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Dopamine modulation in the basal ganglia locks the gate to working memory

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Abstract The prefrontal cortex and basal ganglia are deeply implicated in working memory. Both structures are subject to dopaminergic neuromodulation in a way that exerts a critical influence on the proper operation of working memory. We present a novel network model to elucidate the role of phasic dopamine in the interaction of these two structures in initiating and maintaining mnemonic activity. We argue that neuromodulation plays a critical role in protecting memories against both internal and external sources of noise. Increases in cortical gain engendered by prefrontal dopamine release help make memories robust against external distraction, but do not offer protection against internal noise accompanying recurrent cortical activity. Rather, the output of the basal ganglia provides the gating function of stabilization against noise and distraction by enhancing select memories through targeted disinhibition of cortex. Dopamine in the basal ganglia effectively locks this gate by influencing the stability of up and down states in the striatum. Dopamine's involvement in affective processing endows this gating with specificity to motivational salience. We model a spatial working memory task and show that these combined effects of dopamine lead to superior performance.

Keywords Salience · Spiny neuron · Phasic release · Attention

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Introduction

The three anatomical structures most critically implicated in working memory (WM) are the prefrontal cortex (PFC), the basal ganglia (BG), and the midbrain dopamine nuclei projecting to both (Fuster, 1995; Goldman-Rakic, 1995). Substantial evidence indicates that persistent neural activity in recurrent circuits in the PFC play a central role in the maintenance of information in WM. However, such memories, and particularly those involving continuous or line attractors (Seung, 1996; Zhang, 1996; Camperi and Wang, 1998; Compte et al., 2000; Laing and Chow, 2001; Gutkin et al., 2001) are exquisitely sensitive to two sources of noise: (i) *internal* noise in the recurrent network itself, and (ii) *external* noise coming from distractors. The basal ganglia and dopamine are believed to be involved in helping protect memories against these sources of noise, for instance through *gating*, in a way that has been examined both experimentally and theoretically. However, dopamine notoriously influences the BG as well as the PFC. The importance of this joint influence has not hitherto been explored using computational models, and is our focus.

Various lines of evidence implicate dopamine in WM. The degradation of dopamine-releasing neurons, both in humans afflicted with Parkinson's disease (Lange et al., 1992; Owen

et al., 1992) and in animal models utilizing pharmacological lesions (Kori et al., 1995; Miyoshi et al., 2002), leads to deficit in WM, while low doses of systemically delivered dopamine agonists can enhance WM (Costa et al., 2003; Lidow et al., 1998; Servan-Schreiber et al., 1998; Muller et al., 1998). Part of the effect is due to the direct actions of DA in the cortex, demonstrated by the degradation of WM caused by the application of DA agonists or antagonists into the PFC (Sawaguchi and Goldman-Rakic, 1994; Zahrt et al., 1997). The basal ganglia is also known to play an important role in WM, as seen in human functional neuroimaging (Lewis et al., 2004; Menon et al., 2000; Postle and D'Esposito, 1999), monkey electrophysiology (Kermadi and Joseph, 1995) and inactivation studies (Kalivas et al., 2001). One possible route for this influence (Frank et al., 2001; Djurfeldt et al., 2001) is the prominent projections from ventral striatum to medial dorsal thalamus/PFC (Haber, 2003; Middleton and Strick, 2002; Groenewegen et al., 1997). Since the striatum is itself a major target of dopaminergic innervation (Lynd-Balta and Haber, 1994) and striatal neurons are strongly modulated by DA (Nicola et al., 2000), this pathway provides an additional route by which dopamine can influence working memory. The integration of gating and neuromodulation within and between basal ganglia and cortex raises a rich set of important, and as yet underexplored, issues.

Mathematical and computational models of various levels of biophysical detail have offered some illumination on the separate pieces of the problem, mostly focusing on the role of dopamine in the cortex. For instance, a recent cellular-level model, which includes many known effects of DA on ionic conductances, indicates that tonic DA modulation of pyramidal neurons causes the pattern of network activity at a fixed point attractor to become more robust both to noise and to input-driven disruption of attractor states (Durstewitz et al., 2000). Furthermore, this result is consistent with reported effects of DA in more abstract spiking-based models of WM (Brunel and Wang, 2001; Compte et al., 2000). However, this class of models does not treat the phasic DA release that is evoked by conditioned stimuli (Schultz, 1998; Roitman et al., 2004; Kawagoe et al., 2004). More abstract theories suggest a gating role for this phasic DA release (Dreher et al., 2002; Braver and Cohen, 1999), but do not present a biophysical implementation of the gating mechanism. Some models ascribe a direct gating role to DA, such that DA release is required for read-in to working memory (Braver and Cohen, 1999; Cohen et al., 2002). However, this idea has been criticized (Dreher et al., 2002; Frank et al., 2001) on the grounds that DA projections are too diffuse, the timecourse of DA mediated modulation is too slow, and the information carried by DA neuron activity may not be quite appropriate to implement the gating function directly.

Only few of the models of PFC working memory address the impact of the basal ganglia (most notably that by O'Reilly and colleagues (Frank et al., 2001)). These only treat off-line training effects of DA, rather than its on-line neuromodulatory effects in the basal ganglia. The electophysiological properties of striatal neurons are strongly modulated by dopamine (Nicola et al., 2000), and may account for part of the strong reward dependency of striatal activity (Kawagoe et al., 2004; Nakamura and Hikosaka, 2004). These neuromodulatory effects of DA in the striatum have been studied in a recent model (Gruber et al., 2003), which suggests that the input-dependent 'up/down-state' bimodal behavior of striatal medium spiny neurons (MSNs) (Wilson and Kawaguchi, 1996) develops a narrow region of bistability in conditions of elevated dopamine. The induction of intrinsic bistability, for which some indirect evidence is emerging (Vergara et al., 2003; Hernandez-Lopez et al., 1997), is expected to temporarily 'lock' the response of MSNs following dopamine release (Gruber et al., 2003). This provides a simple mechanism to account for the seemingly paradoxical finding that dopamine can suppress or enhance striatal activity (Kiyatkin and Rebec, 1996; Hernandez-Lopez et al., 1997), and can extend the duration of enhanced activity (Gonon, 1997). In this paper, we integrate the striatal dopamine model with a cortical attractor network with properties similar to those explored previously. This combined network allow us to explore the effect of striatal disinhibition of PFC on working memory, and provides a means of contrasting the effects of dopaminergic modulation in these two structures on working memory encoded by an attractor state in the PFC. We use a memory-guided saccade task (Funahashi et al., 1989) as an example, since the control of standard continuous attractor models of such working memories are particularly sensitive to noise and distraction and thus pose a difficult stability control problem.

In successive sections of this paper, we consider the effect of dopamine on resistance to attractor switching in an isolated cortical line attractor network; the effect of medium spiny neuron activity on gating and resistance to noise; and the effect of dopamine induced bistability in spiny neurons on working memory activity associated with salient stimuli. This sort of dopamine modulation provides a novel biophysically-grounded mechanism for saliency-selective gating of working memory by the basal ganglia. The different, but synergistic, mechanisms by which dopamine gates access to working memory by altering the attractor landscape, both globally through direct modulation in the cortex, and by focally enhancing the targeted output of the basal ganglia, is a key new concept of our network model. These complementary effects in the basal ganglia and cortex result in superior performance in a simulation of a memory-guided spatial working memory task.

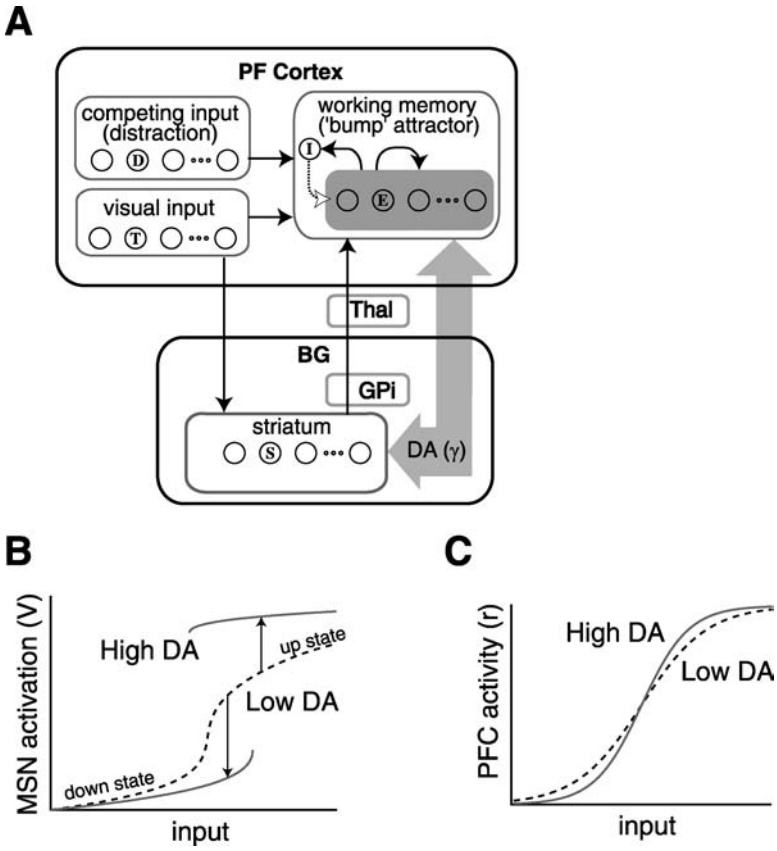

Figure 1 Network model for the encoding of working memory and the modulatory effects of dopamine. (A) The network consists of four modules: one basal ganglia (BG) module, and three modules in prefrontal cortex (PFC); visual input, competing input, and working memory modules. All connections are excitatory except for the global inhibition of the PFC memory network indicated by the open arrow. The PFC memory module is a line attractor that encodes working memory of the target location through a bump of activity sustained beyond stimulus offset. Dopamine modulates response properties in both the BG and PFC memory modules. (B) The sigmoidal activation function of medium spiny neurons (MSNs) in the striatum (STR) of the BG becomes bistable in conditions of elevated dopamine (solid grey curve). (C) The sigmoidal response function of PFC memory units becomes more steep in high dopamine (solid grey curve).

Materials and Methods

Network Architecture

The network model (Figure 1A) used to simulate the working memory activity during a memory-guided saccade task comprises four modules: one associated with the striatum of the basal ganglia (BG), and three associated with prefrontal cortex (PFC). The PFC modules represent visual input, competing non-visual input, and the working memory itself. For illustrative convenience, the cortical modules are shown in the figure as being separate; in fact cortical units with different characteristic selectivities do not seem to be segregated in the PFC (Chafee and Goldman-Rakic, 1998).

The visual input units represent those PFC neurons that have only a sensory response to visual targets, whereas the memory units represent neurons that have sustained activity during delay periods. The sensory units have two connections to the memory module. One pathway is the standard intracortical interaction. The other pathway represents an 'open loop' connection via the direct pathway of the BG. The competing input is just like the visual input, except that being non-visual, it participates in different segregated loops through the BG (as suggested by the apparent modular architecture of cortical-basal ganglionic connectivity (Alexander and Crutcher, 1990; Groenewegen et al., 1997; Middleton and Strick, 2002)), and therefore does not project to the striatum module involved in processing the visual input. The competing input module permits us to study the properties of the gating process controlling read-in to WM in the face of distraction from other signals, such as auditory sources, that can be used to guide saccades.

Although there are multiple pathways through the BG, we focus here on the so called 'direct pathway' as the key component of cortico-striatal interactions for gating information into WM; the activation of spiny neurons in involved in this pathway is thought to evoke disinhibition of thalamocortical circuits by suppressing the tonic inhibition provided by the globus pallidus/substantia nigra (Hikosaka et al., 1998; Mink, 1996). In the model, the disinhibition is achieved

through targeted excitatory input to PFC from MSNs. This direct localized excitation in PFC is mathematically equivalent to a linear mechanism for multisynaptic disinhibition; however, some potentially important nonlinearities in the neural circuit are neglected in the present model for the sake of simplicity and clarity. The pallidal and thalamic nuclei may well influence signals from the striatum (Terman et al., 2002; Destexhe et al., 1996). Their exclusion implements an assumption that the relative magnitude and duration of striatal responses are maintained in the circuit, which we believe to be appropriate for the level of modeling employed here. The model also excludes the indirect pathway through the BG, which is thought to exert a net inhibitory influence on cortex (Hikosaka et al., 1998; Mink, 1996). We speculate on the possible function of this antagonistic effect, but do not include it since the combined effect of both pathways will strongly depend on the structure of their relative projections to cortex, which cannot currently be concisely derived from experimental data, and since an exploration of potential configurations of the connectivity is beyond the scope of the present work.

We adopt a rate-based rather than a spiking description of the units, and do not address issues such as oscillations. Despite the simplicity of the model units, the network exhibits features consistent with more biophysically detailed models.

Visual Input and Competing Input Modules

The visual input module consists of a ring of 120 units (T) with preferred directions uniformly covering the circular interval $[0, 2\pi)$. These units have truncated Gaussian receptive fields modeled loosely on experimental data (Graybiel, 1995; Chafee and Goldman-Rakic, 1998), so that unit i has mean activity to a target at angular location θ_T of

$$r_i^T \propto e^{-\frac{(\theta_T-\theta_p^i)^2}{2(\sigma^T)^2}}, \quad (1)$$

where θ_p^i is the unit's preferred direction, and σ^T controls the width of the receptive field and is chosen ($\sigma^T = 0.2$) so that receptive fields overlap substantially. This results in a bump of activity in the network that encodes the position of the target. Activity centered at different locations along the ring encodes for the position of different targets around the circle, characterized by an angle in the $[0, 2\pi)$ interval.

Visual input happens in response both to targets and superfluous visual cues (visual distractors) that follow targets and which should be ignored. For both sorts of input, activity in the input module is maintained for 300 ms, a characteristic duration of phasic cortical activity in response to brief visual stimuli (Colby et al., 1996). We characterize the robustness of WM to both visual distractors, which are often used in behavioral investigations of spatial WM (Powell, and Goldberg, 2000), and also non-visual distractors that are presented through the competing input module.

In all but one respect, the competing input module is identical to the visual module. The difference is that non-visual distractors only affect activity in the memory module through the direct connections from the competing input units to memory units. The pattern of activity in the distractor module is structurally identical to the pattern in the visual module, and the direct connections from these input units to WM units are equivalent. Therefore, any difference in the efficacy of visual inputs, as compared to non-visual distractors, on the encoded working memory is attributable to the BG module. Contrasting the effects of the two types of input thus provides a tool for assessing the relative contribution of the BG, and its modulation by dopamine, on working memory. As will be shown later, non-visual distractor inputs are equivalent to target related inputs when the visual inputs fail to elicit striatal activity. The circumstances under which this happens to target inputs is primarily when they follow too soon after a conditioned stimulus, because the subsequent release of dopamine can temporarily lock the activity of the MSNs and functionally disconnect the cortical input to the BG (Gruber et al., 2003).

Striatum Module

The striatum module consists of 24 units (S) that represent medium spiny neurons (MSNs), the principal neuron type of the input nuclei of the BG. Each MSN has a preferred direction, uniformly covering the circular interval $[0,2\pi)$, and a Gaussian receptive field conferred by connections from the visual input units. Gaussian connections to striatal units, and also to PFC memory units, are specified by a magnitude $w^k_{\max}$ that controls the height, and width σ^k that determines the extent of the receptive field. The connections are:

$$W^k_{ij} = w^k_{\max} e^{-\frac{(\Delta\theta_p^{ij})^2}{2(\sigma^k)^2}}, \quad (2)$$

where $\Delta\theta_p^{ij} = \theta_p^j - \theta_p^i$ is the difference (mod π) between the preferred directions of units i and j. For the input provided to striatal units from visual input units ($k = ST$), the width ($\sigma^{ST} = 0.15$) and input magnitude ($w^{ST}_{\max} = 0.64$) are chosen so that visual target presentation elicits activity in only a few MSNs with similar preferred directions.

The dynamics of the membrane potential V^S of MSNs arise from a biophysically-grounded single compartment model (Gruber et al., 2003),

$$-C\dot{V}^S = \gamma(I_{\text{Kir2}} + I_{\text{LCa}}) + I_{\text{Ksi}} + I_L + I_T \ , \quad (3)$$

which incorporates three ionic currents: an inward rectifying K^+ current (I_{kir2}), a slowly inactivating outward rectifying K^+ current available on depolarization (I_{ksi}), and an L-type Ca^{2+} current (I_{LCa}). The characterization of these currents is based on available biophysical data on MSNs. The factor γ represents an increase in the magnitude of the I_{Kir2} and I_{LCa} currents due to the activation of D1 dopamine receptors. This DA induced current enhancement renders MSNs bistable for $\gamma \gtrsim 1.2$ (see Fig. 1 for $\gamma = 1.4$). The leakage current is represented by I_{L}. The synaptic input I_{T} is an ohmic term with conductance given by the weighted summed activity of input units within the corresponding receptive field; synaptic input to the j-th MSN is thus given by $I_{\text{T}j} = (b + \Sigma_i \, W^{ST}_{ji} r^{\text{T}}{}_i)V^S$, where W^{ST}_{ji} is the strength of the connection from the i-th visual input neuron to the j-th spiny neuron, and b represents a tonic contribution to the synaptic conductance. The tonic background ($b = 10.5\ \mu\text{S/cm}^2$) causes a moderate persistent depolarization, but does not drive the units into the active up state, and represents the task context that could be provided by PFC (Watanabe et al., 2002) or hippocampus (Goto and O'Donnell, 2001). The firing rate of MSNs is a thresholded logistic function of their membrane potential: $r^S_j = 1/[1 + \exp((-55 - V^S_j)/2.5)]$ for $V^S \geq -58\,\text{mV}$. The values of all parameters for the MSN model, except for the capacitance C, are identical to those used in our previous model (Gruber et al., 2003). The capacitance value used here ($C = 0.1\ \mu\text{F/cm}^2$) is smaller than in our previous model, which was formulated to investigate cellular properties on a timescale of 300-1000 ms; the smaller capacitance used here allows the MSNs to respond to cortical input on a timescale characteristic of biological neurons. Other types of striatal cells are not included in the present model. In particular, the GABA-ergic interneurons may be important (Koos and Tepper, 1999). However, the connectivity, biophysical properties, and response properties of these units are not sufficiently known to guide their inclusion in the present model. In addition, lateral connections among MSNs that have been suggested to implement competition within the striatum (Beiser et al., 1997; Gurney et al., 2001) are not included in this model since the effects of these connections appears to be very weak (Tepper et al., 2004). As discussed later, the inclusion of inhibition within the striatum is not expected to significantly alter the behavior of the network on the simple memory task presented here since no competition or precise timing among striatal units is required.

PFC Module

The PFC memory module implements a line attractor that exhibits either a ground state in which all units have a low rate of activity, or a 'bump' state in which a local group of units remain persistently active (see Fig. 2A). It involves one inhibitory unit (I) representing a pool of GABA-ergic interneurons, and 120 excitatory units (E) representing a group of pyramidal neurons. Each excitatory unit is assigned a preferred direction so that the population uniformly covers the $[0, 2\pi)$ interval.

Cortical units are more abstract than the spiny neuron model. The dynamics of the activation V^E of excitatory PFC units are

$$\begin{aligned}\tau^E \dot{V}^E_j = \ & -V^E_j + \sum_i W^{ES}_{ji} r^S_i + \sum_{i \neq j} w^{EE}_{ji} r^E_i \\ & -r^I + 0.5 r^T_j + 0.5 r^D_j + \sigma_e \eta. \end{aligned} \quad (4)$$

The first sum represents inputs from the BG; the second, inputs from other excitatory PFC units; note that self-connections are excluded. The succeeding three terms represent global inhibition from a single inhibitory PFC unit, information about the visual target provided by visual input, and distractor input. In the absence of inputs, it is the balance between excitation among excitatory units and inhibition from the activity of the inhibitory unit r^I that determines the characteristics of the sustained bump of activity. The magnitude ($w^{EE}_{\text{max}} = 0.18$) and width ($\sigma^{EE} = 0.45$) of the connections among excitatory units are set to produce a stable bump of sustained activity following target presentation (see Fig. 2A).

Each excitatory memory unit E_j receives input from the one visual input unit (r^T_j), and the one competing input unit (r^D_j), that have the same preferred direction as the memory unit. The bump of activity in the input modules is thus copied into WM; it is then subject to the dynamics implemented by the recurrent connectivity in the memory module. The projections W^{ES} from striatal units are determined according to a Gaussian. These excitatory connections represent the net excitation provided by the disinhibition through the direct pathway of the BG. The magnitude ($w^{ES}_{\text{max}} = 0.4$) and width ($\sigma^{ES} = 0.1$) of these projections are set so that the summed input to each PFC memory unit from the BG is close in overall magnitude to the input from visual input units; hence neither the input modules nor the BG has a strongly dominant influence over the line attractor. The effects of weaker input from the BG were also tested, and produced qualitatively similar results.

The last term of eq. 4 provides a stochastic input that models fluctuations in the various activities that contribute to the total input to the excitatory units. The random variable η is drawn from a Gaussian distribution with zero mean and unit variance. The noise amplitude ($\sigma_e = 0.41\,mV/ms^{0.5}$) scales like $(dt)^{-1/2}$, where

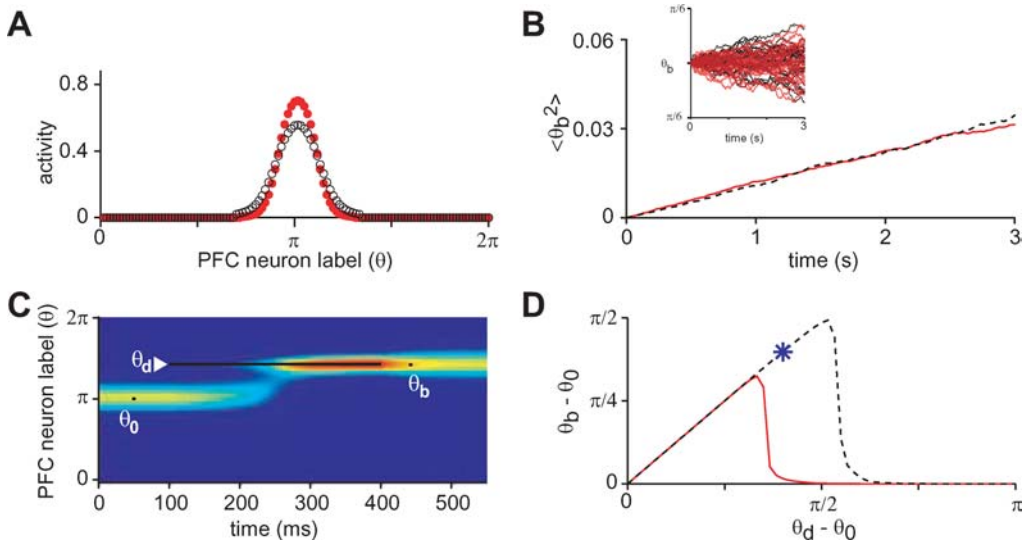

Figure 2 Effects of dopamine (DA) in the isolated PFC network. (A) Activity profile of the bump state in low (○) and high (●) DA conditions. (B) The similarly distributed trajectories (inset) and tightly overlapping variance of the bump location θ_b in low DA (black dashed lines) and high DA (red solid lines) show that dopamine does not enhance the robustness of stored memory to internal noise in PFC memory units. (C) The robustness of the bump to switching is gauged by measuring the bump displacement induced by the presentation of a distractor input for 300 ms. The activity profile shown as a vertical colormap (red indicating highest activity) as a function of time illustrates the displacement of the bump from its initial location at θ_0 to a final location at θ_b due to a distractor input at θ_d. (D) Robustness characteristics of bump activity in low DA (black dashed curve) and high DA (red solid curve); dopamine moderately enhances the robustness to switching. The asterisk corresponds to the bump displacement observed in panel C in low DA conditions; note that the same distractor would only have caused a negligible bump displacement in high DA.

dt is the integration time step, so as to maintain consistent noise amplitude across variable integration steps.

The firing rate of a PFC excitatory unit is taken to be a logistic function of its membrane potential: $r_j^E = 1/[1 + \exp((1 - V_j^E)/E(V_c^E))]$. The slope of this response is determined by V_c^E, which is controlled by DA. The total direct effect of DA on excitatory PFC units in the model arises as a linear change of the slope parameter V_c^E with the dopaminergic modulation parameter γ : $V_c^E = 0.25 - 0.175 * (\gamma - 1)$. As γ increases, the activation function becomes more steep, as shown in Fig. 1C. The effect of dopamine release elicited by conditioned stimuli is implemented by varying γ between its bounds in low ($\gamma = 1$) and high ($\gamma = 1.4$) dopamine conditions. The dynamics of γ are taken from our previous model (Gruber et al., 2003), which is designed to reflect the dynamics of MSN response modulation following evoked DA release *in vivo* (Gonon, 1997). These dynamics reflect the kinetics of dopamine release, receptor binding, and of the intracellular cascades which lead to modulation of membrane properties. In the model, γ begins an exponential rise ($\tau_r = 70$ ms) toward its maximal value after a delay of 80 ms from the onset of visual input. It begins to decay ($\tau_d = 100$ ms) 700 ms after input onset.

The dynamics of the inhibitory unit are $\tau^I \dot{V}^I = \sum_i r_i^E$, where the sum represents the total activity of the excitatory population, and the time constant ($\tau^I = 5$ ms) is smaller than that of excitatory units ($\tau^E = 20$ ms) to achieve stability of the bump activity (Hansel and Mato, 2001).

The firing rate r^I of the inhibitory unit is a linear threshold function: $r^I = V^I$ for $V^I \geq 9\ mV$.

Results

The working memory for the angular position of visual targets is encoded in the PFC line attractor through a localized bump of sustained activity (see Fig. 2A). In turn, this activity is sensitive to the balance of excitation and inhibition in the network, both of which are influenced by visual input, distractors, noise, and dopamine. We first investigate the relative contributions of these network components on the robustness and switching of WM, and then consider their coordinated effect in the fully connected network.

Dopamine Effects on the Cortex: Increased Memory Robustness

In the absence of input from the basal ganglia, dopaminergic modulation of the PFC network is represented as an increase in the slope of the response function of the excitatory cortical units (Fig. 1C). Gain control of this form has been adopted in previous, more abstract, network theories

of cortical neuromodulation (Servan-Schreiber et al., 1990). It is also generally consistent with the sort of contrast enhancement that is observed in biophysically-grounded cortical models (Brunel and Wang, 2001; Durstewitz et al., 2000), for which weak activity is suppressed while strong activity is enhanced. Note that this dopaminergic modulation does not cause PFC memory units to become intrinsically bistable; as in low dopamine conditions, the persistent PFC activity is a network effect associated with recurrent excitation. Here, dopamine focuses the persistent bump of activity triggered by a transient activation of input units, by making it both narrower and higher (Fig. 2A).

The key question is how dopamine affects the stability of the bump, and hence the angle held in working memory, to both internal noise within the WM module and external inputs. Figure 2B shows that, rather surprisingly, the rate at which the bump location diffuses in response to internal noise is not affected by dopaminergic modulation in the cortex. This finding holds for larger ($3\sigma_e/2$) or smaller ($\sigma_e/2$) noise values.

The robustness of WM to external distraction is investigated by activating the competing input module. The pattern of this activity is structurally identical to the pattern associated with the visual targets, but encodes an angle that is different from that stored in WM. The competing input module provides a means for assessing distraction that does not involve the visual BG module, and thus provides a benchmark against which to gauge the contributions of the BG to the WM stability. Unlike the stochastic diffusion of the bump location resulting from the uniformly distributed internal noise, distractors cause the bump of activity to drift toward the location of the distraction (See Fig. 2C). A convenient measure of distractibility is to characterize the distance of drift as a function of distractor location (Compte et al., 2000).

Figure 2C shows that a distractor centered at a location θ_d causes a drift in bump location from its initial position θ_0 to a final position θ_b, closer to the angular location of the distractor. If θ_d is close to θ_0, the distractor is capable of moving the bump completely to the distractor location. This is apparent in the plot of bump displacement ($\theta_b - \theta_0$) versus relative distractor location ($\theta_d - \theta_0$) shown in Fig. 2D, which remains close to the identity for small relative distractor locations. However, as the relative distractor location increases, the displacement of the bump decreases abruptly and becomes negligible; this defines a cutoff above which more distant distractors do not affect the location of the bump.

The generic features of bump stability shown in Fig. 2D apply in conditions of both low DA (dashed curve) and high DA (solid curve). The difference in the corresponding cutoffs reveals that the dopamine induced increase in the gain of the response function of PFC excitatory units *decreases* the sensitivity of the bump to distractors. The actual location of the cutoffs can be altered by varying the intensity and/or the duration of the distractor input, but these changes do not affect the general features of these curves and their relative order. These simulations demonstrate that dopamine increases the robustness of the encoded memory to distractors. This is in sharp contrast to the continued sensitivity to internal noise (Fig. 2B). The continued sensitivity to internal as compared to external noise is a consequence of the difference in spatial distributions of the perturbations with respect to the bump of activity. The internal noise is present in all units, but is only relevant in those units sufficiently above the activation threshold, which are units in or near the bump of activity. Although fewer units participate in the activity bump in high DA, this effect is offset by the increased sensitivity of noise due to the higher gain of the activation function. In contrast, distraction is a localized perturbation that can occur far from the activity bump. The reduction in cutoff distance in high DA reveals a spatially dependent modulation of excitability of network units. Units that are far from the activity bump become less excitable in high DA because of both the increased gain of the activation function and also because the net input to each unit (the balance between inhibition and recurrent excitation) is reduced by the more narrow but taller activity bump. This reduced excitability yields less pulling influence on the bump by distractors.

The enhancement of WM robustness by dopamine in our model is consistent with the stabilization effects of dopamine in more biophyscially detailed line attractor (Compte et al., 2000) and fixed point attractor (Durstewitz et al., 2000; Brunel and Wang, 2001) models. Dopamine modulation in these models increases MNDA and GABA currents, which has the effect of enhancing the activity of units participating in an active attractor state while rendering other units less excitable. This form of contrast enhancement is implemented in our more simple cortical model through an increased gain in the activation function of excitatory cortical units, and results in network properties consistent with these more detailed models. Other dendritic currents and the slow dynamics of NMDA may also enhance stabilization of fixed point attractors (Durstewitz et al., 2000; Brunel and Wang, 2001) and the suppression of diffusion in line attractors (Compte et al., 2000). However, our model demonstrates that even a simple form of contrast enhancement can produce an enhancement of robustness against distraction.

Basal Ganglia Effects on the Cortex in Low DA: Input Gating and Increased Memory Robustness

We next investigate the effects of the BG activity on the initiation, switching and robustness of bump states. Active MSNs exert a measure of control over the encoded memory by providing a phasic input that helps relevant stimuli switch the location of the PFC memory activity bump.

We show in Fig. 3A and B (top plots) the location of the activity bump as a function of time in response to two sequential stimuli at different locations. The memory module response to the second stimulus depends dramatically on whether the MSNs are recruited. The initial stimulus activates a group of adjacent MSNs; this activity in combination with activity from input units elicits a bump of activity in the PFC memory network that encodes for the same angular position. When the input disappears, the MSNs become inactive and the cortical layer relaxes to a persistent bump state centered at the angular position of the stimulus. A second stimulus that fails to activate BG units, either because it follows a lesion of the afferents to MSNs (Fig. 3A) or because of DA modulation in the BG (as discussed later), has a negligible effect on bump location. As expected, a distant subsequent stimulus beyond the cutoff in low DA (see Fig. 2D, dashed curve) is not able to drive changes in WM. However, if the distant subsequent stimulus *does* activate MSNs (Fig. 3B), then it *does* cause a switch in bump location. In this case, the PFC memory is updated to encode for the location of the most recent stimulus. Thus, a direct input to the PFC memory module that by itself is not sufficient to switch attractor states can trigger a switch provided it activates the BG, whose activity yields additional input (disinhibition) to the PFC memory module.

In sum, transient activation of MSNs effectively gates access to working memory in low dopamine conditions. Phasic activation of MSNs can therefore control working memory by driving switches in the location of the bump state.

We next investigate whether a localized tonic activation of MSNs that provides net excitation (disinhibition) to the PFC would enhance the stability of existing bump states. Figure 4 shows the consequence of having a single tonically active MSN that has a preferred direction coinciding with the angular location of an existing cortical bump. Tonic basal ganglia input anchors the bump at its location and increases the robustness of working memory against both noise induced diffusion (Fig. 4A) and distraction (Fig. 4B). The external distractor used here provides direct phasic input to PFC memory units, without disturbing the tonic activity in the BG module. The localized tonic BG input to the PFC memory units effectively breaks the symmetry of the line attractor creating a single stable fixed point attractor: a bump centered at the location of maximal BG input. This transition from a continuous line attractor to a fixed point attractor essentially eliminates noise induced drift (Fig. 4A) and reduces the maximal deviation of the bump by a distractor (Fig. 4B). Although dopaminergic modulation in the cortex does result in similar reductions in distractibility (Fig. 2D), it does not anchor the bump against diffusion (Fig. 2B). Weaker BG input to PFC ($W_{\max}^{ES}/4$) is also capable of suppressing diffusion and distraction.

Dopamine Effects on the Basal Ganglia: Saliency-Based Gating

Ample evidence indicates that phasic dopamine release, associated for instance with the presentation of conditioned

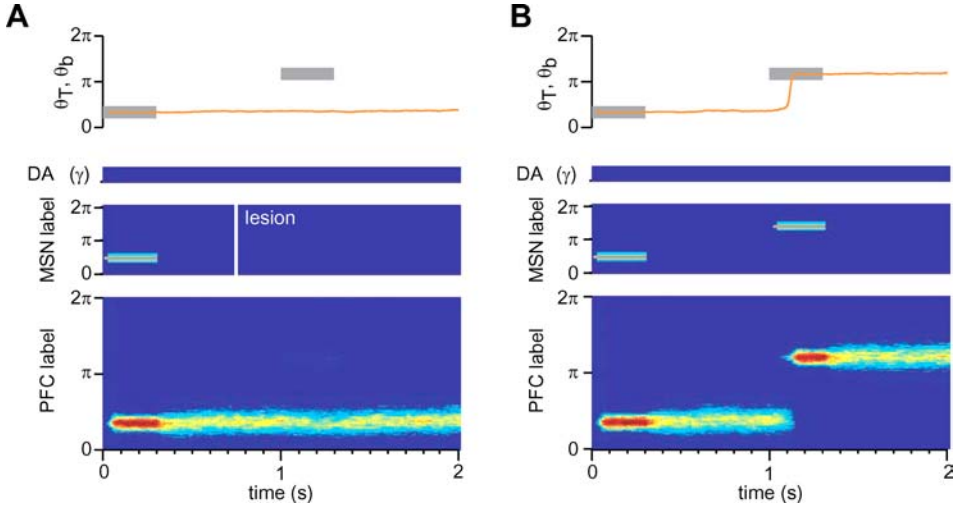

Figure 3 The phasic MSN response to input activity drives switches in the attractor state. Top plots show the location of the encoded memory θ_b as computed by the population vector readout of the activity of the excitatory cortical units (thin orange line) and the location θ_T of visual targets (grey bars) encoded by a Gaussian bump of activity in the input module. The middle and bottom panels show the activity of the striatum and PFC modules, respectively, as colormaps. The dopamine level remains low. (A) Onset of the first target activates MSNs, which help trigger the formation of the appropriate cortical bump state. A lesion of the inputs to MSNs prohibits activation of MSNs to the second target; the direct target-related input to PFC units is not sufficient to drive large switches in attractor location (as shown in Fig. 2D, black dashed line), and the memory is not updated to encode the second target. (B) The response of MSNs to the second target provides additional input to PFC; the combined target-related input to PFC units now suffices to drive a switch in memory.

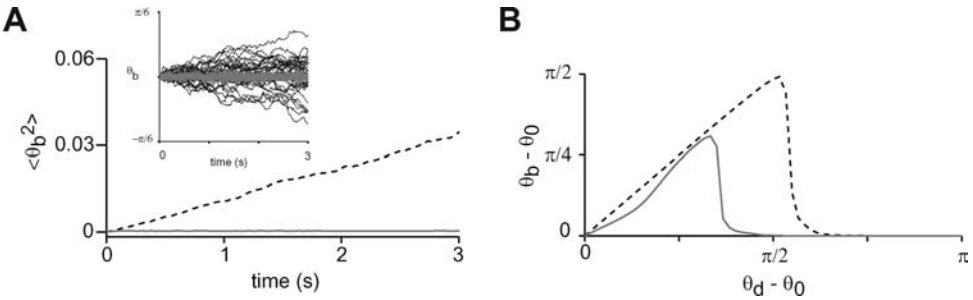

Figure 4 Persistent BG input to PFC enhances the stability of WM. Black dashed lines characterize bump properties of the isolated PFC network in low DA conditions, as in figure 2. Solid grey lines show bump properties in the presence of tonic BG input from a single BG unit whose preferred angular location coincides with that of the existing bump. (A) The trajectories (inset) and variance of bump location θ_b show that the diffusion of the bump location due to noise is greatly reduced by the tonic BG input. (B) The robustness of bump activity to switching is also increased by the tonic BG input.

stimuli (Schultz et al., 1993), modulates the activity of MSNs (Nicola et al., 2000). Our previous computational model of MSNs (Gruber et al., 2003) studied the apparently paradoxical effects of DA modulation, manifested in both suppression and enhancement of MSN activity (Nicola et al., 2000; Kiyatkin and Rebec, 1996; Hernandez-Lopez et al., 1997; Kawagoe et al., 2004). We showed that DA can induce bistability in the response function of model MSNs (see Fig. 1B) through the activation of D1 type receptors, thereby accounting for both enhancement and suppression of activity. In high DA, the effective threshold for reaching the active up state is increased. The activity of a unit that does not exceed this threshold is suppressed into a quiescent down state, while units that reach the up state exhibit a higher firing rate for an extended duration, due to the effects of hysteresis.

We now demonstrate that the dual enhancing/suppressing nature of DA modulation of MSN activity significantly affects the gating properties of the BG, and consequently the response of the PFC memory network to visual targets. Figure 5 shows the evolution of the network activity and angle θ_b encoded in working memory in response to two different sets of three sequential stimuli. The presentation of regular targets θ_A, θ_B, θ_C (Fig. 5A) activates the appropriate MSNs, and all three inputs are duly gated into WM. In contrast, Fig. 5B shows the response to the sequence θ_A, θ_{B*}, θ_C, in which θ_{B*}, is at the same angular position as θ_B, but now elicits dopamine release (for instance, as a conditioned stimulus). The presentation of θ_{B*}, activates the same set of MSNs as θ_B, but all MSNs now become bistable due to elevated dopamine: high activity is enhanced while intermediate activity is suppressed. Only the central MSN remains active with an enhanced amplitude. The two adjacent MSNs that were activated by θ_B in low DA are now suppressed. The activity of the central MSN suffices to gate the location of θ_{B*} into WM; the location of the PFC memory activity bump switches accordingly. Once the bump has switched to encode for the conditioned stimulus, the subsequent presentation of θ_C does not activate the corresponding MSNs, which are locked in the inactive down state. The pattern of activity in the BG continues to encode for θ_{B*} for as long as the effects of dopamine on MSNs persist, and the PFC activity bump thus remains anchored at θ_{B*}. This property of the network depends on appropriate excitatory input to MSNs, which must fall in the region of bistability shown in Fig. 1B. Note that a sufficiently larger excitatory input would suffice to activate other MSNs and switch the WM. Moderately weaker input from BG to PFC ($W^{ES}_{\max}/2$) also produces appropriate salience-based gating, but very weak input ($W^{ES}_{\max}/4$) is not able to prevent distraction to θ_C.

In sum, bistability of MSNs induced by dopamine release, associated for instance with an expectation of reward, imparts salience selectivity to the gating function of the BG. By locking the activation of MSNs following a salient input, the BG activity prevents a switch in PFC activity due to the visual distractor θ_C, and preserves the conditioned stimulus in WM. The robustness of the WM is enhanced by the combined effect of DA through both increasing the gain of PFC neurons and sustaining MSN input during the delay period (Fig. 5C).

Discussion

We have shown how basal ganglia-cortical interactions may provide a sophisticated, dopamine-dependent, control mechanism for cortical attractor-based working memory. Our demonstration involves a working memory model which integrates dopaminergic modulation in the prefrontal cortex, bistability-inducing dopaminergic modulation of striatal spiny neurons, and the effects of basal ganglia output on cortical persistence. A key new concept of our network model is the different, but synergistic, manners by which dopamine gates access to working memory by altering the attractor landscape, both globally, through direct modulation in the cortex, and focally, by enhancing the targeted output of the basal ganglia. While other models have considered

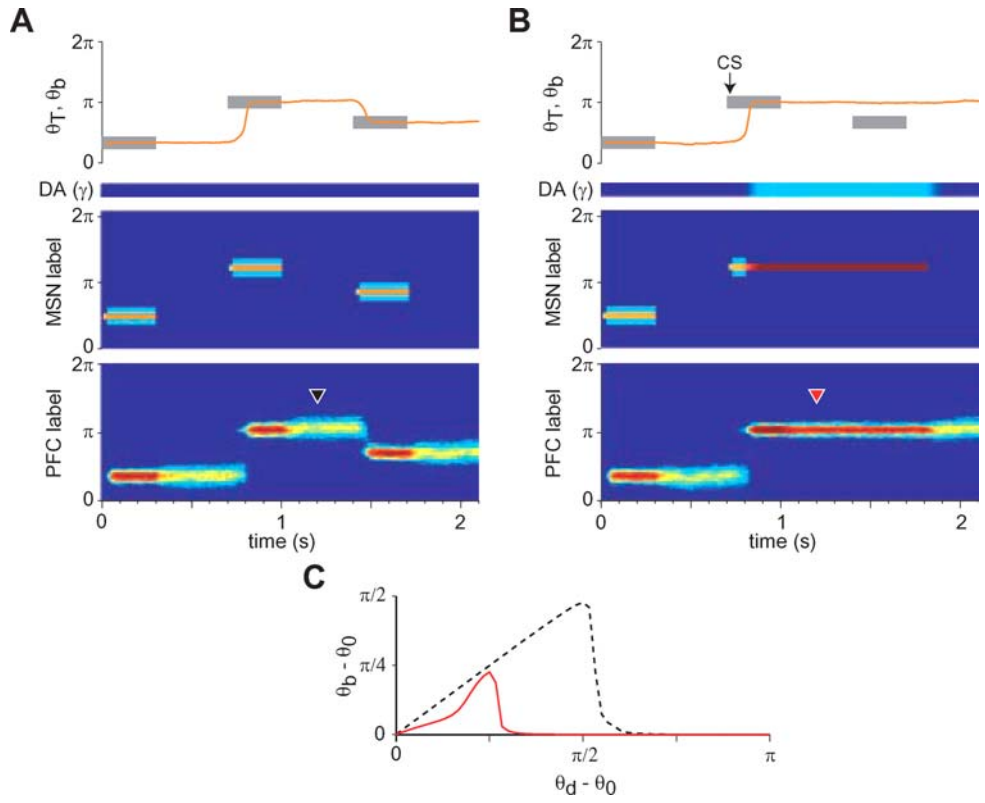

Figure 5 Dopaminergic modulation in the BG implements saliency-based gating and enhances the robustness of memory storage. The layout is the same as in figure 3. (A) The presentation of three sequential stimuli $[\theta_A, \theta_B, \theta_C]$ with no reward contingency activates the corresponding MSNs; all three stimuli are therefore gated into WM. (B) The gating effects of DA in the BG are illustrated by the presentation of three sequential stimuli $[\theta_A, \theta_{B*}, \theta_C]$ with the same angular locations as in panel A, but θ_{B*} is now a conditioned stimulus. The presentation of θ_{B*} activates the same group of MSNs as θ_B, but in addition, it triggers dopamine release. The resulting bistability of MSNs sustains and enhances the response of the most active unit, while all other MSNs become locked in the inactive down sate. The MSNs that would respond to the presentation of θ_C are not activated in this condition; hence the WM continues to encode the conditioned stimulus θ_{B*}. (C) The WM of conditioned stimuli (red solid curve, corresponding to conditions at the red triangle in panel B) are more robust than WMs of unconditioned stimuli (black dashed curve, corresponding to conditions at the black triangle in panel A).

such effects separately, to the best of our knowledge, ours is the first to consider the combined, complementary, effects of dopamine in the prefrontal cortex and the basal ganglia alongside the direct basal ganglia input to cortex.

Two central concerns plague models of working memory: robustness to *external* noise, such as explicit lures presented during the memory delay period or inputs from other sensory modalities that compete for access to working memory, and robustness to *internal* noise, coming from stochastic perturbations to the persistent neuronal activities that constitute the memory. Attractors storing continuous values, such as eye position, are particularly susceptible to the later because of their (intrinsic) direction of null stability. Our model addresses these issues via two basic mechanisms: targeted input to the prefrontal cortex from the basal ganglia and dopaminergic modulation of both the prefrontal cortex and basal ganglia. While other models have considered such effects separately, ours is the first to consider the combined, complementary, effects of dopamine in the prefrontal cortex and the basal ganglia alongside the direct basal ganglia input to cortex. Of course, our mechanisms may work in concert with others that have been proposed to ameliorate the effects of noise.

Robustness to external noise comes from a *gating* process. The requirements for a gating signal are that it be activated at the same time as the stimuli to be stored, and that it provide a (possibly exclusive) means by which a persistent working memory state is established. Following the experimental evidence that perturbing DA leads to disruption of WM (Sawaguchi and Goldman-Rakic, 1994; Zahrt et al., 1997; Romanides et al., 1999), various theories suggested that a phasic DA signal, associated for instance with reward-predicting conditioned stimuli (Schultz et al., 1993), implements the gate directly in the cortex (Braver and Cohen, 1999; Cohen et al., 2002), for instance via its contrast-enhancing effect on cortical activity (Servan-Schreiber et al., 1990; Brunel and Wang, 2001; Durstewitz et al., 2000; Dreher et al., 2002). However, as discussed at length in Frank *et al* (Frank et al., 2001), dopamine is unlikely to form the sole gating mechanism, since the activity patterns

of dopamine neurons in response to predictive stimuli and their diffuse projection make it hard to achieve precise temporal and spatial gating. Our model, along with theirs (Frank et al., 2001), emphasizes the gating role of the BG, in agreement with a variety of experimental evidence (Mink, 1996; Hikosaka et al., 1998; Kalivas et al., 2001). In particular, we demonstrate that even in low dopamine conditions the BG can gate information to PFC by controlling the switching of the attractor states in response to inputs. In our model, this happens even with a simple targeted excitatory input from the BG to the cortex. This input creates or deepens local minima in the landscape of cortical attractors, thereby fashioning or sculpting the working memory. However, whereas Frank *et al* (Frank et al., 2001) incorporate dopamine as a training signal, our model concentrates on the short term modulatory effects in the BG associated with the control of bistability (Gruber et al., 2003) of MSNs. This places the on-line gating under motivationally sophisticated control. The salience selectivity of gating in the model depends on the relative level of excitatory input to units and the level of DA modulation. For a given level of excitation, insufficient phasic DA release prevents the enhancement of salient memories and leads to distractibility, while high levels of tonic DA can cause enhancement of inappropriate memories and perseveration. This pattern is generally consistent with the idea that DA levels must remain in a limited range for normal task performance (Williams and Goldman-Rakic, 1995).

Robustness against noise intrinsic to the persistence of neuronal activity that underlies working memory is of particular importance for line or other continuous attractors, which have one or more global directions of symmetry and thus null stability. We find that increasing the steepness of the cortical response function, for instance by the uniform effects on cortical neurons of dopamine, does not suppress diffusion of the activity bump. Two possibilities, explored in various models, are that cortical neurons by themselves, or the cortical network, can suppress diffusion via intrinsic cellular bistability (Camperi and Wang, 1998) or by slow dynamical elements (Compte et al., 2000; Brunel and Wang, 2001). We explore a third (though not exclusive) possibility, involving weak but persistent input from the striatum. This mechanism, available in both high and low DA conditions, transforms the line attractor into a point attractor at the corresponding location, thus enhancing WM stability.

Striatal dopamine plays two main roles in robustness. First, dopamine-induced bistability of spiny neurons, for which some indirect evidence is now emerging (Vergara et al., 2003; Hernandez-Lopez et al., 1997), significantly enhances stabilization arising from persistent striatal input. The hysteresis associated with this bistability enhances the duration of these effects. Second, dopamine acts to sharpen the targeted output of the striatum. This increases the depth of the induced minimum in the cortical line attractor, which consequently increases the enhancement of robustness. Given that phasic dopamine release is associated with salient events such as reward delivery, the presentation of conditioned stimuli, and novel events (Schultz, 1998), this system is poised to implement saliency-selective gating and maintenance of WM so that this behaviorally important information is preserved. Phasic dopamine release has been proposed to implement a direct gating function in the cortex (Braver and Cohen, 1999; Cohen et al., 2002), in which dopamine is required for the formation of working memories. In contrast to this mechanism in which dopamine opens the gate to working memory, dopamine release in our model has the effect of closing the gate to working memory by stabilizing activity-based memories. This has the benefit that phasic DA release is not required for the encoding of stimuli that have no learned reward contingency, and also relaxes the temporal requirements on the effects of dopamine release such that they can occur following the onset of sensory-related cortical activity.

For WM models based on discrete fixed points rather than continuous attractors, drift is not as much an issue, since the attractor states lack directions of symmetry. However, these memory states are made more robust to switching and drift (Brunel and Wang, 2001; Durstewitz et al., 2000) by the global enhancement of all attractor states resulting from dopamine modulation in the cortex. This global effect would be refined by focal attractor enhancement through targeted input from the BG, which could both stabilize shallow memories and assist switching away from deep memories; these effects would be enhanced by DA induced bistability in the BG.

Various simplifying assumptions were made in constructing our model, and are targets of future work. Only the effects of phasic D1 receptor activation have been included; the effects of other DA receptors classes, which are less well understood (Nicola et al., 2000), and the effects of tonic DA (Grace, 1991) should be incorporated in more detailed models. Collaterals among MSNs, themselves the topic of active debate (Plenz, 2003), are not included in the present model. In models of the striatum (Beiser et al., 1997; Gurney et al., 2001), these collaterals are often assumed to implement a competitive network. This would lead to a sharper striatal code but would not significantly affect the results based on the simple WM task presented here. Something similar may also be true of striatal GABA-ergic interneurons, which are also not included in the present model. These neurons provide powerful inhibition of MSNs (Koos and Tepper, 1999), however, their connectivity and response properties are only incompletely known.

Additional processing in the thalamus and the internal segment of globus pallidus may also influence the gating of signals. The indirect pathway through the BG is not included in the present model; its net inhibitory influence on

the PFC could supply a repulsive 'pushing' effect through the creation of local maxima in the underlying landscape of the PFC bump network. This mechanism would complement the attractive 'pulling' effect of local minima created by activation of the direct pathway in breaking the continuous symmetry of the line attractor, and could assist the transition out of attractor states. Furthermore, the indirect pathway could suppress inappropriate memories, in a way analogous to its proposed role in suppressing motor commands (Hikosaka et al., 1998; Mink, 1996). Finally, cortical targets of the BG may send input back to the BG, forming a closed loop (Alexander and Crutcher, 1990). The inclusion of this recurrent pathway could lead to more complex dynamics, in which activity reverberates in the circuit (Beiser and Houk, 1998). Dopamine induced MSN bistability will then provide a mechanism for suppressing the spread of activity associated with recurrence, helping maintain a sparse representation of reward-related stimuli.

We have focused here on the mechanisms by which dopamine release can influence on-line processing of working memory to implement salience-selective gating. This process suggests a role for the phasic dopamine response elicited by conditioned stimuli in trained animals that have learned stimulus-action-outcome contingencies (Schultz et al., 1993; Kawagoe et al., 2004), and may help account for the enhanced behavioral performance of subjects on trials in which reward is expected (Kawagoe et al., 2004). An important direction for future work is to integrate these on-line effects with the growing understanding of dopamine signaling in terms of reward prediction error, its effects on cortical and striatal synaptic plasticity, and its role in learning the motivational significance of stimuli during the early phases of training.

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