Computational perspectives on dopamine function in prefrontal cortex

Commentary

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Dopamine and the prefrontal cortex are critical for thought and behaviour. Recently, computational models have tried to elucidate the specific and intricate roles of dopamine in the prefrontal cortex, at the neurophysiological, system and behavioral levels, with varying degrees of success.

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Abbreviations

BG	basal ganglia
DA	dopamine
EPSCs	excitatory postsynaptic currents
EPSPs	excitatory postsynatic potentials
IPSCs	inhibitory postsynaptic currents
IPSPs	inhibitory postsynaptic potentials
NMDA	*N*-methyl-D-aspartate
PFC	prefrontal cortex~
SNR	signal-to-noise ratio
VTA	ventral tegmental area

Introduction

Widespread interest in the neuroscience community regards the function of the prefrontal cortex (PFC) and the dopamine (DA) systems. This interest, in part, stems from the longstanding consensus that these neural systems play a critical role in many neuropsychiatric disorders, such as schizophrenia, attention deficit hyperactivity disorder, and Parkinson's disease, as well as in normal and pathologic aging. Scientific interest has also driven the hypothesis that DA and PFC systems are critical for the control of thought and behavior. PFC is of central importance to higher cognition and plays a critical role in working memory and attentional control [1], whereas the DA system is integrally involved with both motor control and reward/motivation [2,3]. Nevertheless, the interaction of DA within PFC likely serves a specialized computational function. Strong bidirectional anatomical connectivity between PFC and midbrain DA neurons supports this view [4]. Moreover, experimental manipulations of the DA system affect behavioral performance in both humans and other animals on tasks thought to be dependent on PFC function [5–13]. Neuroimaging studies in humans [14–16] and single-cell recordings in animals [17–20] have also provided evidence for the effects of DA on PFC activity during task performance. However, as discussed further below, these effects are complex and not easily understood.

In this commentary, we discuss the progress made in understanding the role of DA in PFC. Other recent reviews provide more in-depth summaries of the neurobiological and pharmacological complexities of DA effects in the PFC [21–24] and of computational models of PFC function or working memory more generally [25,26]. Here, we focus on computational modeling work that specifically addresses the functions of DA in PFC at the neurophysiological, systems and behavioral levels.

Connectionist models of dopamine neuromodulation

A long-held hypothesis suggests that catecholamine neurotransmitters, including DA, modulate target neuron responses, by increasing their signal-to-noise (SNR) ratio (i.e. by increasing the differentiation between background or baseline firing rates and those that are evoked by afferent stimulation) [27]. For example, studies in the striatum showed that DA potentiated the response of target neurons to the effect of both excitatory and inhibitory signals [28]. However, the precise biophysical mechanisms underlying these effects were not well understood. Moreover, the view that DA acts as a modulator in PFC has been controversial, because, for many years, DA application or stimulation of DA neurons reliably inhibited spontaneous PFC activity. Thus, many investigators argued that DA served as an inhibitory transmitter in PFC [1,29,30].

The first explicit computational models of the neuromodulatory function of catecholamines [31], and DA in particular [30], were developed within the connectionist framework, and focused on their effects on information processing. Although such models do not typically incorporate biophysical detail, by virtue of their simplicity they have the advantage of simulating system level function and performance in a wide variety of cognitive tasks. Within this framework, DA effects were simulated as a change in the slope (or gain) of the sigmoidally shaped input–output activation function of processing units. Thus, in the presence of DA, both the excitatory and inhibitory influences of afferent inputs are potentiated. Computational analyses showed that this modulatory function would not improve the SNR characteristics of single neurons, but could do so at the network level [31,33,34]. Models implementing these ideas proved useful for accounting for a wide range of phenomena, including the pharmacological effects of DA on performance in tasks thought to rely on PFC [35] and the effects of disturbances of DA in schizophrenia [32].

Biophysically detailed models

In recent work, computational studies have focused on more biophysically detailed accounts of DA action within PFC. Models by Durstewitz *et al.* [36–38] and Brunel and Wang [39], all include data on the different biophysical effects of DA on specific cellular processes. These models have been used to simulate the dynamics of activity in networks that closely parallel the patterns observed *in vivo* within PFC. For example, Durstewitz *et al.* [36] incorporate five empirically observed effects of DA: an enhancement of sodium current, via D1 receptors; a reduction of slow potassium current; a reduction of high-voltage calcium currents; a suppression of glutamate-mediated excitatory postsynaptic potentials (EPSPs); an enhancement of γ-amino butyric acid (GABA)-mediated inhibitory post-synaptic potentials (IPSPs). This model also distinguishes between DA effects in two dendritic compartments, separating its effects on recurrent versus afferent inputs. In later work, the opposing effects of DA on glutamate-mediated EPSPs via *N*-methyl-D-aspartate (NMDA) receptors and α-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptors were also taken into account.

These models synthesize the rapidly growing, but often confusing literature on the neurophysiology of DA within PFC. For example, the biophysical effects of DA are shown to produce a suppressive influence on spontaneous activity, explaining its apparent inhibitory actions, while at the same time causing an enhanced excitability in response to afferent drive. Furthermore, the selective enhancement of inputs from recurrent versus external afferents provides a mechanism for stabilizing sustained activity patterns within PFC that are resistant to interference from external inputs. These computational analyses support the characterization of DA as a modulatory neurotransmitter, rather than a classical excitatory or inhibitory one [24], and explain its role in support sustained activity within PFC.

Strikingly, these models are remarkably consistent with the original hypothesis that DA increases SNR within the PFC, and the expression of this idea in earlier connectionist models. The underlying assumption in both types of models is that short-term storage of information in PFC occurs through recirculating activity within local recurrent networks, which can be described as fixed-point attractor systems. DA activity helps to stabilize attractor states, both by making high activity states more stable (active maintenance), and low activity states (spontaneous background activity) less likely to spuriously transition to high activity states in the absence of strong afferent input. This is accomplished by the concurrent potentiation of excitatory and inhibitory transmission, implemented as changes in ion channel properties in biophysically detailed models and 'summarized' as a change in the gain of the sigmoidal activation function in connectionist models.

These mechanisms can be used to simulate the effects of DA on performance in cognitive tasks that rely on PFC function. For example, in a task emphasizing the role of PFC in working memory [40], increased DA activation in the Durstewitz *et al.* model enhanced the stability of PFC working memory representations by making them less susceptible to interference from the intervening distractors. Within connectionist models, similar effects have been demonstrated by changing the gain of the activation function, and simulating human performance in tasks known to rely on PFC (e.g. [32]), tasks similar to those simulated by Durstewitz *et al.* and Brunel and Wang.

These models also provide accounts of the pharmacological data on the neurophysiological and behavioral effects of DA agonists and antagonists. Thus, in a hypodopaminergic state, PFC representations will be less sharply tuned and unstable, and susceptibility to interference and memory decay should be greater. In contrast, small increases in DA levels should facilitate PFC stability and hence, enhance performance. However, in hyperdopaminergic states, performance may degrade as PFC representations become overly fixed and brittle. Under these conditions, perseverative behavior may dominate. All of these effects have been demonstrated in both biophysically detailed and connectionist models, and all appear to be consistent with previous data [2,19,20,41,43].

The role of dopamine in updating and learning

A critical functional requirement of the DA/PFC system is to properly balance active maintenance of representations with their updating at appropriate times. Specifically, how does this system know to appropriately update its state in response to salient input information but not to interfering distractors? Both of the biophysical models provide partial answers to this question. In the Durstewitz model, the PFC and DA systems interact as a dynamically regulated network. Initial presentation of a to-be-stored input causes PFC activation, which then excites DA neurons. These neurons allow the information to be actively maintained and protected from intervening distractors until a behavioral response is generated. Motor activation associated with the response then suppresses the DA system, which resets PFC, returning activity to baseline levels until a subsequent trial begins. In the Brunel and Wang model, active maintenance and interference protection is not dependent upon DA modulation. Instead, resetting of PFC occurs by a global pulse of excitation delivered to the network following the execution of a response.

The mechanisms proposed by these models face important limitations. For example, both require a motor response to reset PFC and permit a new representation to be stored. This does not explain, however, the updating of PFC representations when no motor response is generated (e.g. the successive encoding of items into working memory during a serial recall task). Furthermore, they do not specify how the appropriate signals for updating might be learned.

Mechanisms that provide a more flexible form of updating have been explored in connectionist models. For example,

Hochreiter and Schmidhuber [44] argue computationally that the only way for an attractor-based network to perform important classes of active memory tasks is if it regulates the entry of information into the network through the use of a gating mechanism, phasically triggered by task-relevant inputs. Zipser *et al.* [45] have employed a similar mechanism in their model of PFC function. However, neither of these models [44,45] specified the neural mechanisms subserving the gating signal.

Phasis versus tonic dopamine release

In our own recent work, we have suggested that phasic bursts of DA activity in PFC may function as a gating mechanism, by signaling when afferent inputs should be selected and stored in PFC, updating the contents of working memory [46–49,51]. Both computational considerations and neurophysiological data motivated this hypothesis. The data suggest that midbrain DA neurons convey important reward-related information regarding external stimuli through phasic bursts of activity [2]. Specifically, these neurons show rapid, transient, stimulus-specific responses to salient environmental stimuli that reliably predict future rewards. The timing of such responses is well suited for signaling the need to update representations in PFC, the function of which is to guide behavior in accord with current goals [1,50]. Thus, updating PFC representations in response to cues that signal the availability of reward can ensure that behavior is guided toward the procurement of that reward. It is also worth noting that when a reward is predicted but not received, the DA system exhibits a phasic depression in activity [52].

Importantly, it is phasic, rather than tonic, changes in DA activity that seem to track the relevant events in working memory tasks thought to rely on PFC function. For example, in such tasks, DA neurons respond phasically to stimuli that must be remembered, whereas they do not show tonic increases in firing during the retention interval, while information is being actively maintained [53].

The dynamics of DA activity in classical conditioning tasks have also been the focus of new theories regarding the role of DA in learning. Modeling work has suggested that phasic DA activity might serve as a reinforcement learning signal, by indicating a mismatch between the prediction and delivery of reinforcements, which can be used to update associative (Hebbian) synaptic connections to reduce the occurrence of subsequent prediction errors [54–58]. These models have demonstrated that DA phasic activity closely parallels the dynamics of the reinforcement learning signal both within task trials and across various stages of learning. The models are also consistent with a growing base of neurobiological data indicating that DA modulates synaptic plasticity in a variety of cortical locations, including PFC [59–62].

Recently, we have integrated the hypothesized updating and reinforcement learning functions of DA into a single model. We suggest that the phasic DA signals trigger a switch in the current attractor state, by transiently enhancing afferent input while potentiating local inhibitory signals [47,48], thus gating new information into PFC. At the same time, the potentiating effects of DA mediate learning, by amplifying the impact of inputs on receiving units. The coincidence of these gating and learning effects allows the system to learn the appropriate timing for the gating signal, by associating the information being gated with a triggering of the gating signal in the future. Furthermore, phasic dips in DA activity following failed rewards can produce rapid deactivation of PFC activity and thus reset the contents of working memory [51]. Similar proposals for a role of phasic changes in DA activity in resetting working memory have been made by other investigators [63].

Connectionist models implementing these mechanisms can learn how and when to gate information into an active maintenance (PFC) layer, and thereby learn to perform simple working memory tasks known to rely on PFC [48,51]. These models suggest an important role of phasic DA responses, both in updating the contents of working memory, and learning when to do so. However, this reliance on a phasic DA signal appears to be at odds with the biophysically detailed models of Durstewitz *et al.* and Brunel and Wang. Durstewitz *et al.* have argued explicitly that it is the tonic rather than phasic actions of DA that are most relevant to PFC function. Moreover, these investigators have suggested that the slow timecourse of DA effects indicates that even phasic bursts of activity may result in sustained postsynaptic effects that take minutes to resolve [37].

Toward an integrated theory of dopamine function in PFC

Is it possible to reconcile tonic DA stabilization of working memory with the hypothesized phasic DA modulation of working memory updating and learning? The literature provides hints that this may be possible. Previous [31,36–38] models focused primarily on DA effects associated with D1 receptor activation, which is thought to be long acting. This emphasis reflects the importance of D1 receptors in PFC from pharmacological studies [21].

However, phasic actions of DA may be mediated by D2 rather than D1 receptors. This is consistent with the hypothesis proposed by Grace [64,65] that tonic and phasic DA release represent two distinct, and antagonistic modes of DA action. Specifically, phasic DA neuron firing may cause DA to be released intrasynaptically in high concentrations, but then be rapidly removed via a fast, high-capacity reuptake system before it diffuses extrasynaptically. Consequently, phasic DA release may not be measurable via extrasynaptic monitoring. In contrast, sustained, tonic changes in DA neuron firing may produce increases in extrasynaptic DA concentrations. Most importantly, increases in tonic DA levels may inhibit phasic (spike-dependent) release of DA via regulation of presynaptic DA terminal autoreceptors. Accordingly, pharmacologic manipulations

that target D1 receptors, or otherwise produce changes in tonic DA activity, may also have an indirect influence on phasic DA release.

D2 mediated effects also tend to be the opposite of, and antagonistic to, D1-mediated effects [37,66,67]. Whereas D1 receptor activation enhances NMDA excitatory postsynaptic currents (EPSCs), inhibitory postsynaptic currents (IPSCs) and interneuron excitability, D2 receptor activation decreases NMDA EPSCs, IPSCs, and interneuron excitability. In addition, D2 receptor effects show a different time course of effect in IPSC modulation, acting more rapidly but then decaying more quickly.

This distinction between tonic D1 and phasic D2 effects, and their reciprocal relationship, may provide a basis for integrating the maintenance (tonic) and updating/learning (phasic) functions of DA. This, in turn, may help explain a number of puzzling findings in the psychopharmacological literature. For example, the effects of DA modulation on behavioral performance are non-monotonic: both too little and too much DA impair performance, and DA effects are dependent on tonic baseline levels of DA activation. However, the behavioral consequences of too little versus too much DA differ, with too little DA producing impulsive behaviors and distractibility, and too much DA resulting in perseveration and stereotypy [12,41,43,68–72]. These results may be explained by the hypothesis that pharmacologic manipulations of tonic DA activity produce indirect changes in phasic activity, changing the balance between the maintenance and updating functions of DA. Thus, a DA agonist with protracted effects would allow representations in PFC to be maintained (high tonic DA), but not effectively updated (low phasic DA). This would produce perseveration and stereotypy. Conversely, a DA antagonist would degrade representations in PFC (low tonic DA), while updating might be intact or even over-reactive (augmented phasic). This would produce impulsivity and distractibility

Although the hypothesis concerning the distinct functions of D1 and D2 receptors has appeal, it is not yet clear how phasic DA release might modulate postsynaptic targets with the rapid time course required for a gating or updating mechanism. Recent evidence suggests that single-pulse stimulation of the ventral tegmental area (VTA), using physiologically realistic parameters, can rapidly and transiently modulate the firing patterns of PFC neurons [73]. However, additional studies are needed, pairing VTA stimulation with thalamocortical (or cortico–cortical) afferent stimulation, and monitoring PFC neuronal activity. Our theory would predict, for example, that in behaving animals, brief VTA stimulation (simulating phasic activity) during the presentation of an external stimulus should result in the representation and maintenance of this input as a sustained pattern of PFC activity.

Even if the integrated tonic/phasic model of DA modulation within PFC is correct, important functional issues regarding active maintenance remain unaddressed. In particular, the phasic gating model suggests that selection and updating of information is determined through the association of that information with predicted future reinforcement. Although this type of reinforcement–association mechanism seems reasonable for some task situations, it may not explain how updating occurs in situations requiring more complex maintenance dynamics. For example, many task situations have a goal–subgoal structure, in which higher-order goals need to be actively maintained while lower-order subgoals are updated. The direct input from the VTA DA system to PFC does not seem well suited for such a function, because this system phasically responds to relevant inputs in a homogeneous and undifferentiated manner [2]. To achieve hierarchical or asynchronous updating, a gating mechanism would need to selectively target PFC subregions. Interestingly, the basal ganglia (BG) appear to be well suited for such a role. This structure plays a critical role in reinforcement-driven learning, and has a highly segregated system of inputs to PFC subregions [3,74,75]. Recent computational analyses of the potential role of the BG in hierarchical updating of PFC have yielded promising results [76]. Thus, one future direction of research will be to determine the relationship between the direct VTA–PFC pathway and the VTA–BG–PFC pathway with regard to their involvement in DA updating of representations in PFC.

In summary, although much remains to be learned about DA function, the empirical data and modeling work reviewed above suggest a possible synthesis of models of tonic DA effects [32,36,39] and those implementing phasic DA effects [48,51,55,57]. Both modes of DA activity may serve to modulate active memory representations within PFC, but in different ways. Tonic DA effects may increase the stability of maintained representations through an increase in the SNR of background versus evoked PFC activity patterns. In contrast, phasic DA effects may serve as a gating signal, indicating when new inputs should be encoded and maintained, or when currently maintained representations should be updated in response to salient, reward-predicting information. The system may dynamically regulate the balance or bias between these modes of activation, through the antagonistic relationship of tonic and phasic DA release, perhaps mediated by D1 and D2 receptor activations, respectively.

Conclusions and future directions

Recent models of DA and PFC function offer the promise, for the first time, of relating phenomena at very different levels of analysis, from the cellular to the behavioral. For example, biophysically detailed models of tonic DA effects on PFC activity [36,37,39] suggest functions that are very similar to those described in more abstract form in connectionist models [31,32]. Although the former provide a more detailed account of the underlying physiological mechanisms, the latter can be (and have been) used to simulate a wide variety of behavioral phenomena. Conceptual contact between these models will offer a host of new opportunities.

Biophysical models can be used to assess the fidelity of the abstractions used in connectionist models. They can also be used to explore which new features of DA modulation may be most relevant to network behavior, and whether and how these may be usefully represented in more abstract connectionist models. This in turn can be used to predict the effects of pharmacological manipulations on behavior. Conversely, connectionist models that implement mechanisms suggested by a functional analysis of the system may help guide future research on the biophysical processes that underlie these mechanisms.

Perhaps the most important message from this work is the value of a multilevel approach to model building. One analogy that has recently been offered is that understanding system-level computation in neural networks is akin to understanding the aerodynamic properties of an airplane: it requires a detailed description of the interactions among many small elements, which cannot be summarized by the effects of a small number of large particles bombarding the wing. We fully respect the fact that some aspects of nervous system function will yield only to such detailed characterization. At the same time, it seems highly likely that other aspects will be most usefully described at more abstract levels, just as the trajectory of an airplane, when properly designed and operated, may be usefully described by principles that do not require recourse to the molecular level.

Research on DA function, and neuromodulators more generally, is in an exciting phase. Clearly, there is much more to be learned to gain a comprehensive understanding of how DA modulation influences PFC dependent cognitive processes. We have focused only on D1 and D2 receptor effects, without addressing the other DA receptors that no doubt carrying out important functions. And, as we have noted, there are certainly close relationships between DA function in PFC and in the basal ganglia. Nevertheless, the progress to date affirms that a close partnership of multilevel empirical and computational research will continue to be a productive path towards making further progress in this area.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Miller EK, Cohen JD: **An integrative theory of prefrontal cortex function**. *Annu Rev Neurosci* 2001, **24**:167-202.
2. Schultz W: **Predicted reward signal of dopamine neurons.** *J Neurophysiol* 1998, **80**:1-27.
3. Beiser DG, Hua SE, Houk JC: **Network models of the basal ganglia.** *Curr Opin Neurobiol* 1997, **7**:185-190.
4. Pirot S, Godbout R, Mantz J, Tassin JP, Glowinski J, Thierry AM: **Inhibitory effects of ventral tegmental area stimulation on the activity of prefrontal cortical neurons: evidence for the involvement of both dopaminergic and gabaergic components.** *Neuroscience* 1992, **49**:857-865.
5. Arnsten AF, Cai JX, Murphy BL, Goldman-Rakic PS: **Dopamine D1 receptor mechanisms in the cognitive performance of young adult and aged monkeys.** *Psychopharmacology (Berl)* 1994, **116**:143-151.
6. Brozoski TJ, Brown RM, Rosvold HE, Goldman PS: **Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey.** *Science* 1979, **205**:929-931.
7. Luciana M, Collins PF, Depue RA: **Opposing roles for dopamine and serotonin in the modulation of human spatial working memory functions.** *Cereb Cortex* 1998, **8**:218-226.
8. Luciana M, Depue RA, Arbisi P, Leon A: **Facilitation of working memory in humans by a D2 dopamine receptor agonist.** *J Cogn Neurosci* 1992, **4**:58-68.
9. Muller U, von Cramon DY, Pollmann S: **D1- versus D2- receptor modulation of visuospatial working memory in humans.** *J Neurosci* 1998, **18**:2720-2728.
10. Murphy BL, Arnsten AFT, Goldman-Rakic PS, Roth RH: **Increased dopamine turnover in the prefrontal cortex impairs spatial working memory performance in rats and monkeys.** *Proc Natl Acad Sci USA* 1996, **93**:1325-1329.
11. Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ, Robbins TW: **6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: possible interactions with subcortical dopamine.** *J Neurosci* 1994, **14**:2531-2544.
12. Sawaguchi T, Goldman-Rakic PS: **D1 dopamine receptors in prefrontal cortex: involvement in working memory.** *Science* 1991, **251**:947-950.
13. Simon H, Scatton B, Le Moal M: **Dopaminergic A10 neurones are involved in cognitive functions.** *Nature* 1980, **286**:150-151.
14. Daniel DG, Weinberger DR, Jones DW, Coppola R, Handel S, Bigelow LB, Goldberg TE, Berman KF, Kleinman JE: **The effect of amphetamine on regional cerebral blood flow during cognitive activation in schizophrenia.** *J Neurosci* 1991, **11**:1907-1917.
15. Mattay VS, Berman KF, Ostrem JL, Esposito G, Van Horn JD, Bigelow LB, Weinberger DR: **Dextroamphetamine enhances 'neural network-specific' physiological signals: a positron-emission tomography rCBF study.** *J Neurosci* 1996, **15**:4816-4822.
16. Mehta MA, Owen AM, Sahakian BJ, Mavaddat N, Pickard JD, Robbins TW: **Methylphenidate enhances working memory by modulating discrete frontal and parietal lobe regions in the human brain.** *J Neurosci* 2000, **20**:1-6.
17. Sawaguchi T: **The effects of dopamine and its antagonists on directional delay-period activity of prefrontal neurons in monkeys during an oculomotor delayed-response task.** *Neurosci Res* 2001, **41**:115-128.
18. Sawaguchi T, Matsumura M, Kubota K: **Catecholaminergic effects on neuronal activity related to a delayed response task in monkey prefrontal cortex.** *J Neurophysiol* 1990, **63**:1385-1400.
19. Sawaguchi T, Matsumura M, Kubota K: **Effects of dopamine antagonists on neuronal activity related to a delayed response task in monkey prefrontal cortex.** *J Neurophysiol* 1990, **63**:1401-1410.
20. Williams GV, Goldman-Rakic PS: **Modulation of memory fields by dopamine D1 receptors in prefrontal cortex.** *Nature* 1995, **376**:572-575.
21. Goldman-Rakic PS, Muly EC, Williams GV: **D1 receptors in prefrontal cells and circuits.** *Brain Res Rev* 2000, **1**:295-301.
22. Robbins TW: **Chemical neuromodulation of frontalexecutive functions in humans and other animals.** *Exp Brain Res* 2000, **133**:130-138.

23. Tzschentke TM: **Pharmacology and behavioral pharmacology of the mesocortical dopamine system.** *Prog Neurobiol* 2001, **63**:241-320.

24. Yang CY, Seamans JK, Gorelova N: **Developing a neuronal model for the pathophysiology of schizophrenia based on the nature of the electrophysiological actions of dopamine in the prefrontal cortex.** *Neuropsychopharmacology* 1999, **21**:161-194.

25. Durstewitz D, Seamans JK, Sejnowski TJ: **Neurocomputational models of working memory.** *Nat Neurosci* 2000, **3**:1184-1191.

26. Tanaka S: **Computational approaches to the architecture and operations of the prefrontal cortical circuit for working memory.** *Prog Neuropsychopharmacol Biol Psychiatry* 2001, **25**:259-281.

27. Foote SL, Morrison JH: **Extrathalamic modulation of cortex.** *Annu Rev Neurosci* 1987, **10**:67-85.

28. Chiodo L, Berger T: **Interactions between dopamine and amino acid induced excitation and inhibition in the striatum.** *Brain Res* 1986, **375**:198-203.

29. Bunney B, Chiodo LA: *Mesocortical Dopamine Systems: Further Electropysiological and Pharmacological Characteristics, Monoamine Innervation of Cerebral Cortex.* New York: Alan R Liss, Inc; 1984:263-277.

30. Ferron A, Thierry AM, Le Douarin C, Glowinski J: **Inhibitory influence of the mesocortical dopaminergic system on spontaneous activity or excitatory response induced from the thalamic mediodorsal nucleus in the rat medial prefrontal cortex.** *Brain Res* 1984, **302**:257-265.

31. Servan-Schreiber D, Printz H, Cohen JD: **A network model of catecholamine effects: gain, signal-to-noise ratio, and behavior.** *Science* 1990, **249**:892-895.

32. Cohen JD and Servan-Schreiber D: **Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia.** *Psychological Review* 1992, **99**: 45-77.

33. Braver TS: **Mechanisms of cognitive control: a neurocomputational model [PhD Thesis].** Pittsburgh, PA: Carnegie Mellon University; 1997.

34. Braver TS, Cohen JD, Servan-Schreiber D: **A computational model of prefrontal cortex function.** In *Advances in Neural Information Processing Systems,* vol 7. Edited by Touretzky DS, Tesauro G, Leen TK. Cambridge, MA: MIT Press; 1995:141-148.

35. Servan-Schreiber D, Bruno R, Carter C & Cohen JD: **Dopamine and the mechanisms of cognition. I. A neural network model predicting dopamine effects on selective attention.** *Biol Psychiatry* 1998, 3: 713-722.

36. Durstewitz D, Kelc M, Gunturkun O: **A neurocomputational theory of the dopaminergic modulation of working memory functions.** *J Neurosci* 1999, **19**:2807-2822.

37. Durstewitz D, Seamans JK: **A neurocomputational theory of the D1 receptor modulation of prefrontal cortex during working memory.** *Neural Networks* 2002, in press.

38. Durstewitz D, Seamans JK, Sejnowski TJ: **Dopamine mediated stabilization of delay-period activity in a network model of prefrontal cortex.** *J Neurophysiol* 2000, **83**:1733-1750.

39. Brunel N, Wang X-J: **Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition.** *J Comput Neurosci* 2001, **11**:63-85.

40. Miller EK, Erickson CA, Desimone R: **Neural mechanisms of visual working memory in prefrontal cortex of the macaque.** *J Neurosci* 1996, **16**:5154-5167.

41. Arnsten AF, Goldman-Rakic PS: **Noise stress impairs prefrontal cortical cognitive function in monkeys: evidence for a hyperdopaminergic mechanism.** *Arch Gen Psychiatry* 1998, **55**:362-368.

43. Zahrt J, Taylor JR, Mathew RG, Arnsten AF: **Supranormal stimulation of D1 dopamine receptors in the rodent prefrontal cortex impairs spatial working memory.** *J Neurosci* 1997, **17**:8528-8535.

44. Hochreiter S, Schmidhuber J: **Long short-term memory.** *Neural Comput* 1997, **9**:1735-1780.

45. Moody SL, Wise SP, di Pellegrino G, Zipser D: **A model that accounts for activity in primate frontal cortex during a delayed-match-to-sample task.** *J Neurosci* 1998, **18**:399-410.

46. Braver TS, Barch DM, Cohen JD: **Cognition and control in schizophrenia: a computational model of dopamine and prefrontal function.** *Biol Psychiatry* 1999, **46**:312-328.

47. Braver TS, Cohen JD: **Dopamine, cognitive control, and schizophrenia: the gating model.** *Prog Brain Res* 1999, **121**:327-349.

48. Braver TS, Cohen JD: **On the control of control: the role of dopamine in regulating prefrontal function and working memory.** In *Attention and Performance XVIII.* Edited by Monsell S, Driver J. Cambridge, MA: MIT Press; 2000:713- 738.

49. Cohen JD, Braver TS, O'Reilly R: **A computational approach to prefrontal cortex, cognitive control, and schizophrenia: recent developments and current challenges.** *Philos Trans R Soc Lond B Biol Sci* 1996, **351**:1515-1527.

50. O'Reilly RC, Braver TS, Cohen JD: **A biologically-based computational model of working memory.** In *Models of Working Memory: Mechanisms of Active Maintenance and Executive Control.* Edited by Miyake A, Shah P. New York: Cambridge University Press; 1999.

51. O'Reilly RC, Noelle DC, Braver TS, Cohen JD: **Prefrontal cortex and dynamic categorization tasks: representational organization and neuromodulatory control.** *Cereb Cortex* 2002, **12**:246-257.

52. Hollerman JR, Tremblay L, Schultz W: **Influence of reward expectation on behavior-related neuronal activity in primate striatum.** *J Neurophysiol* 1998, **80**:947-963.

53. Schultz W, Apicella P, Ljungberg T: **Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task.** *J Neurosci* 1993, **13**:900-913.

54. Houk JC, Adams JL, Barto AG: **A model of how the basal ganglia generate and use neural signals that predict reinforcement.** In *Models of Information Processing in the Basal Ganglia.* Edited by Houk JC, Davis JL, Beiser DG. Cambridge, MA: MIT Press; 1995:249-270.

55. Montague PR, Dayan P, Sejnowski TJ: **A framework for mesencephalic dopamine systems based on predictive Hebbian learning.** *J Neurosci* 1996, **16**:1936-1947.

56. Schultz W, Dayan P, Montague PR: **A neural substrate of prediction and reward.** *Science* 1997, **275**:1593-1599.

57. Suri RE, Schultz W: **A neural network model with dopamine-like reinforcement signal that learns a spatial delayed response task.** *Neuroscience* 1999, **91**:871-890.

58. Brown J, Bullock D, Grossberg S: **How the basal ganglia use parallel excitatory and inhibitory learning pathways to selectively respond to unexpected rewarding cues.** *J Neurosci* 1999, **19**: 10502-10511.

59. Bao S, Chan VT, Merzenich MM: **Cortical remodeling induced by activity of ventral tegmental dopamine neurons.** *Nature* 2001, **412**:79-83.

60. Gurden H, Takita H, Jay TM: **Essential role of D1 but not D2 receptors in the NMDA receptor-dependent long-term potentiation at hippocampal-prefrontal cortex synapses *in vivo.*** *J Neurosci* 2000, **20**:1-5.

61. Law-Tho D, Deuce JM, Crepel F: **Dopamine favours the emergence of long-term depression versus long-term potentiation in slices of rat prefrontal cortex.** *Neurosci Lett* 1995, **188**:125-128.

62. Otani S, Blond O, Desce J-M, Crepel F: **Dopamine facilitates long-term depression of glutamatergic transmission in rat prefrontal cortex.** *Neuroscience* 1998, **85**:669-676.

63. Dehaene S, Changeux J-P: **Reward-dependent learning in neuronal networks for planning and decision making.** *Prog Brain Res* 2000, **126**:217-229.

64. Grace AA: **Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis of the etiology of schizophrenia.** *Neuroscience* 1991, **41**:1-24.

65. Grace AA: **The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving.** *Addiction* 2000, **95**:S119- S128.

66. Seamans JK, Gorelova N, Durstewitz D, Yang CR: **Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical pyramidal neurons.** *J Neurosci* 2001, **21**:3628-3638.

67. Zheng P, Zhang XX, Bunney BS, Shi WX: **Opposite modulation of cortical *N*-methyl-D-aspartate receptor mediated responses by low and high concentrations of dopamine.** *Neuroscience* 1999, **91**:527-535.

68. Kimberg DY, D'Esposito M, Farah MJ: **Effects of bromocriptine on human subjects depend on working memory capacity.** *Neuroreport* 1997, **8**:381-385.

69. Arnsten AFT: **Catecholamine modulation of prefrontal cortical cognitive function.** *Trends Cogn Sci* 1998, **2**:436-447.

70. Oades RD: **The role of noradrenaline in tuning and dopamine in switching between signals in the CNS.** *Neurosci Behav Rev* 1985, **9**:261-282.

71. Robbins TW: **From arousal to cognition: the integrative position of the prefrontal cortex.** *Prog Brain Res* 2000, **126**:469-483.

72. Tucker DM, Williamson PA: **Asymmetric neural control systems in human self-regulation.** *Psychol Rev* 1984, **91**:185-215.

73. Au-Young SMW, Shen H, Yang CR: **Medial prefrontal cortical output neurons to the ventral tegmental area (VTA) and their responses to burst-patterned stimulation of the VTA: Neuroanatomical and *in vivo* electrophysiological analyses.** *Synapse* 1999, **34**:245-255.

74. Alexander GE, DeLong MR, Strick PL: **Parallel organization of functionally segregated circuits linking basal ganglia and cortex.** *Annu Rev Neurosci* 1986, **9**:357-381.

75. Barto AG: (1995) **Adaptive critics and the basal ganglia.** In *Models of Information Processing in the Basal Ganglia*. Edited by Houk JC, Davis JL, Beiser DG. Cambridge, MA: MIT Press; 1995:216-232.

76. Frank MJ, Loughry B, O'Reilly RC: **Interactions between frontal cortex and basal ganglia in working memory: a computational model.** *Cogn Affect Behav Neurosci* 2001, **1**:137-160.