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The computational role of dopamine D1 receptors in working memory

Daniel Durstewitz[a,*,1], Jeremy K. Seamans[b,1]

[a]AE Biopsychologie, Facultät für Psychologie, Ruhr-Universität Bochum, GAFO 04/991, D-44780 Bochum, Germany
[b]Neuroscience Institute, Medical University of South Carolina, 173 Ashley Ave, Charleston, SC 29425, USA

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Abstract

The prefrontal cortex (PFC) is essential for working memory, which is the ability to transiently hold and manipulate information necessary for generating forthcoming action. PFC neurons actively encode working memory information via sustained firing patterns. Dopamine via D1 receptors potently modulates sustained activity of PFC neurons and performance in working memory tasks. In vitro patch-clamp data have revealed many different cellular actions of dopamine on PFC neurons and synapses. These effects were simulated using realistic networks of recurrently connected assemblies of PFC neurons. Simulated D1-mediated modulation led to a deepening and widening of the basins of attraction of high (working memory) activity states of the network, while at the same time background activity was depressed. As a result, self-sustained activity was more robust to distracting stimuli and noise. In this manner, D1 receptor stimulation might regulate the extent to which PFC network activity is focused on a particular goal state versus being open to new goals or information unrelated to the current goal.

Keywords: Dopamine; D1 receptor; Prefrontal cortex; Working memory; Persistent activity; Biophysical model; NMDA; Phase space analysis

1. The prefrontal cortex and working memory

The prefrontal cortex (PFC) is critically involved in the ability to integrate previously acquired information with recent sensory input to guide action according to a goal state (Fuster, 1997; Goldman-Rakic, 1996). Such processes have been termed working memory and allow forthcoming actions to be planned in a contextually relevant and flexible manner. In animal experiments, working memory is often invoked by introducing a delay between the presentation of a relevant stimulus and a choice period. The task can only be accomplished by keeping the earlier shown stimulus (or the anticipated response) in (working) memory as this information is needed in order to correctly respond in the subsequent choice situation after the delay. Neurons in the PFC are thought to actively retain an internal representation of goal-related information throughout this delay period via sustained elevated firing rates, while exhibiting low spontaneous firing when not in a task-context (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster, 1973; Fuster, Bauer, & Jervey, 1985; Kubota & Niki, 1971; Miller, Erickson, & Desimone, 1996; Rainer, Rao, & Miller, 1999; Rosenkilde, Bauer, & Fuster, 1981; Sawaguchi, Matsumura, & Kubota, 1990a). Although initiated and modulated by external inputs, delay-period activity may be maintained by mechanisms intrinsic to the PFC (Goldman-Rakic, 1996)—however, the exact cellular and network mechanisms underlying this maintenance are still unknown (Durstewitz, Seamans, & Sejnowski, 2000b; Tanaka & Yoshida, 2001; Wang, 2001).

2. Dopaminergic modulation of prefrontal neurons and working memory

One important source of extrinsic modulation in the PFC is via dopamine. Dopaminergic input to the PFC originates from a small group of mesencephalic neurons (in the ventral tegmentum and substantia nigra) that projects to various cortical areas, flooding them with dopamine in a diffuse manner (Cass & Gerhardt, 1995; Garris, Collins, Jones, & Wightman, 1993; Wightman & Zimmerman, 1990). Dopamine levels in the PFC specifically rise during working memory tasks (Watanabe, Kodama, & Hikosaka, 1997) and dopaminergic midbrain neurons phasically fire at the onset of such tasks (Schultz, 1998; Schultz, Apicella, &

* Corresponding author. Tel.: +49-234-32-22673; fax: +49-234-32-14377.
E-mail address: Daniel.Durstewitz@ruhr-uni-bochum.de (D. Durstewitz).
[1] Both authors contributed equally to the ideas put forward in this paper.

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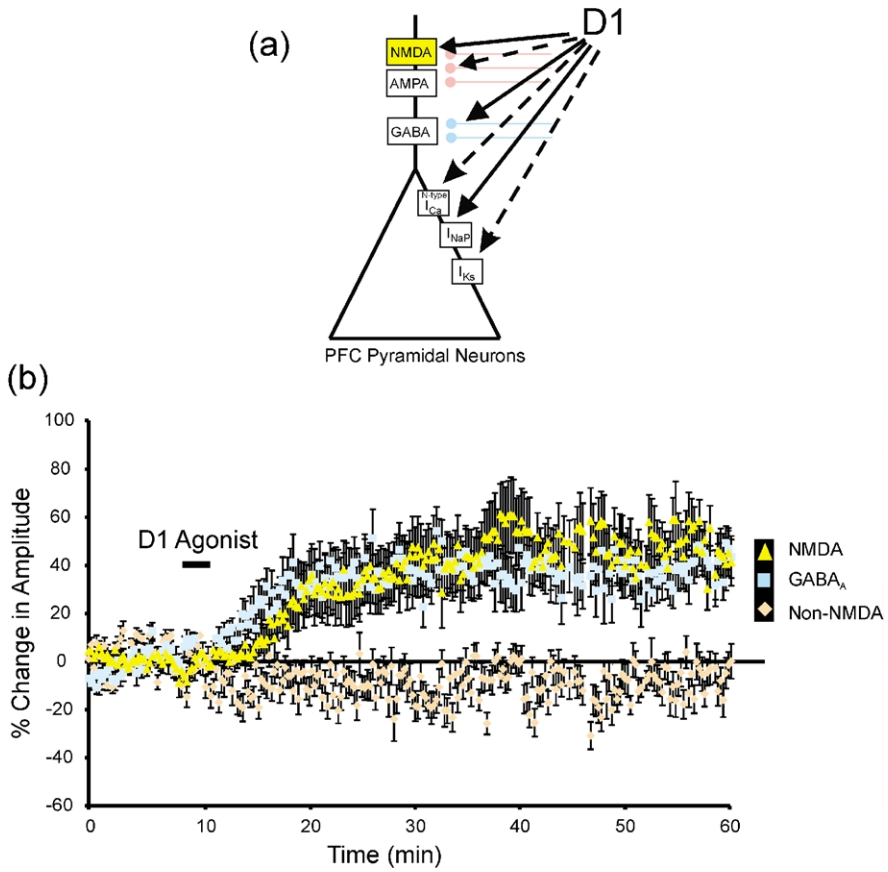


Fig. 1. Schematic summary of known D1 receptor dependent modulation of PFC pyramidal neurons. (a) D1 agonists increase (solid lines) NMDA currents (yellow), IPSCs through an increase in interneuron axonal excitability (blue), and the persistent Na^+ current in deep layer PFC pyramidal neurons. D1 agonists simultaneously decrease (dashed lines) non-NMDA/AMPA EPSCs by reducing glutamate release probability (pink), N-type Ca^{2+} currents, and the slowly inactivating K^+ current. (b) The modulation of synaptic currents is both delayed (possibly due to the slow diffusion of bath-applied D1-agonists within the slice) and long lasting. Group data ($n = 8–10$ neurons/group) showing the mean (and SEM) change in the amplitude of pharmacologically isolated NMDA (yellow triangles), GABA (blue squares) and AMPA (pink diamonds) currents evoked by an extracellular stimulation electrode placed next to layer V PFC neurons recorded using whole-cell patch-clamp techniques in brain slices of the prelimbic region of the rat PFC (for details see Seamans et al., 2001a,b).

Ljungberg, 1993). Blockade of dopaminergic inputs to PFC or D1 receptors locally within the PFC interferes with performance in working memory tasks (Sawaguchi & Goldman-Rakic, 1994; Seamans, Floresco, & Phillips, 1998), while dopaminergic agonists applied locally increase the sustained (task-related) firing activity of PFC neurons encoding both mnemonic information and responses (Sawaguchi, 2001; Sawaguchi, Matsumura, & Kubota, 1986, 1988; Sawaguchi et al., 1990a; Sawaguchi, Matsumura, & Kubota, 1990b); however, the specifics of this modulation are complex (Williams & Goldman-Rakic, 1995). Cognitive (attentional and working memory) deficits in schizophrenic and Parkinson patients have also been linked to dopaminergic malfunction in the PFC (Cools, Barker, Sahakian, & Robbins, 2001; Goldman-Rakic, 1999). In general, D1 but not D2 receptor activation seems to be required for optimal working memory performance (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Müller, von Cramon, & Pollmann, 1998; Sawaguchi & Goldman-Rakic, 1994; Zahrt, Taylor, Mathew, & Arnsten, 1997; but see Luciana, Collins, & Depue, 1998). Understanding the D1-mediated regulation of PFC neurons will therefore provide important insights into the cellular basis of working memory.

On a cellular level, dopamine has many effects on voltage-gated and synaptic currents in PFC neurons (Fig. 1(a)). Acting via D1 receptors, dopamine enhances a persistent Na^+ current (I_{NaP}; but see Maurice, Tkatch, Meisler, Sprunger, & Surmeier, 2001) while reducing a slowly-inactivating, voltage-gated K^+ (I_{KS}) current in intact deep layer PFC neurons in brain slices, thus enhancing cell excitability (Gorelova & Yang, 2000; Henze, Gonzalez-Burgos, Urban, Lewis, & Barrionuevo, 2000; Shi, Smith, Pun, Millet, & Bunney, 1997; Yang & Seamans, 1996; see Hille, 2001 for an overview of voltage-gated ion channels). It furthermore differentially affects various high-voltage-activated Ca^{2+} channels, producing a reduction in N-type currents (Yang & Seamans, 1996). Dopamine via D1 receptors has also a major impact on all main classes of synaptic currents, enhancing both (excitatory) NMDA and (inhibitory) $GABA_A$ currents through various biophysical mechanisms, while slightly reducing (excitatory) AMPA-mediated responses (Fig. 1(b); Gao, Krimer, &

Goldman-Rakic, 2001; Kita, Oda, & Murase, 1999; Seamans, Durstewitz, Christie, Stevens, & Sejnowski, 2001a; Seamans, Gorelova, Durstewitz, & Yang, 2001b; Wang & O'Donnell, 2001; Zheng, Zhang, Bunney, & Shi, 1999; Zhou & Hablitz, 1999). It should be noted that the cellular effects of dopamine might be different in other brain structures like hippocampus or striatum with different network architectures, neuron types, and functional requirements (e.g. Flores-Hernandez et al., 2000).

The cellular effects of D1 receptor stimulation in PFC neurons appear to persist for many minutes after washout, as evident from Fig. 1(b). Thus, the phasic burst by dopaminergic midbrain neurons at the onset of working memory tasks (Schultz, 1998; Schultz et al., 1993) may be sufficient to alter currents in PFC neurons during the entire task period. Such a persistent action outlasting the brief period of D1 receptor activation might be due to a dopamine-regulated protein like DARPP-32 moving into a (phosphorylated) up-state that is sustained through intracellular protein network interactions (Bhalla & Iyengar, 1999; Nishi, Snyder, & Greengard, 1997). The long-term effects of dopamine in vitro mirror the slow and prolonged temporal pattern of dopamine release recorded in PFC during working memory tasks and other behaviors (Ahn, Floresco, & Phillips, 2000; Feenstra & Botterblom, 1996; Feenstra, Botterblom, & Mastenbroek, 2000; Feenstra, Botterblom, & van Uum, 1995; Watanabe et al., 1997).

How can we make sense of all the different effects induced by dopamine observed in vitro, and how do these changes in biophysical parameters of prefrontal neurons and synapses relate to network dynamics and working memory function? On one hand, the commonly employed extracellular recording techniques in behaving animals currently preclude detailed cellular analyses. On the other hand, self-sustained activity comparable to that recorded in vivo is not observed in reduced systems such as rat or primate PFC slices. Given the complex non-linear nature of self-sustained delay-period activity and the lack of a suitable reduced preparation, the best current technique to pursue these questions is computational modeling. We argue that the prolonged extrasynaptic levels of DA and the prolonged postsynaptic effects mediated via D1 receptors exert a sustained 'processing tone' in PFC networks, the details of which are described later.

3. Computational analysis of dopamine action in prefrontal cortex

To assess the impact of dopamine on neural network dynamics, a series of PFC network models with varying levels of abstractness were developed (Durstewitz, Kelc, & Güntürkün, 1999; Durstewitz, Seamans, & Sejnowski, 2000a). The basic idea underlying this approach was to start with a model that captured essential electrophysiological characteristics of neural networks probed in behaving monkeys during the performance of working memory tasks and that implemented basic biophysical properties of PFC neurons derived from in vitro patch-clamp recordings. Having tuned the models to exhibit in vivo-like behavior and activity profiles observed during working memory performance, the functional changes in network dynamics induced by dopamine modulation as determined from in vitro experiments (Fig. 1) were studied. The models were detailed enough to allow for realistic implementation of the physiological effects of dopamine including changes in ion channel conductance strengths or kinetics. In this way the models bridged the gap from detailed cellular properties obtained from in vitro studies while exhibiting the properties of self-sustained activity observed during working memory tasks.

3.1. Model architecture

Excitatory pyramidal cells and inhibitory interneurons were modeled as multiple or single compartments equipped with Hodgkin-Huxley-like channel kinetics (see legend of Fig. 2 and Durstewitz et al., 2000a, for more detailed specifications). These were connected into a PFC network model as depicted in Fig. 2. Cell assemblies were embedded in a network of reciprocally interconnected pyramidal cells by setting the synaptic weights (maximum conductance strengths) between neurons within an assembly particularly high relative to the connections to pyramidal neurons outside the assembly, similar to the 'synaptic' arrangement in an attractor neural network (Amit & Brunel, 1995; Hopfield, 1982). Assemblies were allowed to partially overlap, i.e. to 'share' neurons. Excitatory synapses made between pyramidal cells and from pyramidal cells to interneurons had both AMPA- and NMDA-like conductances (see legend of Fig. 2).

In these models, cell assemblies established the anatomical basis for stimulus-specific persistent activity through recurrent excitation. That is, the weights within an assembly were set high enough to allow maintenance of recurrent activity once neurons within that assembly were stimulated above a certain threshold. NMDA conductances, which might contribute more than 60% of the total charge delivered by excitatory synapses (Spruston, Jonas, & Sakmann, 1995), due to their long offset time constant helped to provide the sustained synaptic drive required to maintain persistent activity at reasonable firing rates (Durstewitz et al., 2000a; Wang, 1999). Note that for the purpose of studying the role of D1 receptors in regulating sustained activity underlying working memory, we were not interested in the actual process of learning such internal representations by cell assemblies. Rather, as a starting point for these studies, the experimental phase was simulated where animals were already familiar with the stimuli and/or had learned the appropriate stimulus-response-relationships.

To ensure stimulus-specificity and prevent uncontrolled

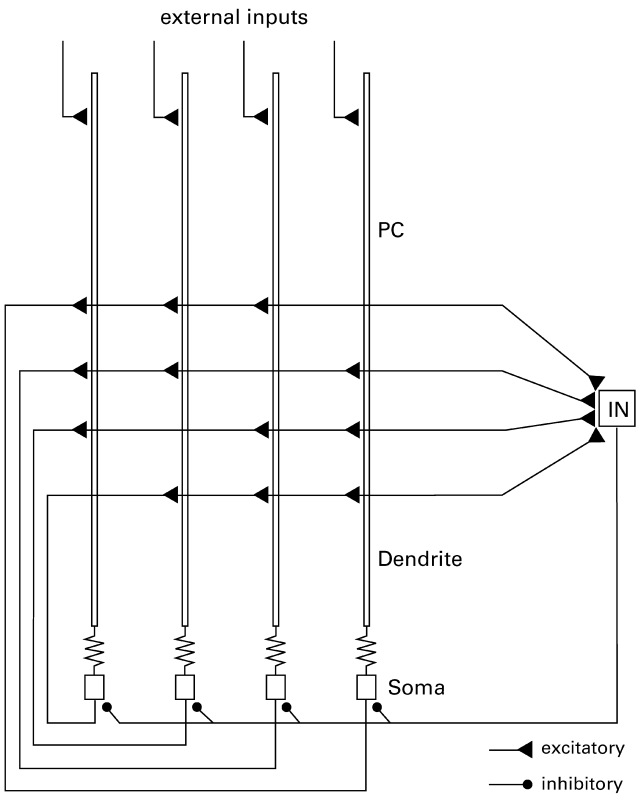


Fig. 2. Anatomy and biophysical properties of the PFC network model. The model network used for the simulations in Fig. 3 consisted of 100 pyramidal cells (PC) and 37 interneurons (IN) which provided feedback inhibition as described in the text. Single pyramidal cells were modeled as a cylindrical dendritic (D) compartment ($l = 650$ μm, $d = 6.5$ μm) connected to a soma (S) compartment ($l = 28.62$ μm, $d = 21.84$ μm). Passive properties were $R_m = 30$ kΩ cm^2, $E_{leak} = -70$ mV, $C_m = 1.2$ μF/cm^2, $R_i = 150$ Ω cm, where R_m was divided by 1.92 and C_m multiplied by 1.92 for the dendritic compartment to account for spines. Ionic conductances included were I_{Na} (densities in mS/cm^2, S: 117, D: 20), I_{NaP} (S: 1.8, D: 0.8), I_{DR} (S: 50, D: 14), I_{KS} (S and D: 0.08), I_C (S and D: 2.1), I_{HVA} (S: 0.4, D: 0.8). Conductance kinetics as well as Ca^{2+} and K^+ dynamics and reversal potentials were all the same as described in Durstewitz et al. (2000a), except for I_{HVA} inactivation was sped up by a factor of 3, I_{KS} inactivation time constant was $\tau_{KS} = 200 + 220/[1 + \exp(-(V_m + 71.6)/6.85)]$, and Ca^{2+} accumulation factors were set to 600×10^{-9}. The interneuron consisted of a single compartment ($d = l = 42$ μm) with the same passive properties as S and equipped with I_{Na} (45 mS/cm^2) and I_{DR} (18 mS/cm^2). Conductance kinetics were the same as for the pyramidal cell but all shifted 10 mV hyperpolarized, except for β-rate of I_{Na} activation which was shifted by 12 mV, and I_{Na} inactivation sped up by a factor of 2. Recurrent network connections had an axonal delay of 1.1 ms and were all modeled according to double exponential functions as given in Durstewitz et al. (2000a), with time constants (in ms) and reversal potentials: g_{AMPA} ($\tau_1 = 0.2$, $\tau_2 = 1$, 0 mV), g_{NMDA} ($\tau_1 = 2.3$, $\tau_2 = 95$, 0 mV), g_{GABAA} ($\tau_1 = 0.5$, $\tau_2 = 5$, −75 mV). For pyramidal cells, excitatory connections were confined to dendritic compartments whereas inhibitory synapses terminated on both soma and dendrite. Maximum conductance strengths for pyramidal cells were (in nS): AMPA (3, dopamine: 2.55), NMDA (0.06, dopamine: 0.0834), $GABA_A$ (0.2, dopamine: 0.28); for interneurons: AMPA (0.74), NMDA (0.0148), $GABA_A$ (0.6). NMDA conductances included a voltage-dependence to simulate the voltage-dependent Mg^{2+}-block as described in Durstewitz et al. (2000a). Background inputs consisted of independent Poisson processes (updated every 1.5 ms) with rates 20 kHz for excitatory inputs to pyramidal cells (corresponding to, e.g. 4000 input neurons firing at an average rate of 5 Hz), 13.125 kHz for inhibitory inputs to pyramidal cells, and half these values for likewise inputs to interneurons. Maximum conductances of these inputs were for pyramidal cells (in nS): AMPA (1, dopamine: 0.85), NMDA (0.02, dopamine: 0.0278), $GABA_A$ (0.6, dopamine: 0.84); for interneurons: AMPA (0.74), NMDA (0.0148), $GABA_A$ (0.6).

spreading of excitation throughout the entire network, a population of interneurons was included that received input from all pyramidal cells and provided feedback inhibition via $GABA_A$-like synaptic conductances. The monotonic increase of GABAergic inhibitory activity with the number of activated pyramidal cells effectively prevented more than one cell assembly from becoming active at a time (Amit & Brunel, 1995; Durstewitz et al., 1999, 2000a). Thus, similar to the tuning of visual receptive fields in V1, GABAergic neurons tune working memory fields in PFC (Rao, Williams, & Goldman-Rakic, 1999).

Neurons in the network also received two sorts of inputs from external sources (Durstewitz et al., 2000a): (1) Afferents conveying stimulus information, loosely representing inputs to PFC from higher order association areas (Chafee & Goldman-Rakic, 2000). Using these input lines, stimuli could be presented to the network by synaptically activating subgroups of neurons. Like the recurrent excitatory network connections, these afferents activated both AMPA- and NMDA-like conductances. (2) Random inputs from a population of excitatory and inhibitory presynaptic neurons simulated by Poisson processes activating AMPA + NMDA-like, or $GABA_A$-like synapses. These inputs were meant to represent background inputs from various cortical and subcortical sources, and served to induce spontaneous activity in the network with firing rates of 0.5–3 Hz approximating those observed in the PFC in vivo during task-unrelated periods (Fuster, 1973; Fuster et al., 1985; Rosenkilde et al., 1981; Sawaguchi et al., 1990a).

3.2. Dopaminergic modulation of network dynamics

The model networks exhibited two basic activity modes corresponding to the in vivo situation: uniform low spontaneous activity in the absence of any working memory content, and stimulus-selective high persistent activity reflecting the active (online) maintenance of a stimulus representation (Fig. 3(a); Amit & Brunel, 1997; Durstewitz et al., 2000a). Persistent high activity within a cell assembly is assumed to constitute the active representation (working memory) of a previously presented stimulus or a forthcoming response, as opposed to the passive long-term storage of the same stimulus/response within the synaptic connection matrix. Switching between the low (spontaneous) stable state and one of the stable persistent high states of the network can be induced by brief stimulation of excitatory or, respectively, inhibitory afferents (or by direct current injection)—that is, the network exhibits hysteresis as required for working memory by staying in the state

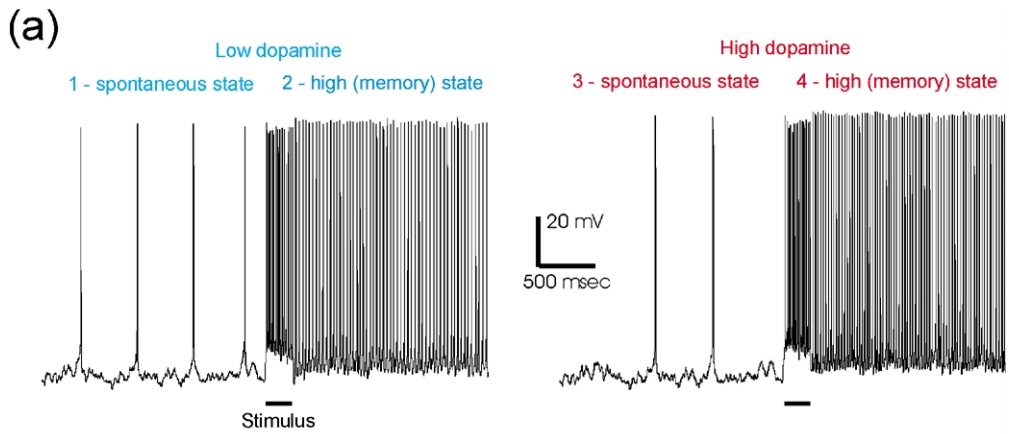
induced by the brief stimulation (Fig. 3(a)). The low spontaneous activity state might enable the network to respond faster to incoming stimuli, establishing a kind of 'ready-state' (Amit & Brunel, 1997; van Vreeswijk & Sompolinsky, 1996).

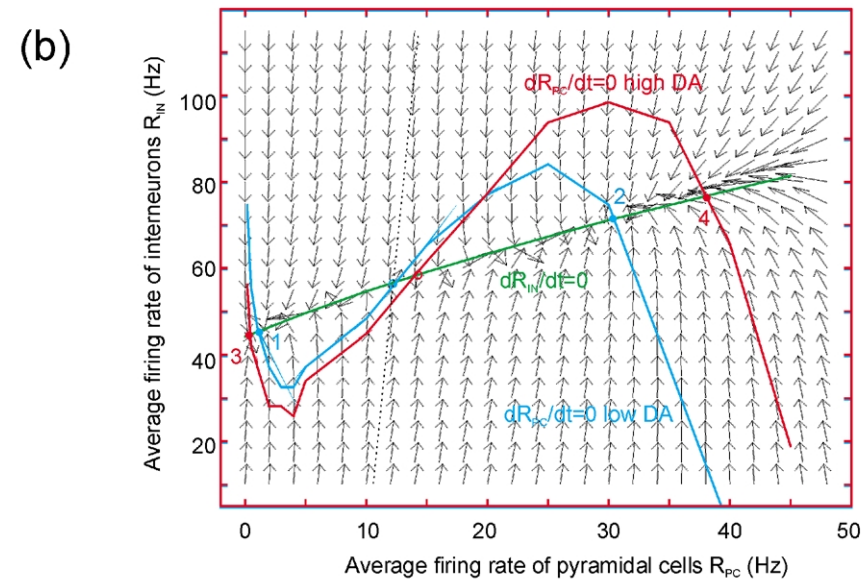
Fig. 3(a) shows that simulated D1 receptor activation has differential effects on spontaneous and high activity states in the network: Persistent high activity states as evoked by brief stimulation of a cell assembly are enhanced, whereas spontaneous activity is depressed. For clarity, in the simulations shown in Fig. 3 only the known effects of D1 receptor activation on synaptic currents in pyramidal cells were taken into account: Specifically, NMDA and $GABA_A$ conductances were increased by about 40% in Fig. 3(a) (right hand side) while AMPA conductances were reduced by 15%. Essentially the same results could be obtained when dopaminergic modulation of intrinsic voltage-gated currents were also implemented in simulations (Durstewitz et al., 1999, 2000a).

More information about the D1-mediated effects on network dynamics might be obtained by drawing a two-dimensional projection of the state space of the system as in Fig. 3(b). The space is spanned by the average firing rates of the inhibitory interneurons and the pyramidal cells of one cell assembly. Nullclines for pyramidal cells were numerically computed by isolating a single pyramidal cell from the network, replacing the rest of the network by an equivalent number of input lines whose rates could be controlled, fixing the rate of the excitatory input lines (which mimic the network population of presynaptic pyramidal cells) at a particular value, and varying the rate of the inhibitory input lines systematically until the average pyramidal cell input rate to the isolated pyramidal neuron matched its steady-state average output rate. In other words, the synaptic feedback loops of the network were disrupted and replaced by controllable inputs, and the output was read off when the steady state was reached. The nullcline for the inhibitory population and flow vectors were obtained in a similar way. In interpreting such a graph one should keep in mind that in general a steady-state output rate might not necessarily be reached (there could be oscillations) and the flow at a particular point in the firing rate state space is not necessarily uniquely determined (there could be—although unlikely for the present system—more than one steady-state associated with a given pair of inputs). Moreover, there can be long-lasting transients, e.g. due to I_{NaP} inactivation, such that trajectories of the full system will depend on the state of I_{NaP} inactivation and will not tightly follow the flow depicted in the steady state graph. Finally, all dynamical properties due to the precise relation of spiking times between different neurons are ignored—however, the strength and variance of the (independent) random background inputs to the network neurons (as well as NMDA currents, see later) were so high that their firing was largely uncorrelated, and therefore this kind of mean-field approximation used in constructing the graph should be valid. (It might be important to point out, however, that largely uncorrelated activity just favors this type of analysis while correlated neural activity could still be consistent with the dopamine results reported later.) Despite these limitations, the reduced phase portrait can provide valuable insights into the functioning of the system.

Fig. 3(b) shows that the system has three fixed points in terms of firing rates, the lower and upper ones being stable (attractors), separated by an unstable node whose stable manifold divides the plane into two basins of attraction. The lower and upper fixed points correspond to the low spontaneous and persistent high activity states shown in Fig. 3(a), with the firing rates as indicated by the crossings of the nullclines agreeing reasonably well with those obtained in full network simulations. The stability of the upper fixed point depends, besides other factors, on the g_{AMPA}/g_{NMDA} ratio and on firing synchrony. If the g_{AMPA}/g_{NMDA} ratio is high, i.e. if the excitatory feedback is dominated by brief-duration currents, neurons tend to synchronize which could cause oscillations around the upper fixed point (Compte, Brunel, Goldman-Rakic, & Wang, 2000; Koulakov, 2001; Wang, 1999). The stronger these oscillations that bring the system periodically closer to the border of the basin of attraction of the lower fixed point, the higher the probability that persistent activity breaks down. Even in the absence of oscillations in firing rates, spiking-time synchrony will cause large fluctuations in recurrent excitation that might move the network out of the high state (Gutkin, Laing, Colby, Chow, & Ermentrout, 2001; Koulakov, 2001).

Changing synaptic strengths of AMPA, NMDA, and $GABA_A$ conductances in pyramidal cells in accordance with D1 mediated effects measured in vitro (Fig. 1) results in a change of the nullcline of the pyramidal cells. Note the stable lower and upper fixed points are pushed further apart along the interneuron nullcline by simulated D1 mediated effects, recapitulating the differential effect of D1 receptors on spontaneous and persistent states shown in Fig. 3(a). In addition, the deeper trough of the pyramidal cell nullcline within the low state basin of attraction indicates that in general less firing of inhibitory interneurons is required to keep the network in the spontaneous state (passing from the low to the high state the system will in general move through a region close to the inhibitory nullcline where the force pushing the system back to the low state attractor is larger in the high versus the low dopamine condition). On the other hand, the higher peak of the pyramidal cell nullcline within the high state basin of attraction indicates that higher rates of inhibitory interneuron firing are required to move the system out of the high state regime. Hence, dopamine via D1 receptors might widen and deepen the basins of attraction of low (spontaneous) and high (working memory) states of the network, making it more difficult to switch between different activity states. Note that this could be the case even if there were *no* changes in average firing rate associated with dopamine action—the deepening of the





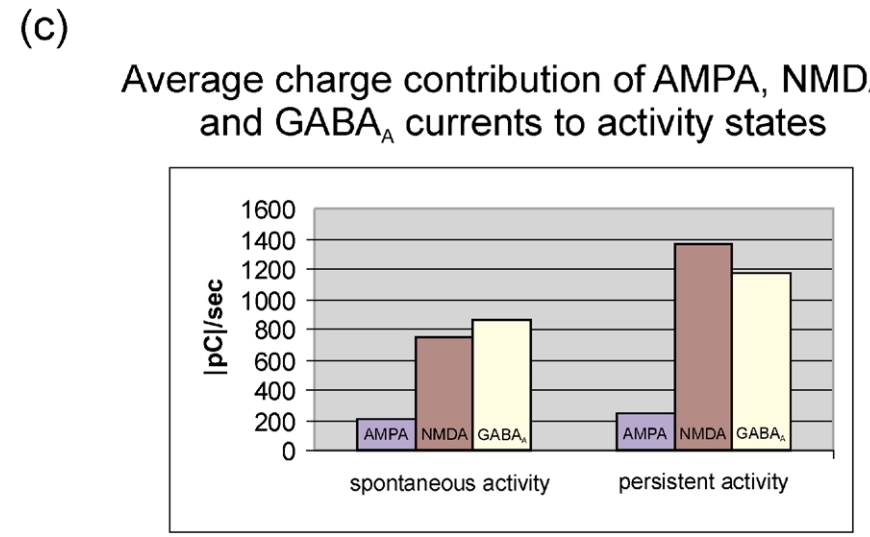


Fig. 3. Differential modulation of low and high activity states by dopamine. (For the purpose of these simulations, all 100 pyramidal cells were connected within one cell assembly, but see Durstewitz et al., 2000a). (a) The network exhibits low spontaneous and high persistent activity states that can be induced by brief stimulation. A simulation of D1-mediated effects on synaptic conductances (right hand side) leads to a suppression of low and an enhancement of high activity states. (b) Reduced phase portrait of the model system showing the nullclines and flow field of the firing rates of the pyramidal cells (blue) and interneurons (green) for the low dopamine condition (see text). In addition, the change in pyramidal cell-nullcline according to D1 receptor activation (red) is

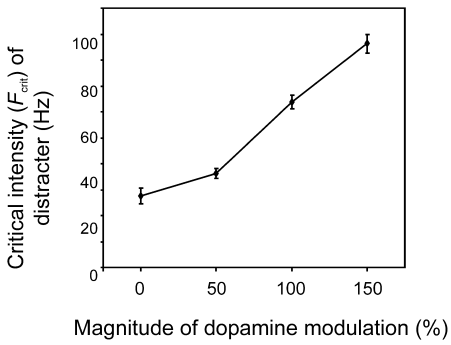


Fig. 4. The robustness of an active working memory representation increases with the amount of dopamine modulation, as assessed by the minimal afferent stimulation frequency (F_{crit}) of a distracter pattern that is required to disrupt the target pattern. The percentage change in dopamine-modulated parameters refers to baseline values measured in vitro (for more details see Durstewitz et al., 2000a). Reproduced from Durstewitz et al. (2000a) with permission. Axis labels were modified.

basins of attraction as witnessed by the deeper trough and higher peak of the pyramidal cell nullcline alone are sufficient to make switching between attractor states harder. This point has to be emphasized as it has important implications for the interpretation of in vivo physiology: Even in the absence of any observable effect on firing rates, a neuromodulator like dopamine can fundamentally alter the functioning of the network. This insight derived from computational modeling would be difficult to stumble upon using solely in vivo extracellular recording techniques.

How can the differential effect of D1 receptor activation on spontaneous and persistent activity states be explained? Fig. 3(c) plots the (absolute) average charge contributed by AMPA, NMDA, and $GABA_A$ synaptic currents in the spontaneous and persistent activity state. Whereas $GABA_A$ currents contribute more absolute charge than NMDA currents in the low state, this relationship reverses in the high state. Hence, because D1 receptor activation enhances both these currents by about the same amount there will be differential effects on low and high states. NMDA currents surpass $GABA_A$ currents when switching from the low to high states because: (1) During high states recurrent activity strongly increases relative to background activity, with a larger recurrent excitatory than feedback inhibitory component in foreground neurons. (2) As the dendrites of pyramidal cells settle at a higher average membrane voltage in the high state (Fig. 3(a)), NMDA conductances due to their voltage-dependence experience a non-linear boost. In contrast, AMPA and $GABA_A$ conductances are not voltage-dependent and hence are not affected by the increase in membrane potential.

Two qualifying statements have to be made at this point. First, especially during spontaneous activity the variance of synaptic input in addition to its mean plays a major role for spiking activity—hence the simple explanation given above is only approximate as it does not take into account the full complexity of the situation. Second, a deepening of the basins of attraction of both the high working memory states as well as the low spontaneous state requires the right (sensitive) balance in the magnitudes of D1-mediated parameter changes: if, for instance, the NMDA relative to the $GABA_A$ conductance change is too high or too low, the dopamine-modulated pyramidal cell-nullcline will shift upwards or downwards, enhancing one basin of attraction while reducing the other (yet, importantly, the pyramidal cell-nullcline would still expand along the vertical (R_{IN}) dimension in Fig. 3(b), for the reasons mentioned above). Ultimately, whether dopamine achieves this balance will of course be an experimental question, but the experimental evidence reviewed below favors the interpretation that dopamine-mediated changes might be within the right regime.

What might be the functional implications of the D1-induced changes in PFC attractor landscapes? On one hand, because D1 receptor actions make it harder to push the network from the spontaneous activity state to one of the working memory persistent states for the parameter settings illustrated in Fig. 3(b), the overlap of a pattern presented to the network with one of the patterns stored in the synaptic weight matrix will have to be higher to induce the high state. Thus, the criterion of the network for recognition of a stimulus pattern becomes stricter. More importantly, once a prefrontal network is in a persistent activity state, it becomes much harder to interrupt this maintained activity by interfering stimuli or noise (Brunel & Wang, 2001; Durstewitz et al., 1999, 2000a). This is shown in Fig. 4 where the robustness of the working memory state is plotted against the magnitude of change in D1-dependent parameters. Thus, under D1 receptor activation the network becomes more resistant to distracters. For this to occur, it is not necessary that both, the low and the high basins of attraction, will be deepened and/or widened as in Fig. 3(b) as long as the overall effect produced by dopamine is an increase in the 'energy barrier' between different working memory states.

It might also be interesting to note that dopamine's effects on synaptic currents are such (as reviewed in Wilson, 1999, Chapter 12; see also Compte et al., 2000) that they should favor desynchronization of network activity which could furthermore enhance robustness (Gutkin et al., 2001;

shown: the fixed point corresponding to the stable low and high activity states are pushed further apart and their basins of attraction become steeper (note that the flow of the pyramidal cells tends to the right below the blue nullcline and to the left above their nullcline—although this is not readily apparent from the figure as the derivative of interneuron rates is much higher except for regions close to the interneuron nullcline). Vectors were normalized to unity length to better indicate the direction of flow close to the nullclines. The dotted line indicates the approximate location of the stable manifold of the saddle node that separates the basins of attraction. (c) Total absolute charge contribution of AMPA, NMDA, and $GABA_A$ currents in low and high activity states. The relative contribution of NMDA and $GABA_A$ currents reverses when going from the low to the high state, forming one basis for the differential dopamine effect.

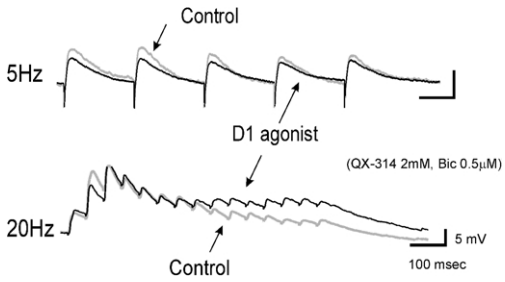


Fig. 5. D1 receptor stimulation differentially regulates responses to excitatory synaptic inputs at different frequencies. (Top) Extracellular stimulation at 5 Hz evoked EPSPs that did not summate in a layer V PFC neuron in vitro (gray trace). Giving the same 5 Hz train following D1 agonist (SKF81297, 10 μM) application caused all EPSPs in the train to be relatively reduced. (Bottom) In a different layer V PFC neuron, with 20 Hz stimulation EPSPs summated since there was insufficient time between inputs to allow for repolarization (gray trace). When repeated after application of a D1 agonist, the same 20 Hz stimulation depressed early responses but evoked a greater response to pulses 10–15 in the train (black trace). Previously we have shown that this pattern is due to a D1 mediated decrease in release probability coupled with an increase in NMDA currents that become relevant during summation of EPSPs. For details see Seamans et al. (2001a).

Koulakov, 2001). Resistance to distracters is highly important in the context of working memory which is assumed to underlie goal-directed behavior, since pursuing goals over longer periods of time becomes impossible if any arbitrary distracting stimulus or behavioral tendency overrides the present contents of working memory. Again, this increase in robustness of working memory representations might in principle be achieved independently from a change in firing rates, simply by modulating the steepness of the basins of attraction. Brunel and Wang (2001) reached similar conclusions as reported here and in Durstewitz et al. (1999, 2000a) through both numerical simulations and analysis of the mean-field equations of a large network of leaky-integrate-and-fire neurons with conductance-based synaptic inputs (see also Compte et al., 2000), namely that increasing NMDA and $GABA_A$ conductances simultaneously enhances both signal-to-noise-ratio and robustness to distracters.

While reducing AMPA and enhancing NMDA currents might have a robustness-increasing effect on their own (Durstewitz et al., 2000a), increasing $GABA_A$ currents by themselves in the absence of other changes might either diminish or enhance robustness depending on the strength of the attractors involved (as determined by the strength of recurrent excitation), their firing rates, and the magnitude of the change in $GABA_A$ conductances. In particular, if the firing rate of a cell assembly is a convex (from above) function of the total synaptic current, then for a strong high-state attractor, receiving much recurrent excitation, the same increase in average inhibitory synaptic current will have less of an effect on firing rates than for a weaker high-state state attractor, firing at comparatively lower rates. D1-mediated changes in voltage-dependent currents like I_{NaP} and I_{Ca} could further boost robustness (Durstewitz et al., 1999, 2000a). Thus, although D1 receptors at first glance appear to regulate a number of diverse and unrelated currents, all these actions might converge on a common function; namely augmenting robustness of working memory representations.

4. Experimental evidence for the model

Although the behavioral, in vivo and in vitro findings summarized in Section 2 are consistent with the model described here, direct evidence is still lacking. In favor of the model, behavioral findings indicate that animals where the dopaminergic input to the PFC has been lesioned by 6-OHDA are in fact not only more susceptible to distraction (as postulated by the model), they actually show improved performance on tasks requiring high response flexibility (Crofts et al., 2001; Roberts et al., 1994). Extrapolating from the network simulations presented here, if dopamine levels fall below baseline (as in 6-OHDA-lesioned animals), spontaneous activity would increase further while inhibition would decrease, and cell assemblies might start to pop out spontaneously, but be very unstable. As a result, within a given time window many different cell assemblies distributed over large areas might become active in close succession, albeit at relatively low firing rates, possibly causing distraction within working memory (Durstewitz et al., 2000a; Seamans et al., 2001b). At higher dopamine levels, as activity within cell assemblies becomes more robust and persistent, the network would narrow down on a few relevant representations, held active at high firing rates. This picture agrees well with activity profiles recorded in cortex when dopamine levels are elevated by administration of amphetamine (Mattay et al., 1996) or VTA stimulation (Bao, Chan, & Merzenich, 2001). Finally, hyperstimulation of DA receptors could lead to perseveration, i.e. the inability of an animal to switch its response pattern (Ridley, 1994). The model summarized here would account for this inability by the fact that a large dopamine increase would cause representations to become so robust and persistent that it might not be possible to switch them off even across trials.

Moreover, according to an in vivo experiment performed by Miller et al. (1996), delay activity in the PFC seems in fact to be more robust to interfering stimuli than delay-activity in posterior cortices (Constantinidis & Steinmetz, 1996; Di Pellegrino & Wise, 1993; Miller et al., 1996; see also D'Esposito, Postle, Jonides, & Smith, 1999). However, this observation still remains to be linked to the presence of dopamine. In this context it is important to note that the PFC might be distinguished from posterior cortical regions not that much by the density or strength of its dopaminergic input but by the density of the synaptic channels modulated by dopamine. For instance, the density of NMDA receptors

seems to be higher in PFC than in any other cortical area (Scherzer et al., 1998).

According to the model, D1 receptor activation should increase the effects of inputs in the frequency range relevant for delay-period activity (~20 Hz) yet reduce the effect of inputs in lower frequency ranges. In in vitro experiments, we have observed that D1 agonists produce a mild depression of single EPSPs or EPSPs evoked at the relatively low rate of 5 Hz (Fig. 5), a typical frequency for spontaneous activity in primate PFC when the animal is not actively performing a task (Fuster, 1973; Fuster et al., 1985; Rosenkilde et al., 1981; Sawaguchi et al., 1990a). In contrast, D1 agonists produce a pronounced increase in EPSPs when presynaptic fibers are stimulated at a relatively high rate of 20 Hz, a typical frequency for delay-type activity in a working memory context. This frequency-dependent effect is a direct result of the differential modulation of NMDA currents and non-NMDA currents by D1 receptors (Seamans et al., 2001a). While NMDA currents are enhanced by D1 stimulation (Seamans et al., 2001a; Wang & O'Donnell, 2001; Zheng et al., 1999), non-NMDA currents are reduced through a D1-mediated decrease in glutamate release probability (Gao et al., 2001; Seamans et al., 2001a). The contribution of NMDA currents grows relative to that of non-NMDA currents when going from low to higher input rates because the sustained depolarization associated with 20 Hz trains effectively activates NMDA receptors that in turn promote additional temporal summation of subsequent EPSPs. D1 activation therefore specifically favors inputs at high rates over those at low rates.

Even within a high rate input train of 20 Hz, the first couple of EPSPs are suppressed while only later ones are enhanced, again due to the differential effects of D1 activation on NMDA and non-NMDA components of excitatory synaptic inputs (Seamans et al., 2001a; see Fig. 5). Thus, in addition to dopamine's effects on activity sustained at low spontaneous versus high rates, D1 receptor activation might blunt *transient* inputs, even if they occur at higher rates, but might specifically enhance sustained activity states maintained by temporal summation of NMDA EPSPs. This could explain how both a reduction in AMPA currents as well as an increase in NMDA currents might together augment robustness of active representations. Fellous and Sejnowski (2001) in addition observed that dopamine facilitates persistent activity states driven by artificial synaptic inputs in a feedback loop with the recorded neuron using conductance-clamp techniques in vitro. This effect was probably due to both an increase of the artificial NMDA currents as well as the actual modulation of voltage-gated channels by dopamine, again illustrating how the multiple actions of dopamine might act in concert to enhance persistent activity states in PFC.

5. Conclusions

Based on the simulation results and the available experimental evidence, the dopamine system might have a somewhat different function than commonly believed. Dopaminergic midbrain neurons typically exhibit a phasic burst in response to a stimulus indicating (or predicting) behaviorally important events or at the onset of a working memory task (Schultz, 1998). Yet it is important to note that although dopamine midbrain neurons respond transiently to a novel or important event, dopamine levels in target structures rise slowly in anticipation of task onset, remain elevated during the duration of the task, and slowly decline to baseline many minutes after an event (Ahn et al., 2000; Feenstra & Botterblom, 1996; Feenstra et al., 1995, 2000; Watanabe et al., 1997). Likewise, in vitro dopamine appears to have extremely long lasting effects postsynaptically, as a brief application of a D1 agonist can alter excitability, NMDA or GABA currents for many tens of minutes after washout (Fig. 1). In this way, dopamine appears to alter the processing mode of PFC networks on longer time scales. (It should be noted, however, that activation of the ventral tegmental area might engage other transmitter systems besides the dopaminergic, which could exert faster effects; e.g. Pirot et al., 1992.) According to the scheme presented here, this change of processing mode consists of a change in the prefrontal attractor landscape such that transitions between different working memory states become more difficult, due to a deepening and/or widening of basins of attraction. In our scheme, dopamine neurons in the midbrain need not provide any specific information to PFC because it is the tonic level of dopamine that modulates the dynamics of delayed-period activity generated by other transmitter systems. As a functional consequence, with sufficient D1 receptor tone, active working memory representations become more robust to input interfering with the current goal state and to noise over many minutes.

A role of dopamine in modulating signal-to-noise ratio and distractability, and its relation to behavior has been hypothesized and explored previously in connectionist-like network models (Braver, Barch, & Cohen, 1999; Servan-Schreiber, Printz, & Cohen, 1990). In striatal networks, dopamine seems to exert similar effects as described here, enhancing depolarized up-states while diminishing responses during hyperpolarized down-states (Hernandez-Lopez, Bargas, Surmeier, Reyes, & Galarraga, 1997), but the mechanisms of modulation are different from the ones for PFC networks reported here.

In general there must be a trade-off between robustness in goal-directed behavior and the ability to respond flexibly to novel behavioral demands. D1 mediated effects can be interpreted as a shift in this balance towards a higher priority of the current behavioral goals at the expense of subordinate goals or other interfering behavioral tendencies. The trade-off between robustness in goal-directed behavior and the

ability to respond flexibly to novel behavioral demands may actually depend on the relative balance of D1 and D2 receptor activation in PFC assemblies. Recent data suggest that in many cases D1 and D2 effects are antagonistic. For instance, D1 stimulation enhances NMDA EPSCs, IPSCs and interneuron and pyramidal cell excitability while D2 stimulation not only reverses the D1 mediated enhancement, but actually produces the opposite effect and decreases NMDA EPSCs, IPSCs and both interneuron and pyramidal cell excitability (Gorelova, Seamans, Yang, unpublished observations; Gorelova & Yang, 2000; Gulledge & Jaffe, 1998; Seamans et al., 2001b; Zheng et al., 1999). Expanding on network simulations like the ones presented here, to include D2 effects and more detailed anatomical specifications of D1 and D2 densities in PFC networks, could provide novel insights into how dopamine receptors alter prefrontal attractor landscapes to dynamically regulate PFC function in a wide variety of task contexts with different cognitive requirements.

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