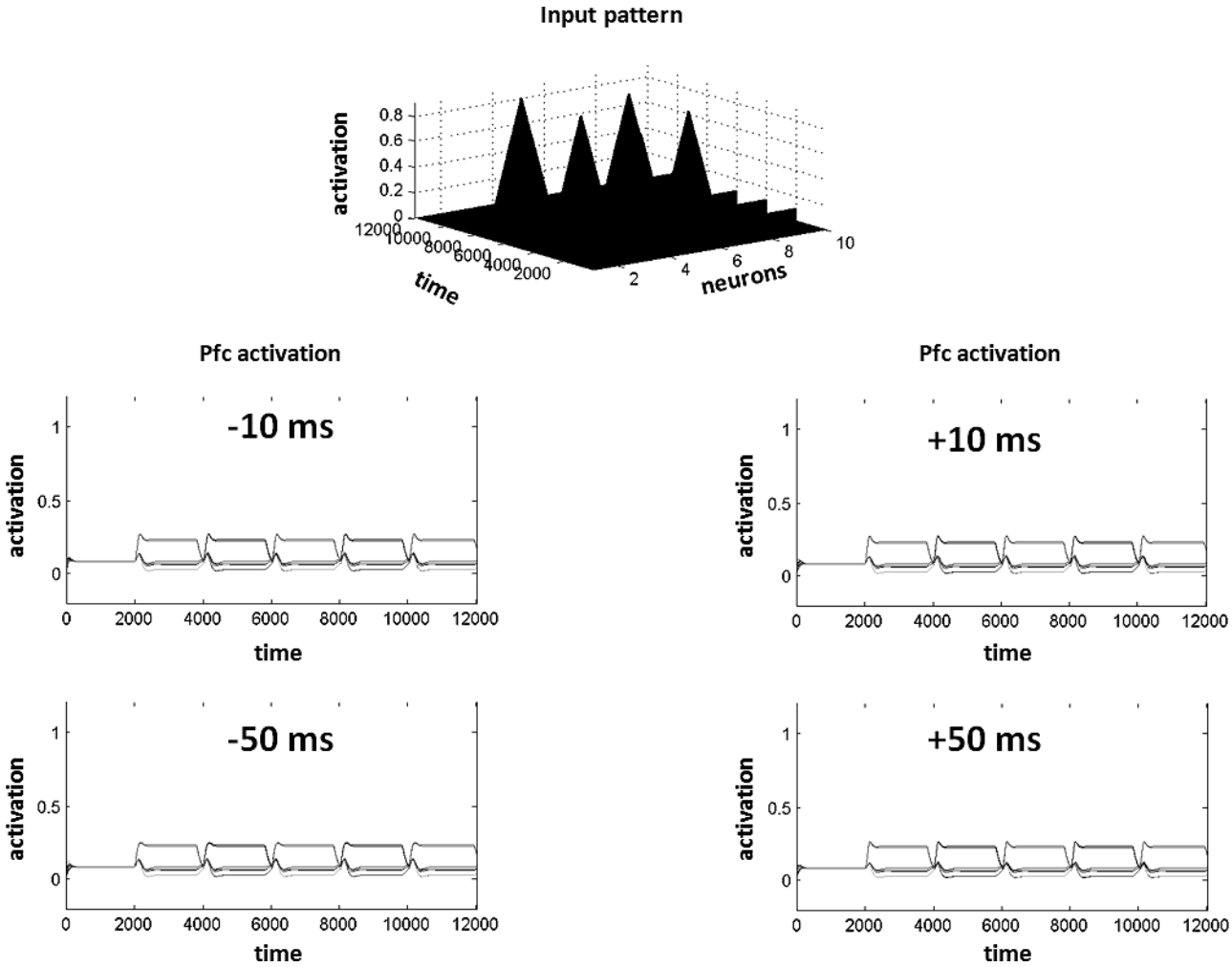


Fig. 6. Effect of time jitter in the arrival of the DAergic input in Pfc during the DaAT task. A jitter of $+/-10$ ms and $+/-50$ ms in the DAergic spike with respect to the arrival time of the input produces no qualitative change in network behavior.

generated planning. The model proposes a mechanistic explanation of the role of *DA* in the maintenance of recurrent activation in simulated Pfc neurons. This effect is achieved by allowing DAergic innervations to simultaneously open the gate in model's recurrent connections, and close the gate in the model's Pfc input pathway. In this sense, *DA* switches the behavior of the network from being input-driven to being internally-driven. The study of a reduced version of the model allows for a direct comparison between the action of *DA* to the choice of the parameters of the signal function $f(x)$. The shape of this function greatly affects the shape of the phase plane describing the behavior of the two-neuron-network, suggesting that neuromodulatory, unspecific input might be able to dynamically switch the behavior of the network from one functional state to the other by acting on the input/output mapping. Such an insight would be difficult to achieve in more complex models,[10,67] in which the core computational properties are overshadowed by the amount of biophysical details incorporated in the model. We argue that the level of abstraction of the present model allows to capture the crucial functional properties of DAergic modulation in Pfc without compromising its biological plausibility.

The results show that the quality of WM storage of an arbitrary input pattern in Pfc is influenced by DAergic innervation, in line with experimental findings.[29] The simulations further suggest that the

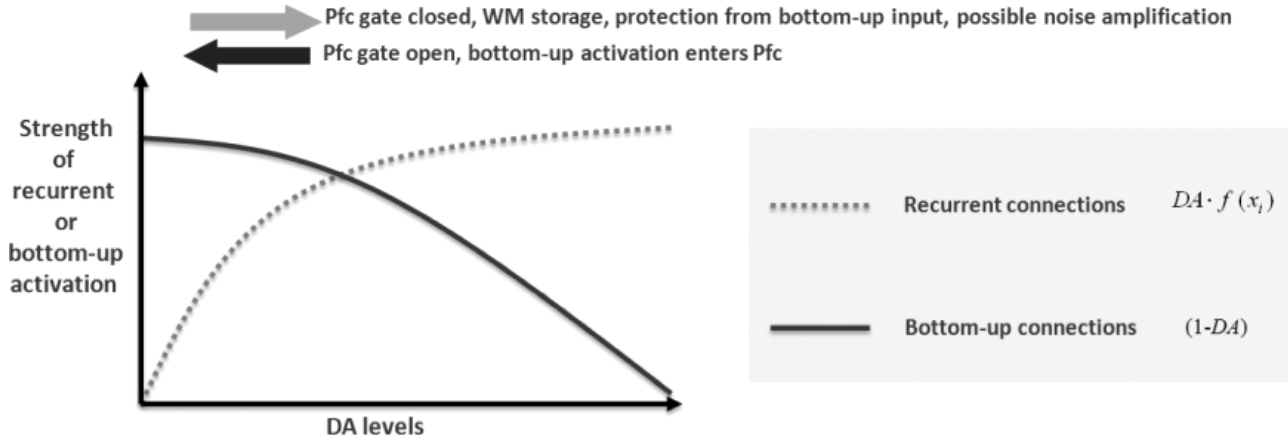


Fig. 7. The DAergic gate has differential modulatory effects on the activation of Pfc pyramidal cells. A DAergic spike prevents bottom-up input from previous cortical stages to modify Pfc activation through the term $(1 - DA)$ (continuous line), whereas recurrent connections are amplified through the term $DA \cdot f(x_i)$ (dashed line). These combined processes have the effect of protecting Pfc from interference and favoring WM storage. The opposite is true at low levels of DAergic stimulation, when the Pfc gate is open and sensory/higher associative information can enter Pfc and can be eventually stored if a DAergic spike occurs. WM is therefore greatly affected by DAergic modulation, and an inverted "U" relationship is found between "goodness" of WM storage and *DA* levels.

DAergic input does not necessarily need to be exactly timed with the input from previous cortical stages, as proposed by Braver and Cohen,[8] but should follow the input from the previous cortical stage. Simulation results show little effect of delaying or anticipating the the phasic DAergic spike with respect to the time of arrival of the input from the previous cortical stage. On the other hand, a precise coincidence of DAergic spike with the external input would *prevent* the WM of a given stimulus to be instated. This is a sharp discrepancy between the present model and the one proposed by Braver and Cohen,[8] since in their model the DAergic spike needs to be exactly timed with the input in order to cause update in WM. This is unlikely to happen as discussed in Dreher and Burnod,[17] because of the delay between the time of VTA activation and DAergic action in Pfc,[56] and the time required to the bottom-up stimulation for reaching the Pfc. In the current model, the DAergic input should follow the pattern to be stored within a few tens or even hundreds of milliseconds, depending on the strength of the input pattern and the DAergic spike, and the presence of noise.

The simulations show that a phasic DAergic spike can boost the relevant information into a maintained state, while a lower tonic level can be enough to keep that information maintained, since associated neural activities are already high, pushing the network into an emergent self-sustaining state while being too low to boost new, distracting information into a maintenance state. If instead of a phasic spike, a higher DAergic level is instated, it will boost intervening distractor inputs into a maintenance state.

An additional result of the present simulations is that tonic DAergic hyper and hypo-activity cause different pattern of impairment in the model WM. DAergic hypoactivity prevents the instantiation of the WM pattern, causing the Pfc field to be driven by external input, and could be considered the network analogue of the increased distractibility shown by patients with a Pfc lesion, in particular the fact that hypofrontal patients are easily distractible by environmental events. On the other hand, DAergic hyperactivity causes a very different pattern of deficits; WM is in fact maintained and activation patterns are formed in WM. Depending on the input pattern, the length of the delay, and the degree of DAergic hyperactivity, the network can show interference of inappropriate (i.e., noise) patterns in WM, or the expression of non-preponderant, or weaker, unit activation due to the amplification of the recurrent activation. This pattern of deficits can therefore be regarded as a candidate biophysical substrate for some of the positive symptoms of schizophrenia, such as odd behaviors, auditory and visual hallucinations,

and others.[38,24] An unbalanced Pfc functioning could prevent filtering out of patterns of activation from lower cortical areas to Pfc that, under normal conditions, would not be able to access higher cortices and control behavior.

In order for the network to alternate between rapidly changing input patterns and responses, as in the DaAT task, a DAergic "pause" was required at the time of the reward delivery in the DaAT. This pause was necessary for the WM pattern to decay and for enabling the new pattern to generate WM activity. DAergic pauses are often present in electrophysiological recordings,[54] but their functional meaning is still under debate. Dopaminergic dips have also been correlated with unpredicted non-occurrence of reward[54] (Waelti *et al.*, 2001). Although recent evidence has linked increased *in vivo DA* efflux in the PFC to accurate recall during a delayed response task,[63,49] no specific study has explicitly investigated the role of *DA* dips in WM. The present model therefore predicts that a DAergic dip should be present in highly demanding tasks in which rapid alternation of responses are required. DAergic dips may therefore be essential in promoting the reset of a WM pattern in a given neural ensemble. Under this interpretation, a DAergic dip can be essential in those situations where the non-occurrence of an expected reward should elicit the disengagement of the behavioral plan that has led to the non-occurrence of reward.

The paper proposes that the main role of *DA* is input specific, increasing recurrent excitation, storage and code sharpening within the Pfc network, while at the same isolating Pfc neurons from the input of previous cortical stages. The effect of *DA* in Pfc neurons are subtle and greatly vary depending on experimental conditions. $D1$ and $D5$ agonists have been shown to suppress Ca^{++} potentials in apical dendrites of Pfc neurons,[64] a mechanism that can decrease the ability of distal, depolarizing currents in generating Ca^{++} spikes in target Pfc neurons. Overall, *DA* agonists have input-specific effect on Pfc neurons. Urban *et al.*[60] has found that stimulation evoked EPSCs are decreased by *DA* release, while paired-cell EPSPs were not. However, more targeted research is needed to effectively isolate the action of *DA* on different input sources (local input within Pfc vs. distal input from other cortical areas) targeting Pfc neurons.

In conclusion, a final consideration concerns the fragility of the brain structures involved in cognitive control. Balancing the level of DAergic stimulation and the various parameters of the network is a demanding task, and is probably among the greatest challenges for the ontogenetic and phylogenetic development of an organism's higher cognitive functions. It is therefore not surprising that Pfc dysfunctions are involved in a variety of neuropsychological deficits. Pfc damage has been associated with increased distractibility and perseveration,[16] and a deficit in Pfc cortex functioning has been correlated with schizophrenia.[29,50] An underactive or impaired Pfc is believed to be responsible for some of the major deficits seen in schizophrenia, such as thought process disturbances.[48,29] The link between an imbalanced DAergic system, a poor Pfc activation and some key symptoms of schizophrenia[29] is one of the major issues in schizophrenia research[44,8,50] (Benes, 1999). Although the present model does not openly address any psychopathological data, several interesting results have emerged. The simulations have shown, in fact, how DAergic hyper and hypo-activity cause different patterns of WM impairment.[38,58] These results are promising, but further work is needed to investigate how imbalances in the system can shape our understanding of psychopathology.

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